Clinical Trials Involving Advanced Therapies:

What do I need to know?

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Objectives

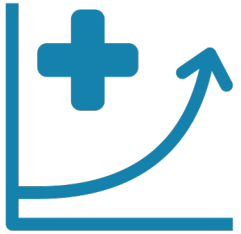
- What are Advanced Therapies and the different types?
- Why is a Gene Modification Safety Committee required?
- ATGMSC Remit
  - Committee Membership
- ATGMSC Specific Documents
  - Clinical Trial Set up and approval
  - Amendments
- Risk Assessment Considerations and Responsibilities
- Lessons Learned
- Main contacts
- Further Information

What are Advanced Therapies and what are the different types?

Advanced therapy medicinal products (ATMPs)

Biological medicines based on genes, cells or tissues.

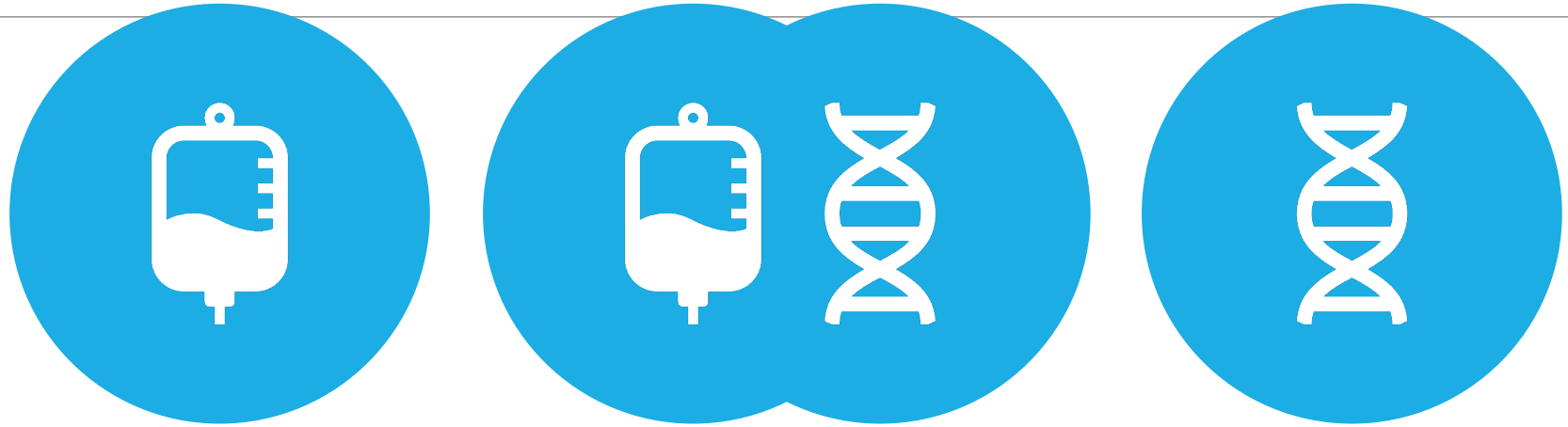
Potential benefits for a wide range of clinical indications.



Rapidly expanding number of products.

Complex products with diverse requirements. Challenges to clinical delivery.

What about “cell and gene therapy”?



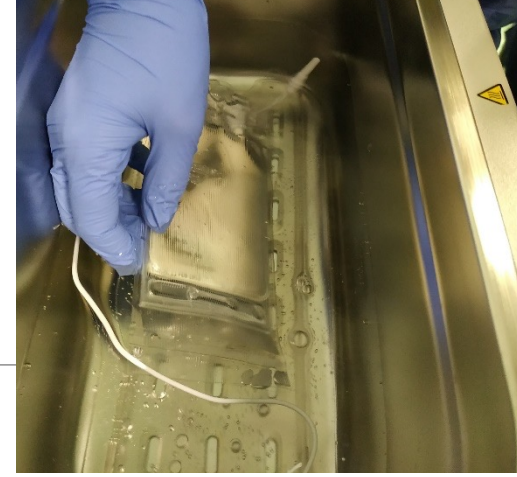
CELL THERAPY is a general term for a therapeutic approach that uses human cells as a “living therapy”

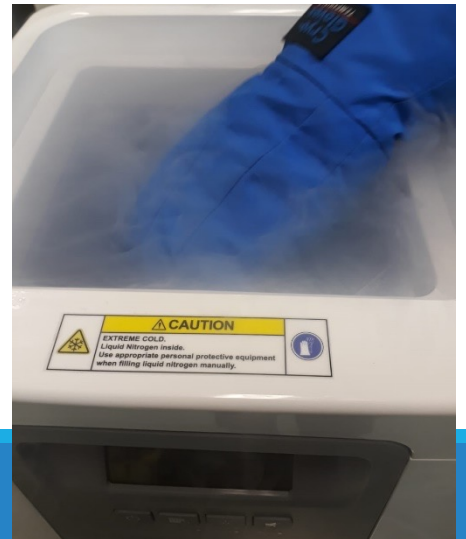
GENE THERAPY treats or prevents disease using recombinant nucleic acids that can either be introduced directly into the patient’s body, **IN-VIVO…**

…or into cells that are outside of the patient’s body (also called gene-modified cell therapy or **EX VIVO** gene therapy)

New and challenging medicines to deliver

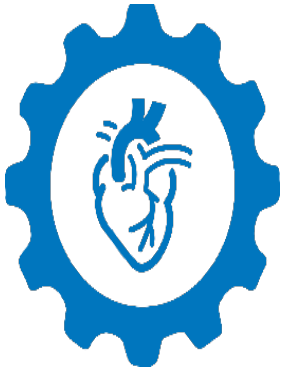
- **Close coordination** across teams/external organisations.
- **Carefully controlled shipments** with clear chain of custody.
- Severe **side effects** for some products.





Types of advanced therapy medicinal product

A somatic cell therapy medicinal product



A tissue engineered product

A gene therapy medicinal product

Somatic cell therapy medicinal products

A somatic cell therapy medicinal product (sCTMP) is a biological **medicine** with cells that are used to treat, prevent or diagnose a disease through the pharmacological, immunological or metabolic action of the cells.

Have been subject to **substantial manipulation** to change their biological characteristics, physiological functions or structural properties,

and/or

That are not intended to be used for the same **essential function(s)** in the body.

Tissue engineered products

A tissue engineered product (TEP) is a biological **medicine** which contains engineered tissues that are used to regenerate, repair or replace human tissue.

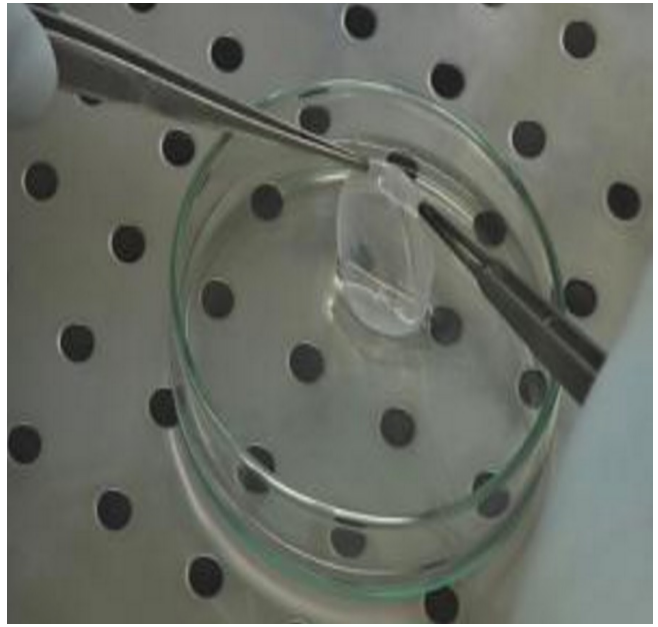
“Engineered” cells or tissues:

have been subjected to **substantial manipulation**

and/or

are not intended for the same **essential function(s)** in the body

It may also contain additional substances, such as scaffolds or matrices.



Gene therapy medicinal products

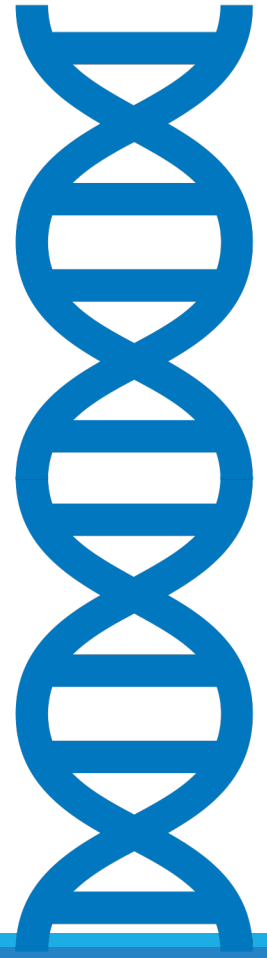
A gene therapy medicinal product (GTMP) is a biological **medicine** containing an active substance which:

- contains or consists of **recombinant nucleic acid(s)**

AND

- is administered to patients to regulate, repair, replace, add or delete a genetic sequence.

Its mechanism of action must be directly related to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.



Genetically modified organisms (GMOs)

A gene therapy medicinal product will usually contain or consist of a genetically modified organism (GMO):

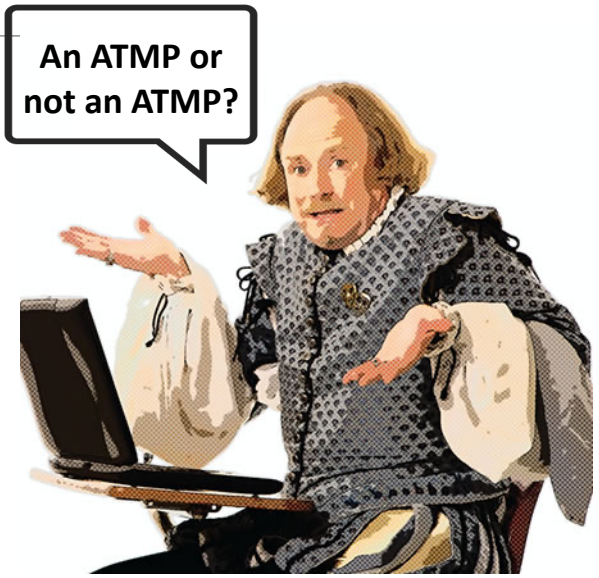
> an organism in which the **genetic material has been altered** in a way that does not occur naturally.
>
> *Human beings are exempt from this definition*

GMOs are defined in Directive 2001/83/EC, Article 2

When is a “gene therapy” not an ATMP?

- Nucleic acid vaccine products for infectious disease
  - Where the mechanism of action is intended **to treat or prevent an infectious disease** these technologies are not classified as an ATMP.
  - E.g. Pfizer-BioNTech and Moderna vaccines for COVID-19

- **Synthetic** oligonucleotide-based products
  - Not formally classified as ATMPs as they are chemically synthesised
  - E.g. Spinraza® for spinal muscular atrophy

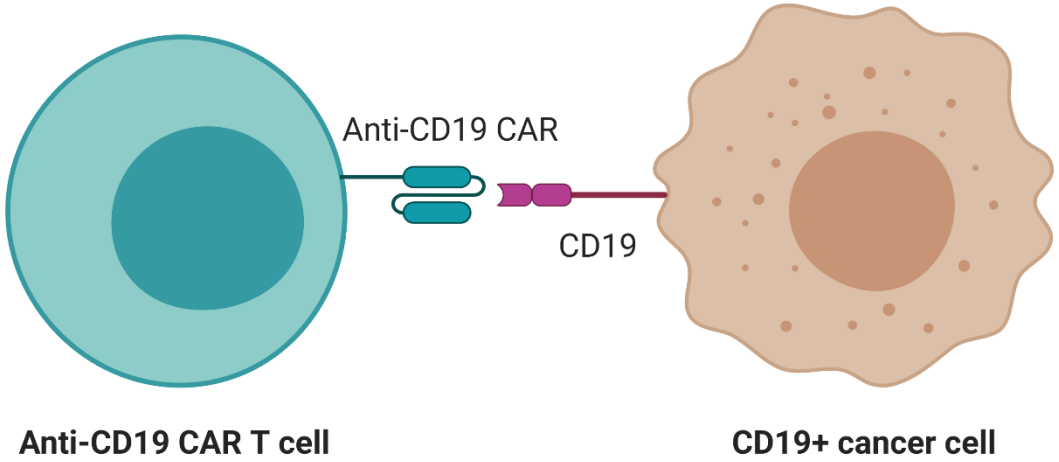


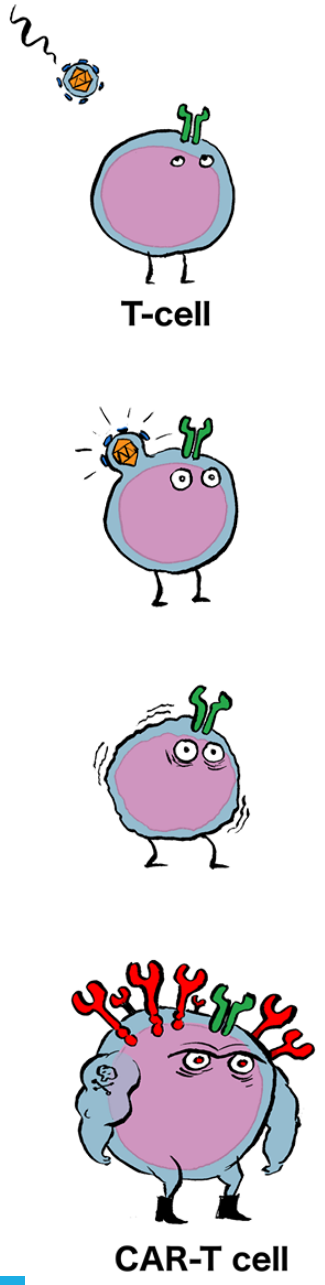
CAR T cell therapy

CAR T cell therapies have proven very effective in treating certain types of blood cancer, even in patients for whom standard lines of therapy have not been effective.

T cells can be genetically engineered in the lab to express an artificial receptor on their cell surface: a **chimeric antigen receptor (CAR).**

The CAR enables the CAR T cell to target cancer cells that express a specific surface marker (or antigen`



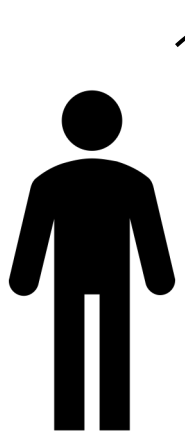


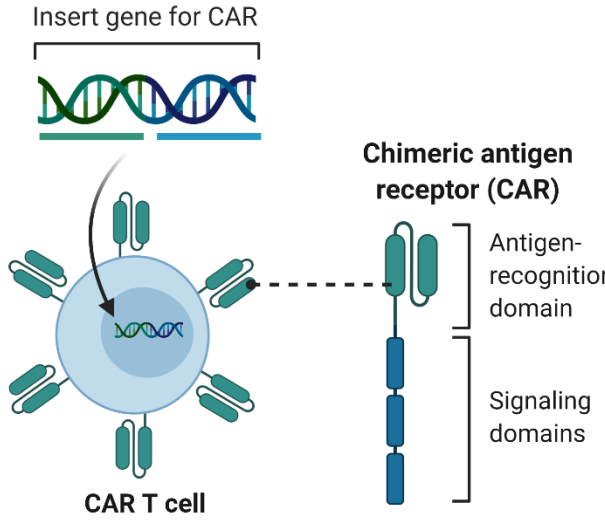
CAR T production

Clinical site | **Manufacturing lab**

1 T cells are collected from the patient's blood by apheresis.

2 A chimeric antigen receptor (CAR) gene is delivered into the patient's T cells ex vivo using a viral vector.

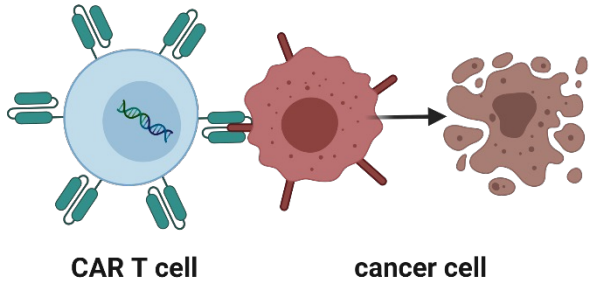




The CAR is specific for an antigen (marker) on the patient's cancer cells.

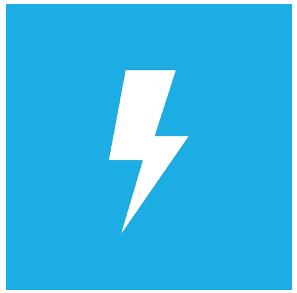
3 The CAR T cells are expanded (grown in the laboratory) to produce millions more cells, all expressing an identical CAR on their surface.

4 The CAR T cells are infused back into the patient's bloodstream, then can bind to and kill cancer cells.



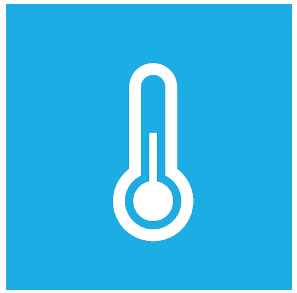
CAR T cells side effects and toxicities

Side effects and toxicities associated with CAR T treatment can in some cases be **life-threatening.**



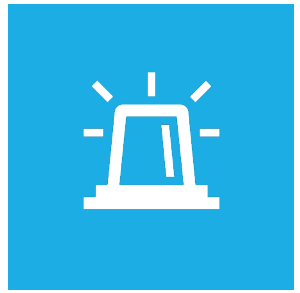
Cytokine release syndrome (CRS)

Neurotoxicity



Tumour lysis syndrome

On-target, off-tumour toxicity



Allergic reactions and anaphylaxis

Why is a Gene Modification Safety Committee required?

Why is a Gene Modification Safety Committee required?

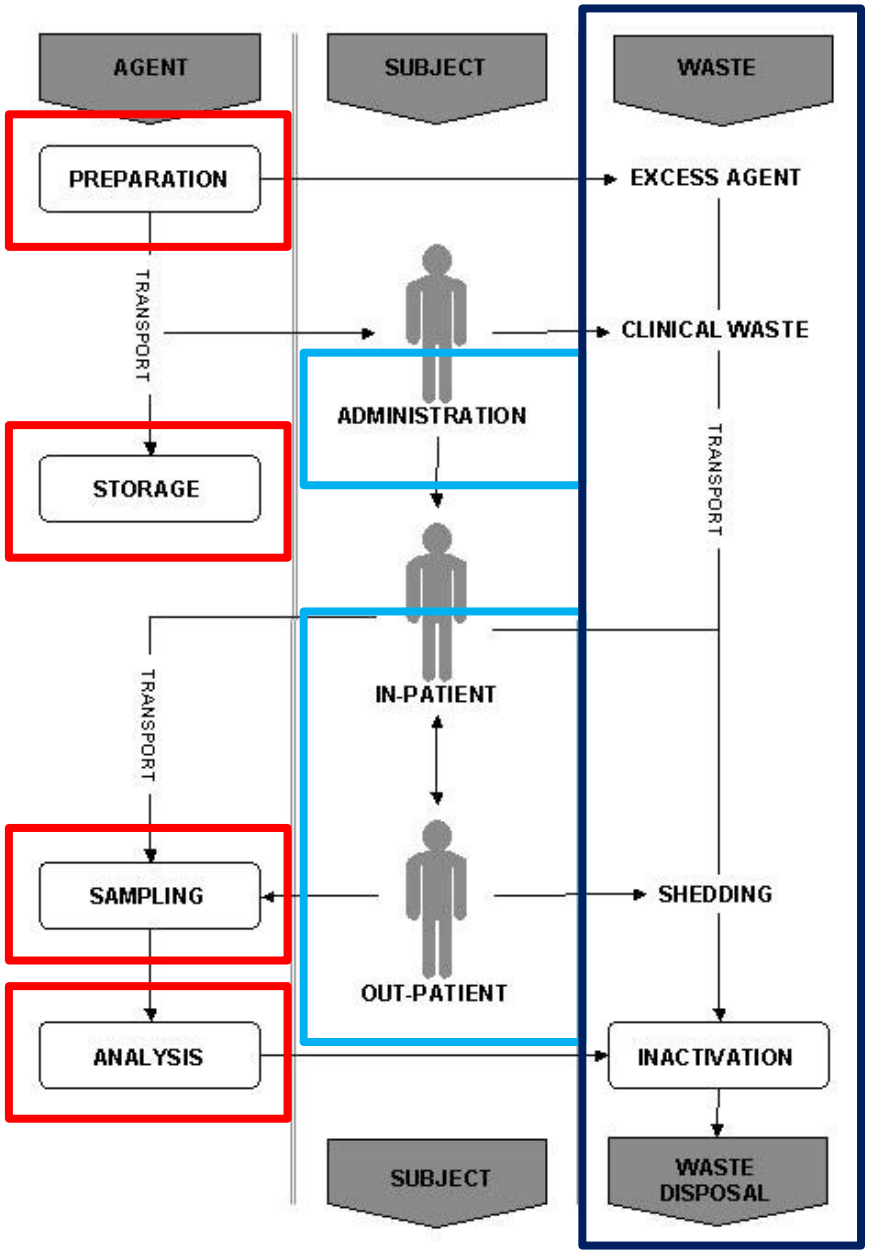
The primary piece of legislation that applies to the use of genetically modified organisms (GMOs) in the workplace is the **Genetically Modified Organisms (Contained Use) Regulations 2014**

The GMO Regulations requires anyone intending to use GMOs ensure **risks to human health or the environment are minimised** through the application of appropriate control measures.

The GMO Regulations require:

- Risk Assessment for both human and the environment
- Assignment of containment and control measures and classification of the activity (four classes)
- Establishment of a gene modification safety committee (GMSC) to review any risk assessment carried out
- Notification of first use of premises
- Notification of certain individual activities (class 2 and above)

Diagrammatic summary of the ‘three pathways’ approach to the identification of areas for consideration in GM risk assessments relevant to a clinical setting



Class	Risk level
Class 1†	Negligible risk
Class 2*†	Low risk
Class 3*	Moderate risk
Class 4*	High risk

* Class 2 -4 need to be notified separately to the HSE

† Most clinical trials will involve Class 1 or 2

Taken from The SACGM Compendium of guidance. Part 6

ATGMSC Remit

- Convened to provide expert review of clinical trials of AT(I)MPs or gene therapy products (GM, GMO).
- Broad membership and select members convened depending on the type of product/trial being reviewed

- **AT(I)MPs**
  - Trials are reviewed by ACCORD
  - Committee can provide additional expertise if required
  - Review and assess safety/storage/transport/prep/disposal

- **GM(O):**
  - Serves as a committee for NHS Lothian and is registered with HSE
  - Review projects for NHS Lothian in addition to review undertaken by ACCORD
  - GMSC review will take into consideration the local infrastructure and capacity to support the research, and assess the risks to the Board, staff and patients.

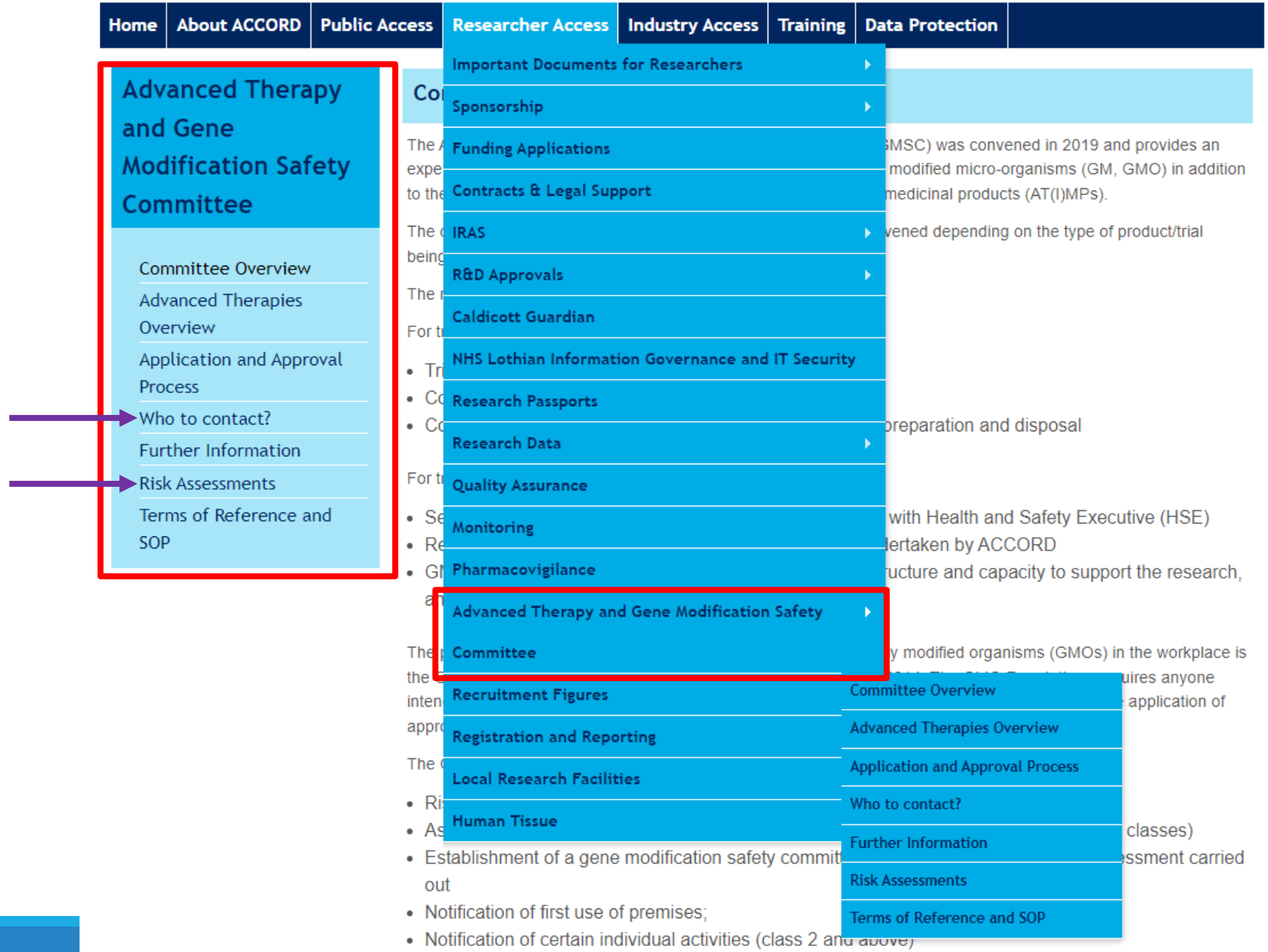
Both AT(I)MPs and GM(O) trials require a Risk Assessment completion and approval before NHS Lothian R&D Management approval can be given

Committee Members

Core Membership (AT(I)MP review)	GM(O) review (in addition to core)
Clinician (Chair)	R&D
Pharmacy	Infection Control
Clinical Research Facility/Operational	Biological Safety Officer
Senior Nurse	University Biological Safety Advisor
Quality Assurance	Gene Therapy Scientific Advisor
Secretary	Virologist
R&D representative	Health and Safety
ATMP Clinician	Waste/Facilities management
	Occupational Health
	ICU Representative

Committee Role	Name	Position
Clinician (Chair)	**Dr Huw Roddie**	Consultant Haematologist, NHS Lothian/ SNBTS Stem Cell Processing
ATMP Clinician	**Dr Victoria Campbell**	Consultant Haematologist, NHS Lothian
Pharmacy	**Ruaridh Buchan** **Ben Elliott**	Advanced Pharmacists Clinical Trials, NHS Lothian
Nurse	**Rachael MacAngus** **Lois Eddie**	Research Nurses, Haematology, NHS Lothian
Health and Safety	**Ian Wilson**	Head of Health and Safety, NHS Lothian
Waste/Facilities Management	**Danny Gillan**	Head of Soft Facilities Management, Waste Management Officer, NHS Lothian
Occupational Health	**Dr Alastair Leckie**	Head of Occupational Health, NHS Lothian
R&D	**Fiona McArdle** **Dr Heather Charles**	Deputy Director, NHS Lothian R&D Head of Research Governance, NHS Lothian
Clinical Research Facility	**Dr Steve McSwiggan**	Deputy Director, Edinburgh Clinical Research Facility
Quality Assurance	**James Gibson**	QA Lead Edinburgh, Edinburgh Clinical Research Facility
Infection Control	**Lindsay Guthrie**	Lead Infection and Prevention Control Nurse, NHS Lothian
Biological Safety (NHS Lothian)	**Rachael MacAngus** **Lois Eddie**	Biological Safety Officers
University Biological Safety Advisor (UoE)	**Dr Phil Walsh**	Biological Safety Advisor, University of Edinburgh
Gene Therapy Scientific Advisor	**Professor Andy Baker**	Head of Centre for Cardiovascular Science, Vascular Biology
Virologist	**Professor Jürgen Haas**	Head of Infection Medicine, Professor of Viral Genomics
Intensive Care	**David Hope**	Research Manager, Critical Care, NHS Lothian
Secretary	**Lisa Wotherspoon**	Advanced Therapies Quality and Product Manager, NHS Lothian

https://accord.scot/researcher-access-advanced-therapy-and-gene-modification-safety-committee/committee-overview



ATGMSC Specific Documents

Terms of Reference (available on website)

ACCORD SOP: GS012 Advanced Therapy and Gene Modification Safety Committee Approval for Research

Risk Assessment Forms:

GS012-F01 FORM A: Genetically Modified Organisms

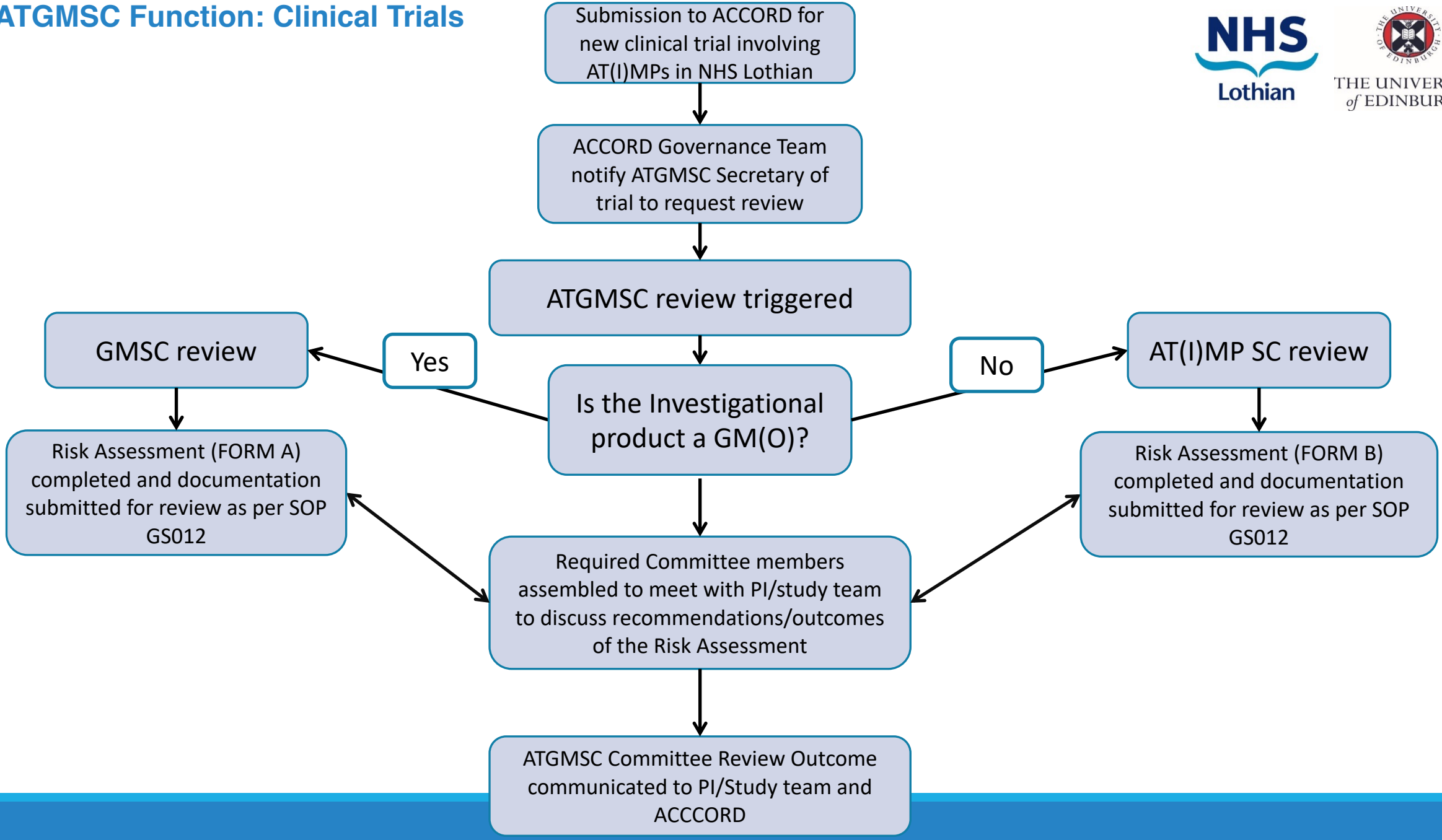
GS012-F02 FORM B: ATIMPs

Guidance Notes:

GL004 Guidance notes FORM A: Genetically Modified Organisms

GL005 Guidance notes FORM B: ATIMPs

ATGMSC Function: Clinical Trials



Study Amendments

As per **SOP GS012**:

Any amendments to the trial protocol or documents pertaining to the IMP, investigator notifications of important safety information or new Investigators conducting the study must be reviewed by the ATGMSC.

The amendment, in conjunction with the current version of the RA is reviewed by the PI to ascertain whether the amendment will impact the content of the current RA

At this stage, PI can request via the Secretary to consult additional Committee members for opinion and guidance

No Amendments Required

If the PI deems the amendment to have no impact on the RA and safety of the trial within NHSL, this will be confirmed to the ATGMSC Secretary via email.

Secretary then notifies Sponsor Reviewer/R&D Governance reviewer and PI via email that no review is required by the ATGMSC.

The email will confirm the current version of the RA.

Amendments Required

If the amendment is deemed to impact the RA and/or safety of trial within NHSL, the PI will amend the RA appropriately and submit this, and any applicable documents, to the ATGMSC Secretary

Secretary will inform the PI, Sponsor Reviewer/R&D Governance Reviewer of the required changes to ensure that the amendment is not implemented in NHSL before the ATGMSC approval of the amendment is in place.

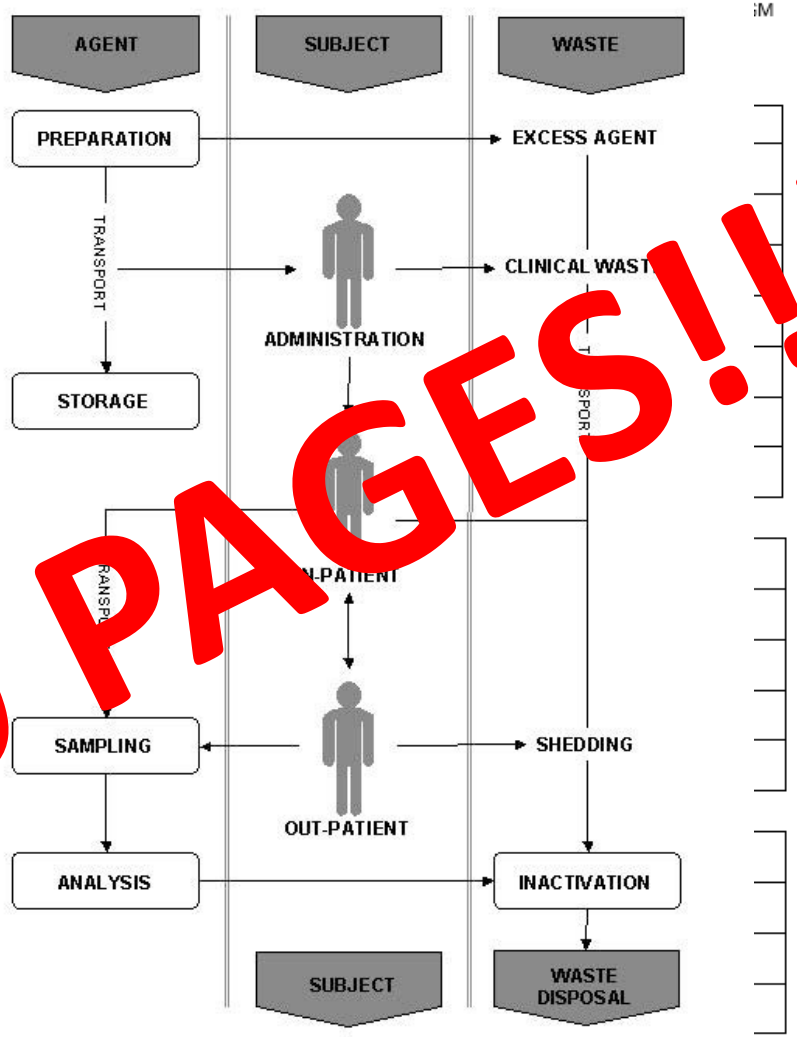
ATGMSC review takes place to review amendments and applicable documents

Risk Assessment - Responsibilities

Responsibility for completion lies with the **Principle Investigator and Study Team**

Committee members can assist/offer advice with completion of certain sections (i.e pharmacy, waste etc)

Risk Assessment is a local form – do not send to sponsor for completion.



Sections Include:

Details of the Research

Approvals

L

S

D

R

R

C

A

V

A

Personnel

Pharmacy (prep/handling/storage)

20 PAGES!!!

Lessons Learned……

Plan in advance – don't underestimate it, manage sponsor expectations with regards to approval

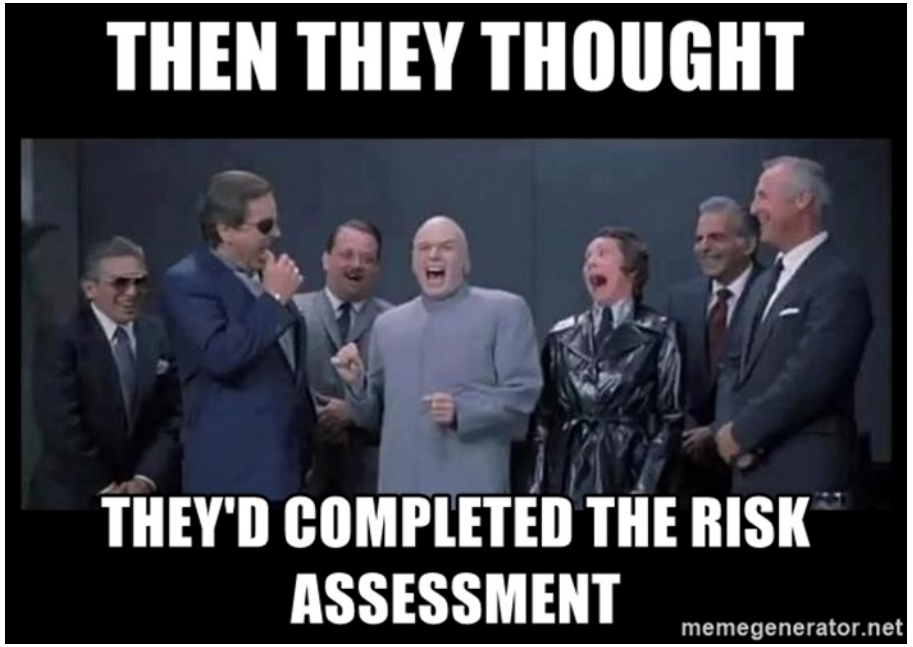
Early engagement with support departments (i.e waste, pharmacy)

Pathway of product through clinical area – last 100m, receipt, transport, transfer, preparation/ administration, waste management

Waste disposal – some products need inactivated before disposal (chemical or physical)

Pathway of patient – patient ID, inpatient treatment, toxicities and delayed toxicities, proximity to treating centre, shedding considerations

Lastly – please submit a fully completed Risk Assessment to the committee to avoid delay!



ATGMSC Main Contacts

Initial contact and enquires to Secretary

- Lisa Wotherspoon (loth.atgmcommittee@nhslothian.scot.nhs.uk)

Chair: Dr Huw Roddie

Biological Safety Officers (NHS Lothian): Rachael MacAngus/Lois Eddie

Pharmacy: Ruaridh Buchan / Ben Elliott

Further information

NIHR training video (ATMPs):
https://www.youtube.com/watch?v=AI517maCPuM&feature=youtu.be

HSE Compendium of guidance: Part 6: Guidance on the use of genetically modified microorganisms in a clinical setting
https://www.hse.gov.uk/biosafety/gmo/acgm/acgmcomp/part6.pdf

ATMP Webinar series: (accessed at https://www.theattcnetwork.co.uk/network/advanced-therapy-education-webinar-series)

ATTC NHS Readiness Toolkit: https://www.theattcnetwork.co.uk/advanced-therapies-nhs-readiness-toolkit

E-Learning for Healthcare>ATMP e-learning programme: www.e-lfh.org.uk/programmes/advanced-therapy-medicinal-products

Thank You for Listening!

ANY QUESTIONS?