# Gene Therapies and Aseptics - a practical guide


Anne Black

Regional QA Specialist Pharmacist

Pan UK Pharmacy Working Group for ATMPs – Chair

@anneblackpharm

anne.black7@nhs.net

Charlotte Ollerenshaw-Ward

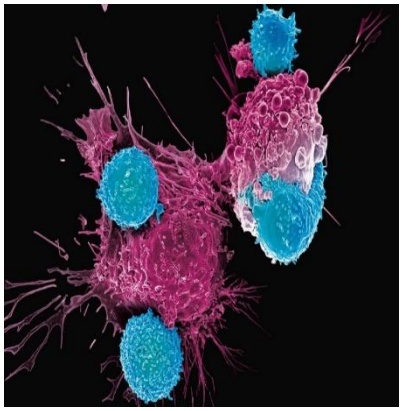
Aseptic Service Manager

Salford Royal Hospital part of the Northern Care Alliance NHS Foundation Trust

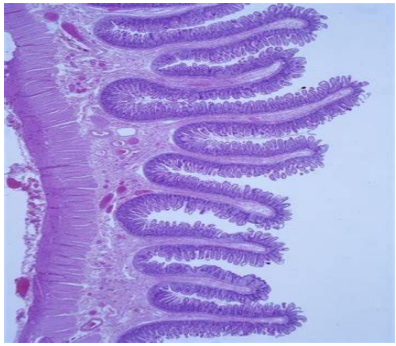
@lotteoward

Charlotte.OllerenshawWard@nca.nhs.ukt

Specialist Pharmacy Service
www.sps.nhs.uk

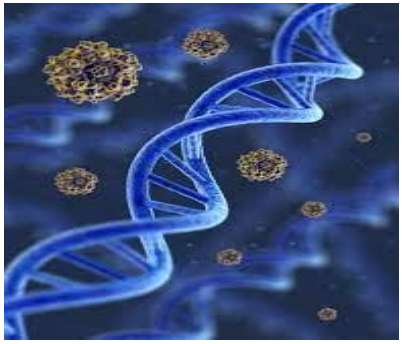


# Advanced Therapy Medicinal Products - ATMPs



- An ATMP is a biological medicine.
- Regulation (EC) No 1394/2007 **classified** ATMPs as:
  - Somatic Cell Therapy Medicinal Product
  - Tissue Engineered Products
  - Gene Therapy Medicinal Product (GTMP)

Combined ATMPs are any of the above + a device.



Specialist Pharmacy Service
www.sps.nhs.uk

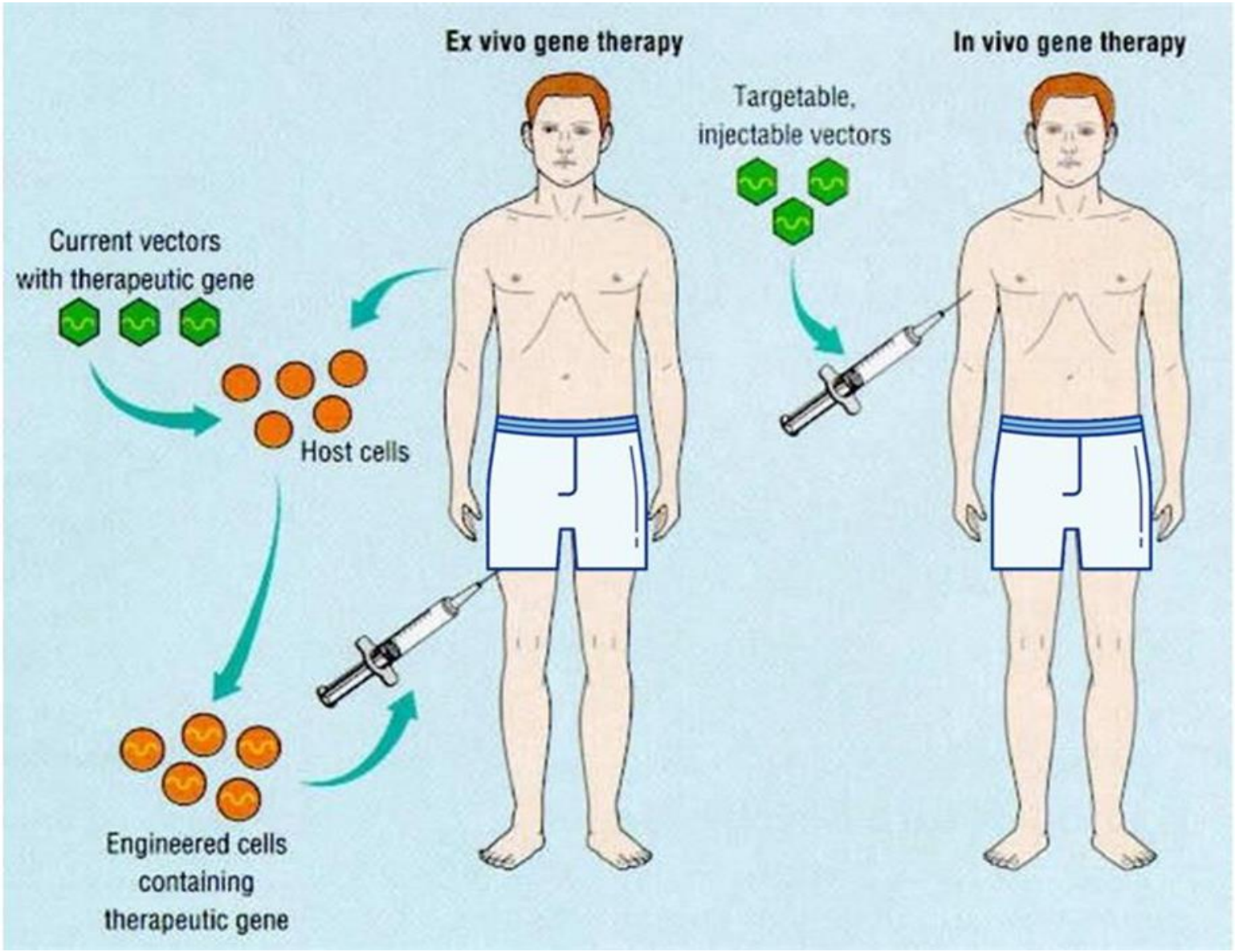
# *Under UK legislation (HMRs 2012 Regulation 2A):*

*A "gene therapy medicinal product" is a biological medicinal product which has the following characteristics—*

- *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; and*

- *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.*

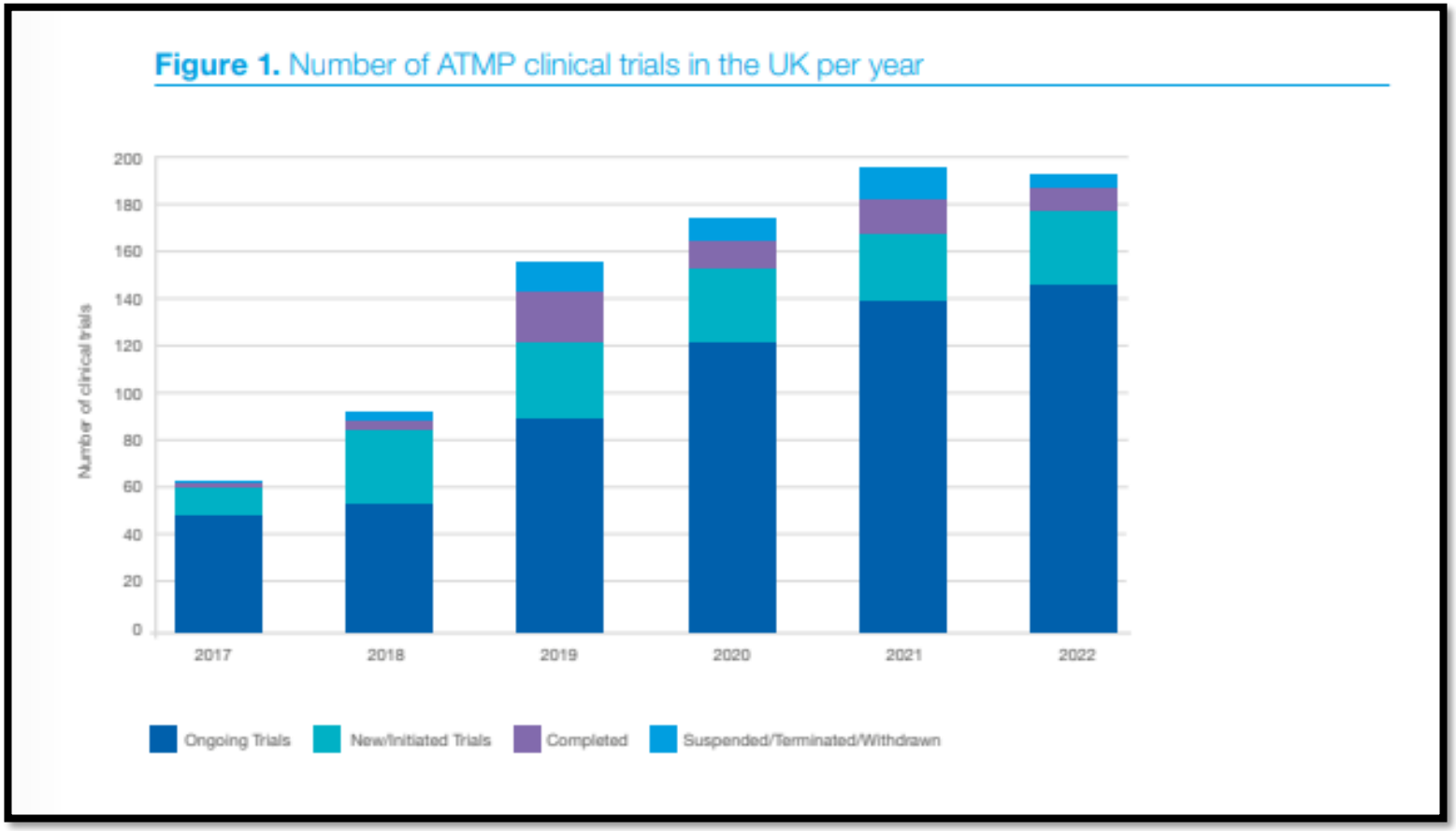
*A vaccine against infectious diseases is not to be treated as a gene therapy medicinal product.*


Ex vivo gene therapy
In vivo gene therapy
Targetable, injectable vectors
Current vectors with therapeutic gene
Host cells
Engineered cells containing therapeutic gene

| Generic name | *Brand name* | Indication | Type of ATMP |
|---|---|---|---|
| atidarsagene autotemcel | *Libmeldy* | Pre-symptomatic early onset (late infantile and early juvenile) metachromatic leukodystrophy | Ex vivo GTMP |
| autologous anti CD19 transduced CD3+ cells (brexucabtagene autoleucel) | *Tecartus* | Mantle cell lymphoma in adults<br><br>ALL in adults | Ex vivo GTMP |
| autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence | *Strimvelis* | Severe combined immunodeficiency due to adenosine deaminase deficiency | Ex vivo GTMP |
| axicabtagene ciloleucel | *Yescarta* | Diffuse large B-cell lymphoma in adults – third-line and second line | Ex vivo GTMP |
| ex vivo expanded autologous human corneal epithelial cells containing stem cells | *Holoclar* | Limbal stem-cell deficiency due to ocular burns in adults | TEP |
| onasemnogene abeparvovec | *Zolgensma* | Spinal muscular atrophy | In vivo GTMP |
| spheroids of human autologous matrix-associated chondrocytes | *Spherox* | Articular cartilage disorders | TEP |
| talimogene laherparepvec | *Imlygic* | Malignant melanoma | In vivo GTMP |
| tisagenlecleucel | *Kymriah* | Diffuse large B-cell lymphoma in adults – third-line | Ex vivo GTMP |
| tisagenlecleucel | *Kymriah* | Acute lymphoblastic leukaemia in children and young adults | Ex vivo GTMP |
| voretigene neparvovec | *Luxturna* | Leber congenital amaurosis or retinitis pigmentosa caused by confirmed biallelic RPE65 mutations | In vivo GTMP |
| eladocagene exuparvovec | *Upstaza* | Aromatic L-amino acid decarboxylase deficiency >18months old | In vivo GTMP |

Specialist Pharmacy Service
www.sps.nhs.uk

# Clinical Trials




https://cgt.ams3.cdn.digitaloceanspaces.com/Clinical-Trials-Database-2022-report.pdf

Specialist Pharmacy Service
www.sps.nhs.uk

# What does this mean for Aseptics…….?

- More work, more complexity: Preparation capacity will be required

- Recognised by ISMB / Aseptic Transformation process and the O'Shaunessey review.

Specialist Pharmacy Service

www.sps.nhs.uk

Date published: 17 March, 2023
Date last updated: 1 June, 2023

## Assurance of aseptic preparation of medicines

Publication (/publication)

**Content**


- 1. Purpose
- 2. Introduction
- 3. Definitions
- 4. Scope of guidance
- 5. Restrictions for aseptic preparation
- 6. Roles and responsibilities
- 7. Revised assessment process
- 8. Assurance and performance management
- 9. Compliance management and escalation
- 10. Improvement process
- 11. Reporting
- 12. Glossary
- Appendix 1: iQAAPS
- Appendix 2: Explanatory notes regarding definitions
- Appendix 3: Roles and responsibilities
- Appendix 4: iQAAPS quality indicators
- Appendix 5: EL(97)52 Review Working Group


**NHS Infusions and Special Medicines Programme: Guidance to replace EL(97)52 in England**

Aseptic preparation is defined as: reconstitution of an injectable medicine or any other aseptic manipulation when undertaken within NHS aseptic facilities to produce a labelled ready-to-administer presentation of a medicine, in accordance with a prescription provided by a practitioner, for a specific patient.

Aseptic reconstitution of any medicinal products or IMPs, where this is performed in a pharmacy aseptic facility.

Aseptic reconstitution of innovative therapies such as ATMPs where this is performed in any NHS aseptic facility with pharmacy oversight

Specialist Pharmacy Service
www.sps.nhs.uk


GOV.UK

Menu

Home › Health and social care › Medicines, medical devices › Clinical trials and investigations › Commercial clinical trials in the UK: the Lord O'Shaughnessy review

Department for Science, Innovation & Technology

Department of Health & Social Care

Office for Life Sciences

Independent report

Commercial clinical trials in the UK: the Lord O'Shaughnessy review - final report

Updated 26 May 2023

Contents

Foreword

Executive summary

Part 1: context, operating environment and existing commitments

Part 2: problem statements and significant actions

Part 3: transforming how the UK does clinical trials

Foreword

The UK is blessed with a rich, diverse and creative academic sector with 4 of the world's 10 leading universities in the field of international research. Matched with an entrepreneurial culture that is second only to the United States, this makes our science sector the envy of the world. But in the fields of medicine and life sciences, inventions and discoveries alone do not change lives. For a therapy, device, diagnostic or digital tool to reach patients, a long, often laborious process of translating insights into products and then testing their safety and efficacy through clinical trials is required.

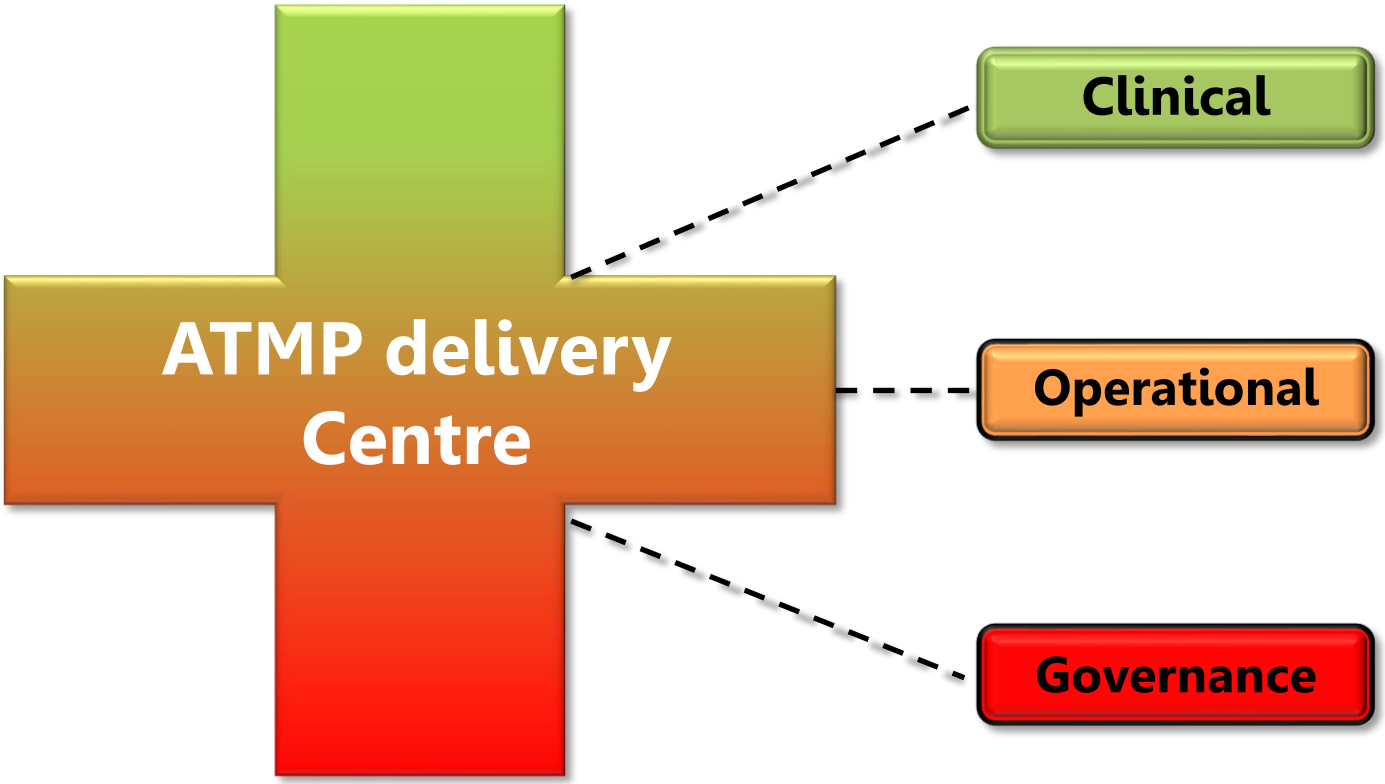
**Problem statement 4:**
**research is not systematically prioritised by or within the NHS**

Stakeholders to this review have cited a shortfall of research nurses, pharmacy and imaging resources, and aseptic teams as constraints to delivery of clinical trials

We also need to make sure that the infrastructure is in place to conduct research;

**Recommendation 12: income generated by commercial sponsors should be explicitly directed to units and departments leading trials in NHS sites to provide direct financial incentives to take part in commercial trials**

Hospital consultants who take part in research studies are more likely to promote the uptake of innovative therapies or devices once they have been licensed, improving access for all patients.


ATMP delivery Centre
Clinical
Operational
Governance

# Local Governance


**Feasibility**

- Facility for preparation / capacity
- Technical Assessment

# Organisational Governance

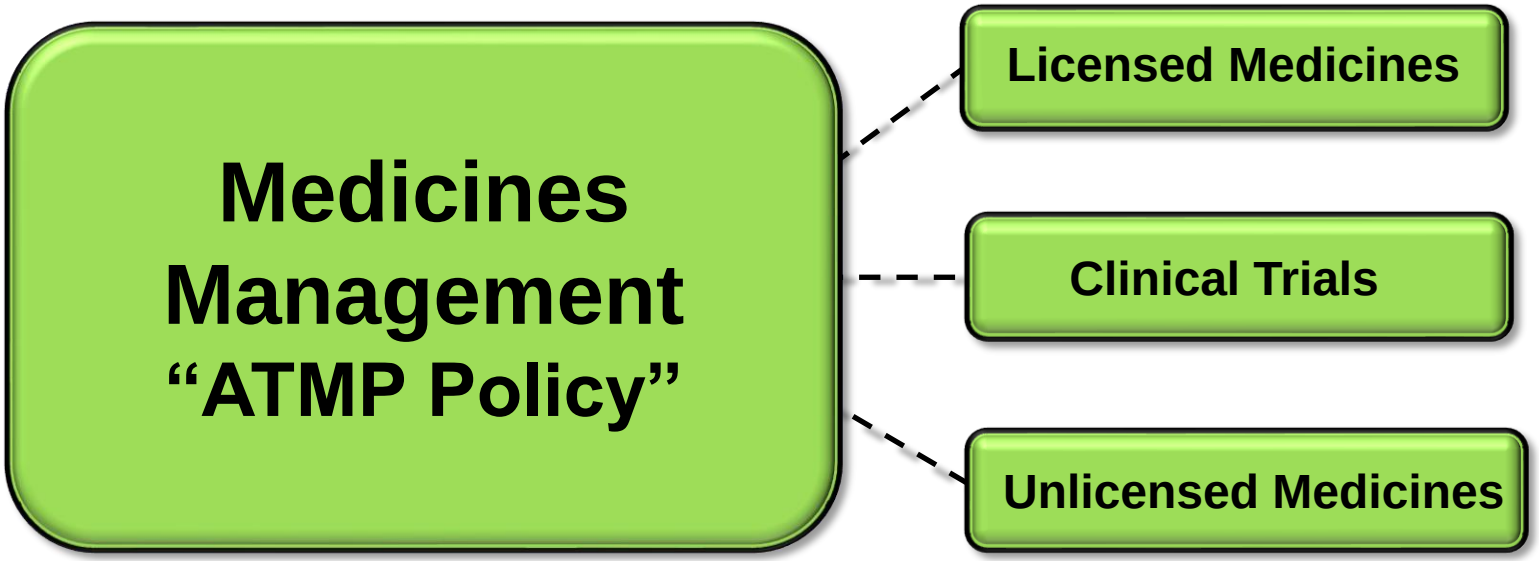
Specialist Pharmacy Service
www.sps.nhs.uk

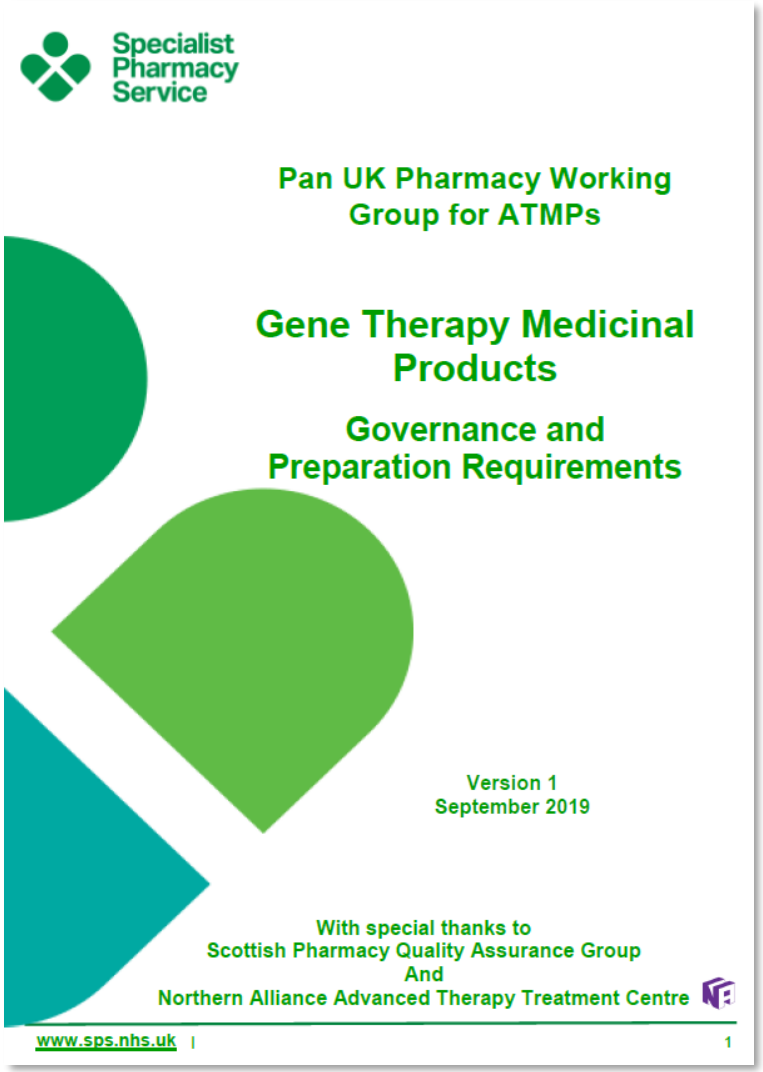
- Additional to local R & D processes for ATIMP trials

- Why?
  - Innovative medicines
  - Innovative administration techniques
  - Committees e.g.  ATMP
  - Regulatory Change e.g. GMSC (HSE)
  - Media Interest

How?

ATMP Policy



Medicines Management
"ATMP Policy"
Licensed Medicines
Clinical Trials
Unlicensed Medicines




- Gene Therapies require additional scrutiny.
- Establish Classification of the gene therapy and any containment required.

How to set up a GMSC

# Risk assessment - GMSC

- Review safety of products and risk to health
- Ensure all parts of pathway including receipt, preparation and infusion are risk assessed and control measures in place.
- Mandatory requirements apply only to clinical trials
- Technically only required for any GTMP that is also a GMO
- **But the Pan UK PWG for ATMPs recommend all products have full safety overview**
- Notification to HSE where applicable

Specialist Pharmacy Service

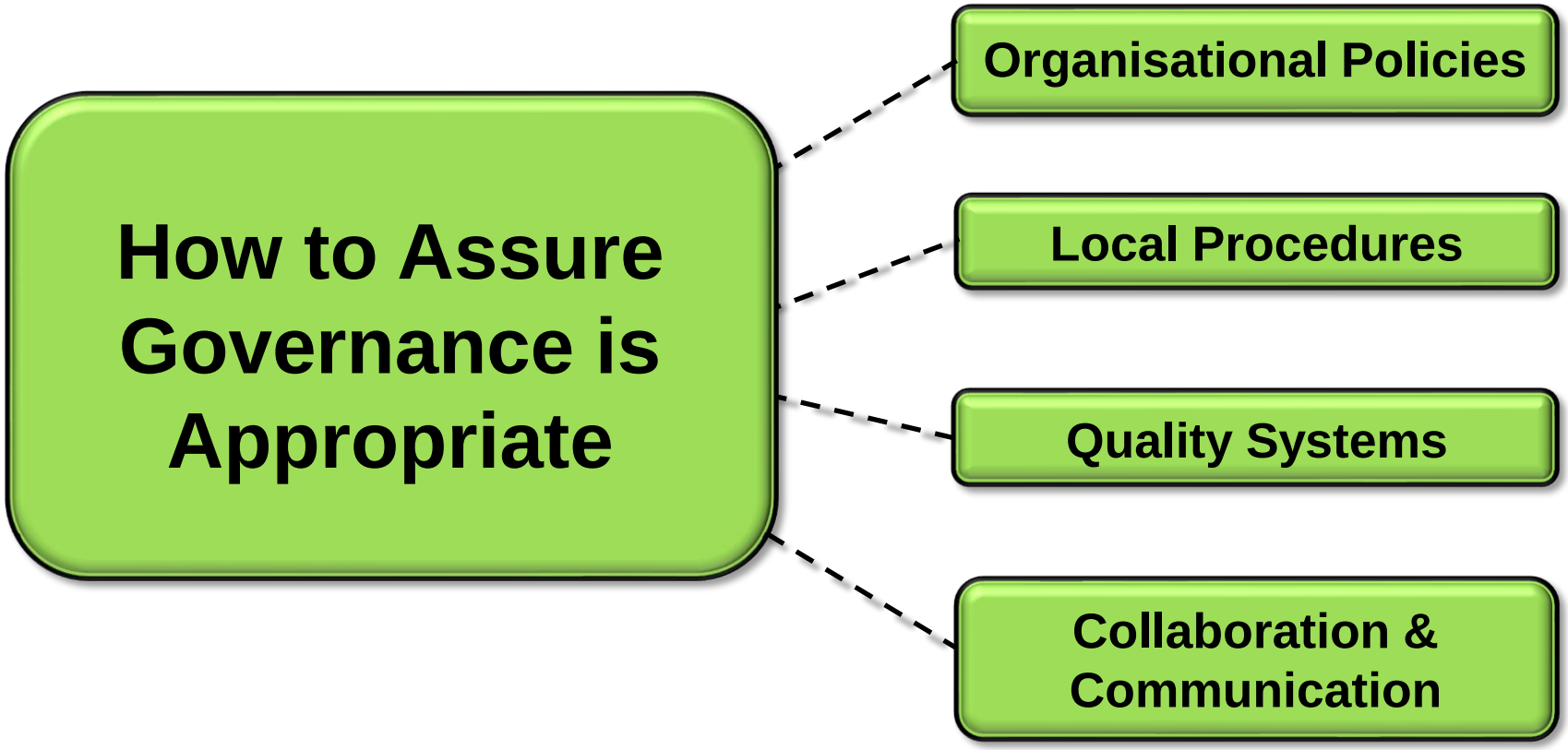
Appendix 2

# Example of a GMSC Risk Assessment

## RISK ASSESSMENT FOR HANDLING OF GENETICALLY MODIFIED MICRO-ORGANISMS FOR GENETIC MODIFICATION SAFETY COMMITTEE (GMSC)

### SECTION 1
### Basic Information

| | |
|---|---|
| **Project Title** | |
| **Trial Organisers/Sponsor** | |
| **Principle Investigator (PI)** | |
| **PI Address** | |
| **PI Telephone** | |

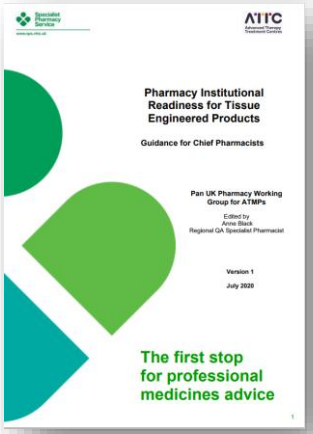

How to Assure Governance is Appropriate
Organisational Policies
Local Procedures
Quality Systems
Collaboration & Communication

# Site Selection → Site Initiation

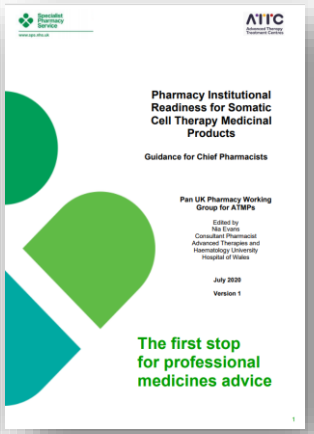
Specialist Pharmacy Service
www.sps.nhs.uk

## Pharmacy Institutional Readiness Guidance

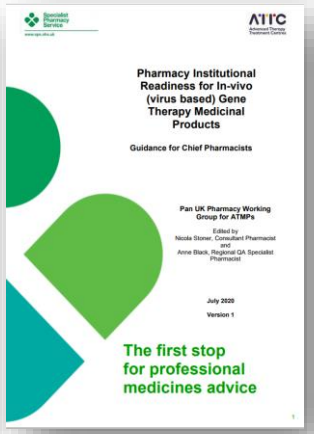
**Tissue Engineered**



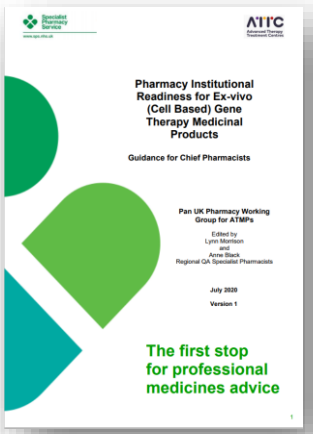

**Somatic Cell Therapy**




**Virus Based (in vivo)**




**Cell Based (ex vivo)**




https://www.sps.nhs.uk/networks/pan-uk-pharmacy-working-group-for-atmps/

# Operational Implementation

- Map processes from placing order through to administration and monitoring of ATMPS
- Key principles for each stage to facilitate consistency of implementation

Specialist Pharmacy Service

www.sps.nhs.uk

# Pharmacy Institutional Readiness for In vivo Gene Therapy

**Product Receipt**

- In-vivo (virus based) GTMPs are suitable for handling in Pharmacy. See Gene Therapy and Preparation for more information. On occasion they may require handling of dry ice and Pharmacy receiving areas require competency to undertake this activity.
- An SOP for receipt of GTMPs covering those holding marketing authorisation as well as investigational medicinal products (IMPs) is required. Checks on receipt should include integrity of the product, labelling, temperature compliance during transit, and Certificate of Analysis / QP certificates detailing the dose, if applicable. These should be reviewed by an appropriately trained clinical pharmacist or Clinical Trials pharmacist. Handling precautions should also be considered, including spillage kit when required.

**An exemplar Product Receipt checklist is available in Appendix 5**

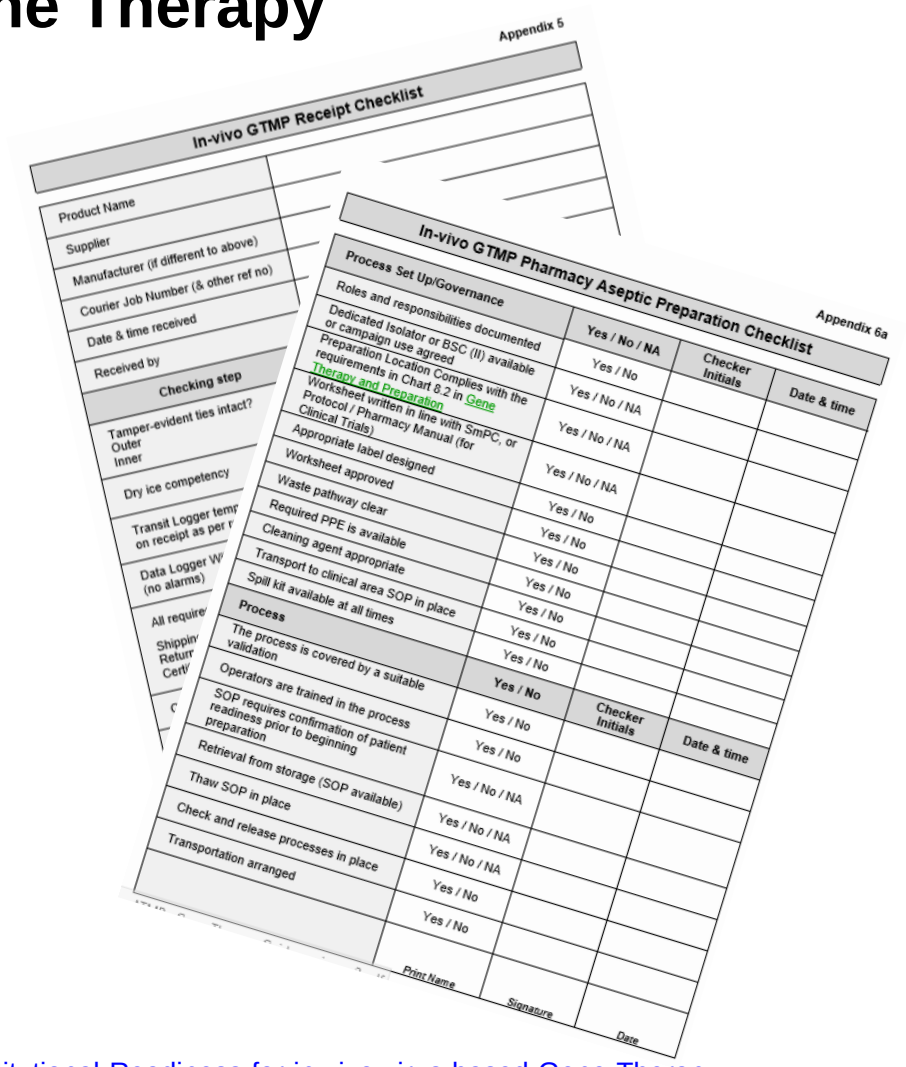
**Storage**

- Storage requirement is likely to be in -20°C to -90°C for GTMPs. Room temperature stability is often short.
- Continuous temperature monitoring and alarms are required from receipt through to administration. Actions in the event of an alarm should be specified (and in line with anything detailed in the supply agreement with the company/sponsor).
- Deviation processes should be clarified e.g. if short period temperature out-of-specification occurs, the SOP should state that risk assessment and actions to be taken are documented. Pharmacy should be made aware of any on-site storage deviations.

**The exemplar Product Receipt checklist is available in Appendix 5 which covers aspects of storage**

**Preparation Location Decision**

- Some in-vivo GTMPs will require a thaw/preparation/reconstitution step. Optimal location for in-vivo gene therapy will be as per SmPC or clinical trial protocol. Where the location is not specified guidance can be found in Gene Therapy and Preparation. Preparation location should have been defined in the GMSC risk assessment. Where stability data allows aseptic preparation should occur within a pharmacy aseptic unit.



Appendix 5

**In-vivo GTMP Receipt Checklist**

| | |
|---|---|
| Product Name | |
| Supplier | |
| Manufacturer (if different to above) | |
| Courier Job Number (& other ref no) | |
| Date & time received | |
| Received by | |
| **Checking step** | |
| Tamper-evident ties intact? Outer | |
| Inner | |
| Dry ice competency | |
| Transit Logger temp on receipt as per r | |
| Data Logger W (no alarms) | |
| All require | |
| Shippin Return Cert | |
| C | |

Appendix 6a

**In-vivo GTMP Pharmacy Aseptic Preparation Checklist**

| Process Set Up/Governance | Yes / No / NA | Checker Initials | Date & time |
|---|---|---|---|
| Roles and responsibilities documented | Yes / No | | |
| Dedicated Isolator or BSC (II) available or campaign use agreed | Yes / No / NA | | |
| Preparation Location Complies with the requirements in Chart 8.2 in Gene Therapy and Preparation | Yes / No / NA | | |
| Worksheet written in line with SmPC, or Protocol / Pharmacy Manual (for Clinical Trials) | Yes / No / NA | | |
| Appropriate label designed | Yes / No | | |
| Worksheet approved | Yes / No | | |
| Waste pathway clear | Yes / No | | |
| Required PPE is available | Yes / No | | |
| Cleaning agent appropriate | Yes / No | | |
| Transport to clinical area SOP in place | Yes / No | | |
| Spill kit available at all times | Yes / No | | |
| **Process** | **Yes / No** | **Checker Initials** | **Date & time** |
| The process is covered by a suitable validation | Yes / No | | |
| Operators are trained in the process | Yes / No | | |
| SOP requires confirmation of patient readiness prior to beginning preparation | Yes / No / NA | | |
| Retrieval from storage (SOP available) | Yes / No / NA | | |
| Thaw SOP in place | Yes / No / NA | | |
| Check and release processes in place | Yes / No | | |
| Transportation arranged | Yes / No | | |
| | Print Name | Signature | Date |

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

# ATIMP Considerations at FEASIBILITY

Specialist Pharmacy Service
www.sps.nhs.uk

- Storage
  - Ambient
  - Fridge
  - Freezer
  - Ultralow
  - Cryostorage
  - Transportation

- **Preparation / Reconstitution Step**

Needed?

**NO**

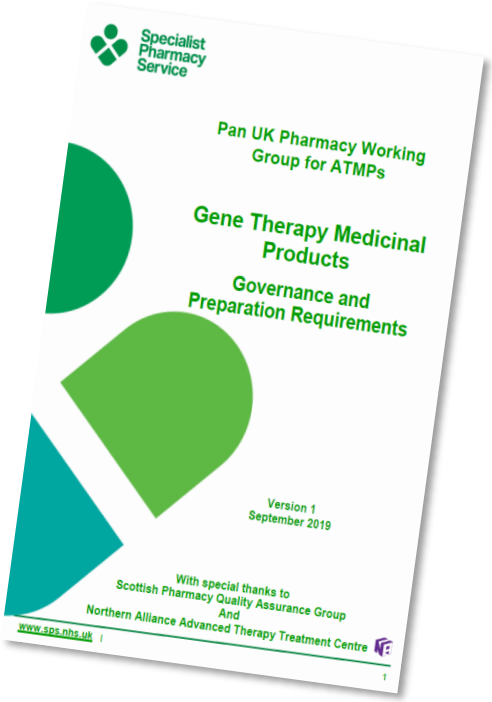
Stability of IMP

**YES**

In-use stability post preparation
Optimal preparation location
Suitable facilities
Suitable Capacity
Post Recon labelling – annex 13

compliant

Pharmacist supervision



# SOPs and training

- SOPs for all tasks and only to be carried out by trained staff:
  - Receipt, handling, storage
  - Preparation
  - Transport
  - Administration
  - Waste management / shedding / spills
  - Containment / potential exposure to patients,
  - Clinical Toxicity Management
  - Supportive medicines
  - Washout periods

# Site Initiation

- Distribution arrangements
  - Import:  QP oversight
- Receipt
  - Documentation e.g. QP certificate
  - Cold chain deviations
  - Storage
  - Preparation
    - Components
    - UKCA/ CE marked
  - Administration


**TOP TIP:** undertake a dry run of the whole process

Specialist Pharmacy Service

Pan UK Pharmacy Working Group for ATMPs

# Gene Therapy Medicinal Products

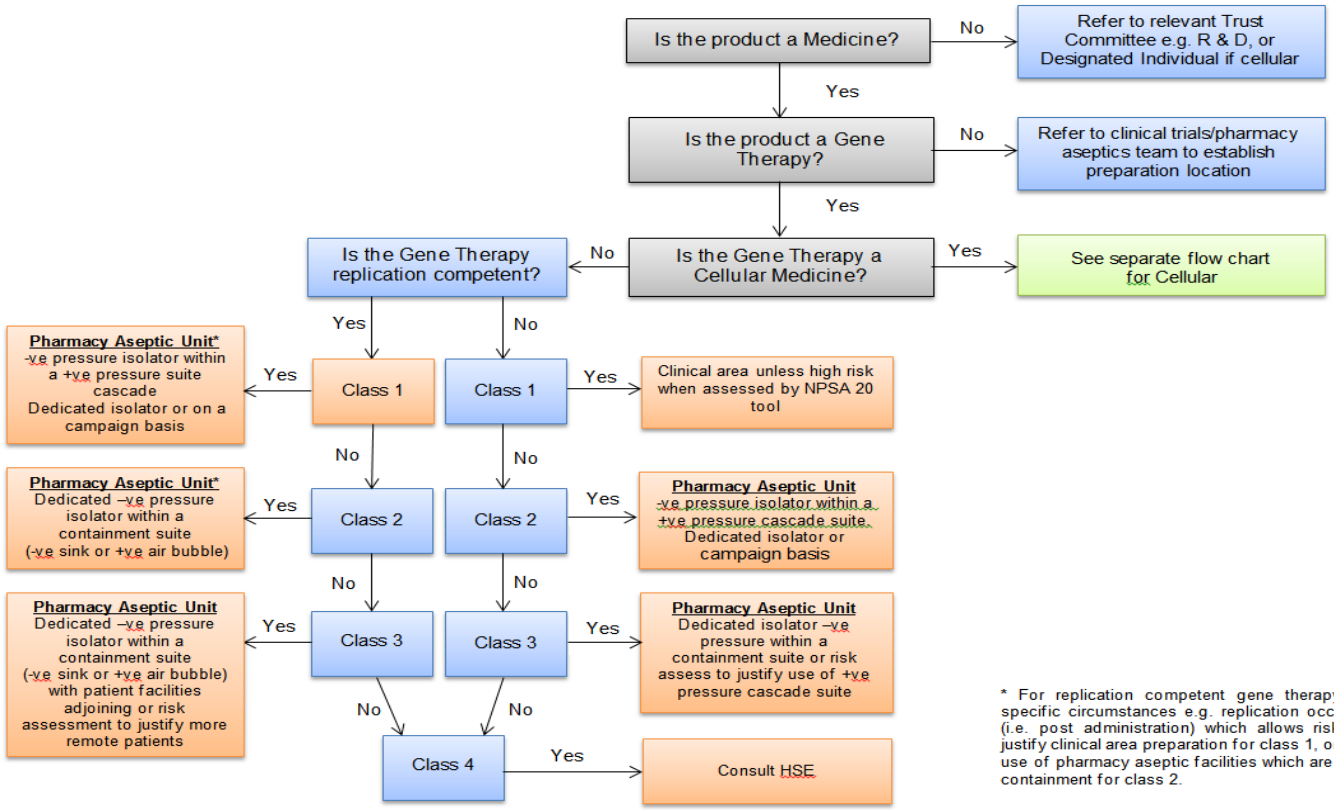
## Governance and Preparation Requirements

Version 1
September 2019

With special thanks to
Scottish Pharmacy Quality Assurance Group
And
Northern Alliance Advanced Therapy Treatment Centre

# In-Vivo Gene Therapy Preparation Location Guidance

Specialist Pharmacy Service
www.sps.nhs.uk

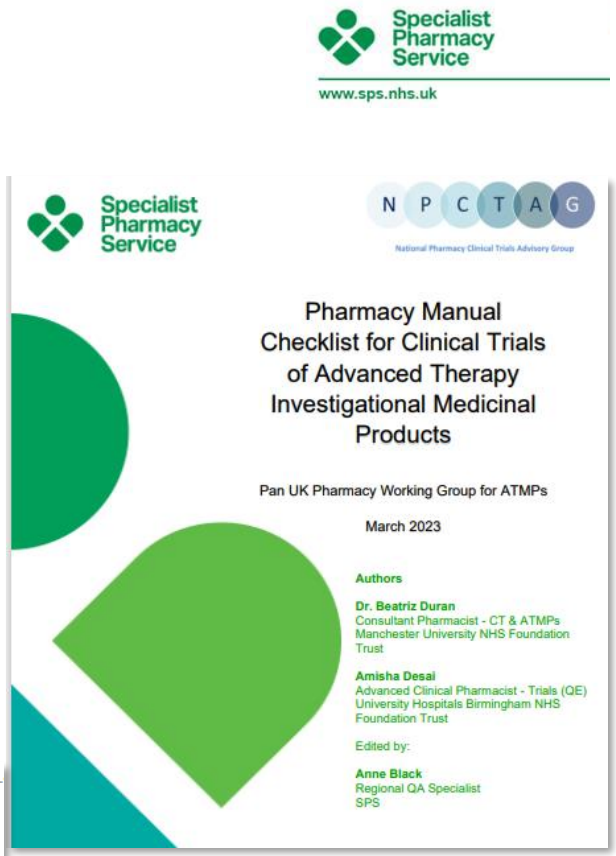


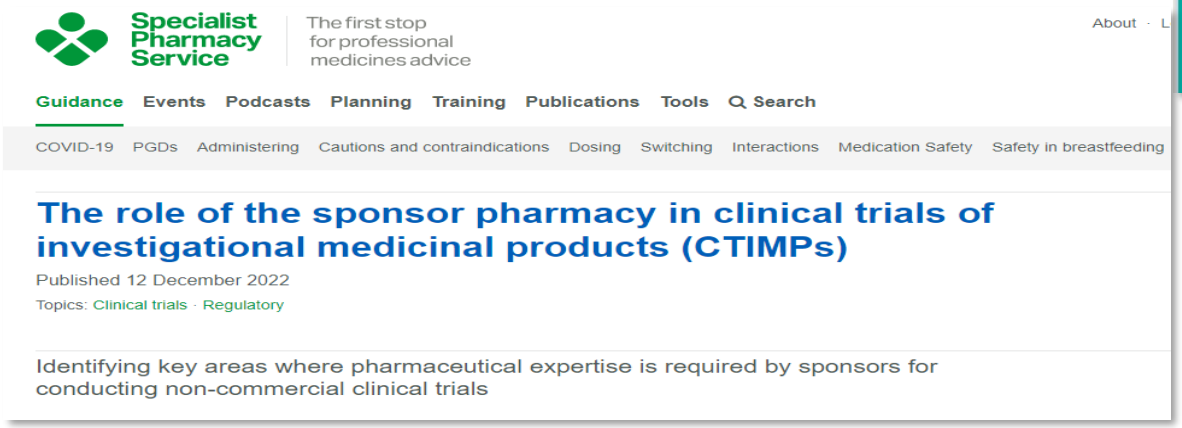

* For replication competent gene therapy there may be specific circumstances e.g. replication occurs in VIVO only (i.e. post administration) which allows risk assessment to justify clinical area preparation for class 1, or campaign basis use of pharmacy aseptic facilities which are not designed for containment for class 2.

**TOP TIP:** Specify required environment rather than device

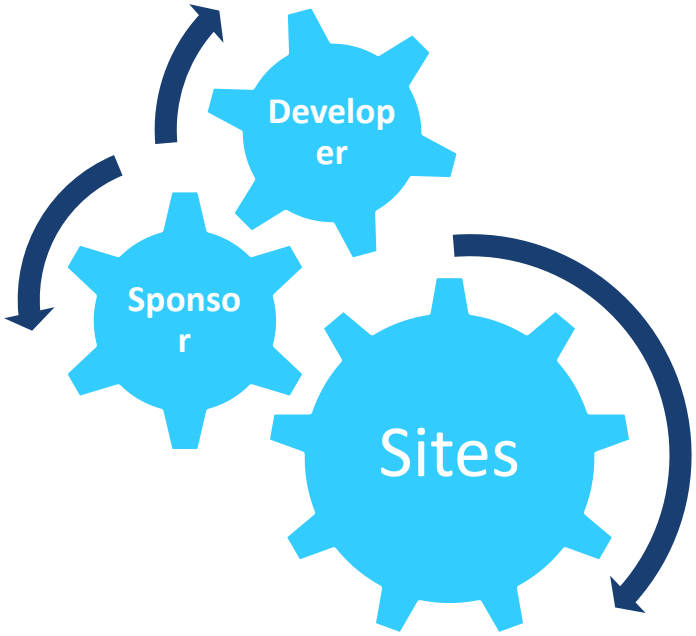
# Top Tips for Sponsors

- Understand site requirements
- Pre-empt questions
- Design a deliverable process
- Understand the role of the
- Sponsor Pharmacy



# Pharmacy Learning and Resources Support at all levels




Pan UK PWG resources support each sector to optimise implementation

Advanced therapy medicinal products – SPS - Specialist Pharmacy Service – The first stop for professional medicines advice

ATTC Network Clinical Trials Section on NHS Readiness Toolkit

https://www.theattcnetwork.co.uk/clinical-trials/

Saving lives,
Improving lives

NHS
Diagnostics and
Pharmacy Group
Northern Care Alliance
NHS Foundation Trust

# Experience from an Aseptic Unit

Saving lives, Improving lives

NHS
Diagnostics and Pharmacy Group
Northern Care Alliance NHS Foundation Trust

# Background

- Salford Royal Hospital
- Dedicated Gene Therapy in aseptic unit since 2011
- As a trust we have been working on gene therapy (in-vivo ATMP) implementation since 2021
- All ATMP are currently trials – metabolic medicine
- Several trails pulled during set up
- Patient screening/eligibility
- Due to dose first patient 11th October 2023

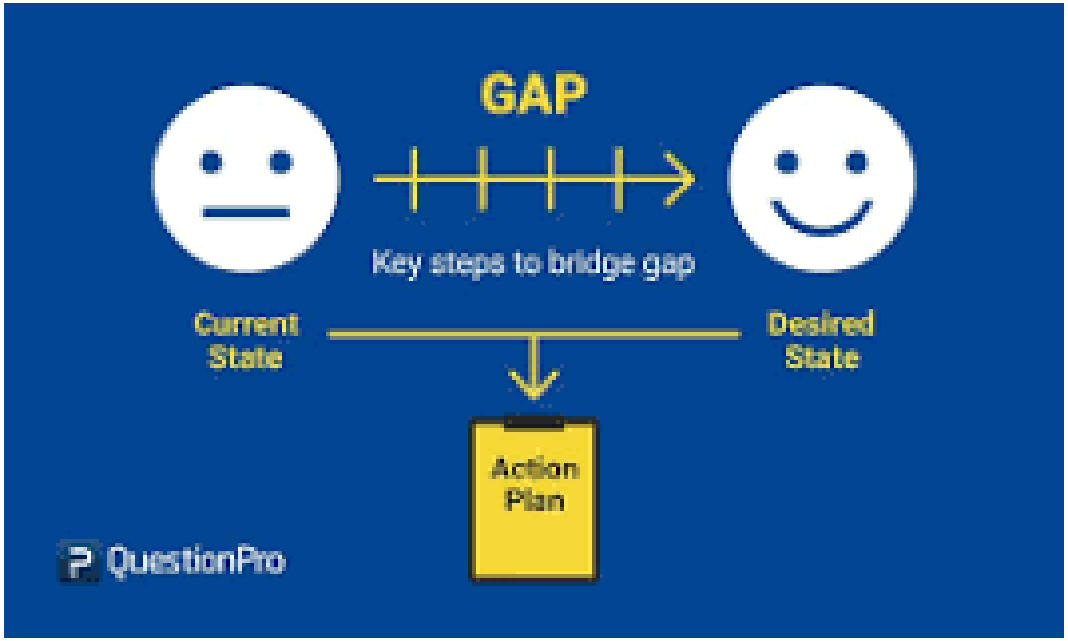
Saving lives, Improving lives

NHS
Diagnostics and Pharmacy Group
Northern Care Alliance NHS Foundation Trust

# Governance arrangements

- Driven by pharmacy
- Importance of GMSC and appropriate membership (joint ATMPC and GMSC)
- In vivo vs ex-vivo
- Robust risk assessment process

# GAP ANALYSIS



Saving lives, Improving lives

NHS
Diagnostics and Pharmacy Group
Northern Care Alliance NHS Foundation Trust

# Aseptic Processing

- Pharmacy Manual with all relevant information
- Optimal presentation of IMP
  - Size
  - Number of manipulations
  - Disinfection time
  - Preparation time
- **Consider**
  - Validation of processes
  - Gowning
  - Monitoring

Saving lives, Improving lives

# Facilities

Do you need a dedicated gene therapy suite?

## Risks

- Complex production methods
- Containment level required
- Is vector replication competent?

Saving lives, Improving lives

NHS Diagnostics and Pharmacy Group
Northern Care Alliance NHS Foundation Trust

# Storage and waste handling

*Our concerns:*

- Storage -20ºC to -90ºC for GTMPs within aseptics
- Prevention of cross contamination


- *Solutions:*
  - ATMPs are not stored in aseptics
  - Vials kept in Pharmacy Clinical Trials
  - Products collected/delivered immediately
  - Waste collected immediately
    - Trained porters to collect
    - GMO waste transfer logs

***Dummy run to test all procedures and processes***

# Spillage / Needlestick

- Procedures can't cover the intricacies of every individual product.
- The place of the GMSC Risk Assessment is to determine if any additional precautions required.
- Spill kits
  - Specific to Trial/product
  - Transported with the product
- Training for all staff

Saving lives, Improving lives

NHS
Diagnostics and Pharmacy Group
Northern Care Alliance NHS Foundation Trust

# Aseptic Capacity

- Complex treatments to prepare, store, distribute

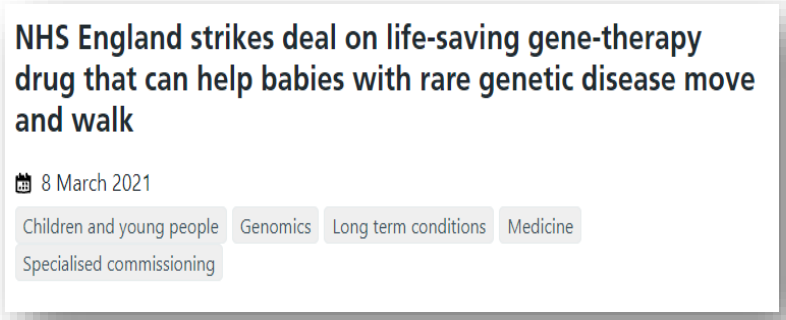
*However,*

- Most are one off treatments
- If effective may prevent need for longer term treatment – potentially releasing aseptic capacity
- Small patient cohorts
- Eligibility and screening

# Don’t get bogged down with planning what you should/would do for Class 3 and 4 ……. it’s unlikely to happen

# Don’t forget why!

# In vivo Gene Therapy: Adeno Associated Virus


Spinal Muscular Atrophy

- Rare Genetic Progressive Neuromuscular Disorder
- SMN1 gene is missing or not working
- Onasemnogene abeparvovec replaces the function with a working copy of a human SMN
- Life changing
- Needs early treatment

'Gene therapy is a game changer for our son' - BBC News

# Conclusion

Specialist Pharmacy Service
www.sps.nhs.uk

- GTMPs are game changing for patients
- GTIMP trials are challenging
- GTMP delivery can be disruptive
- Planning and collaboration are key to consistent quality implementation for patient safety and robust data.
- Getting it Right First Time requires Organisational Governance and System Leadership

For more information about the Pan UK PWG for atmps contact anne.black7@nhs.net