ATMP Pharmacy Gene Therapy Presentation

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ATMP Pharmacy Considerations -Gene Therapy

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Agenda:

1. **Introduction: ATMPs**

   ATTC, iMATCH

2. **Gene Therapy**

   Legislation

   Local Governance

   Operational Considerations: Classification, Risk Assessment, Containment, Training

3. **Treating a Patient**
4. **The Role of Pharmacy**
5. **ATMP trials in MFT**
6. **Licensed Products**
7. **Summary**

ATMPs

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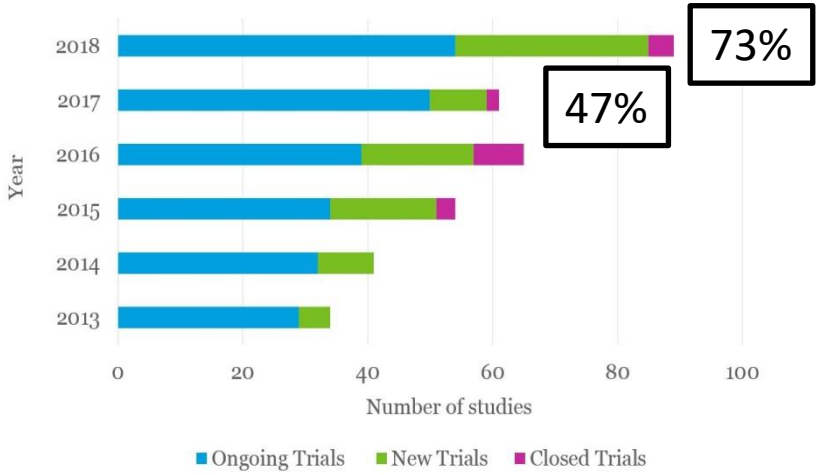
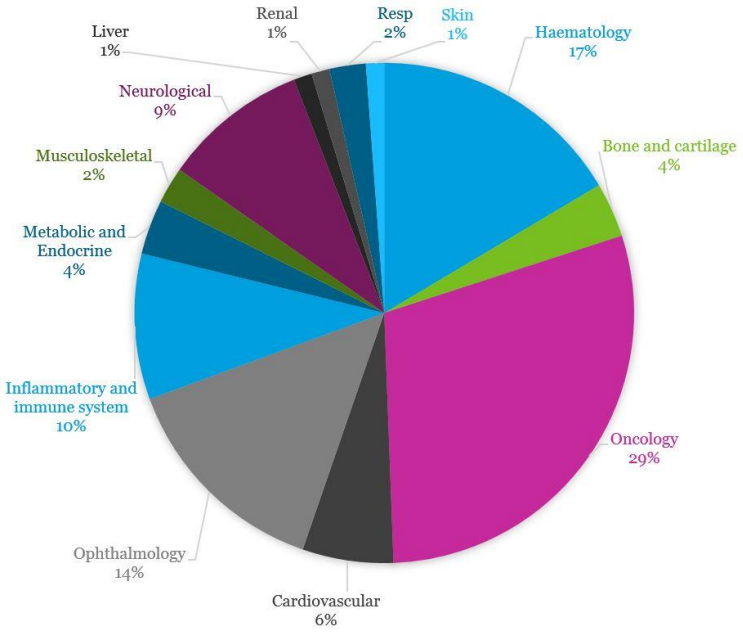
- **Gene Therapy Medicinal Product** | CAR-T
- **Somatic Cell Therapy Medicinal Product**
- **Tissue Engineered Medicinal Product**

Combination of any of the above with Medical Device

UK





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DEFINITIONS

Gene Therapy:- a biological medicinal product which 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.

Somatic cell therapy (SCT):- a biological medicinal product which contains or consists of cells or tissues that; 1)have been substantially manipulated *ex vivo,* or 2) - are not intended to be used for the same essential function(s) in the recipient and the donor.

Tissue Engineered Product (TEP):- a biological medicinal product that contains or consists of cells or tissues 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.
ATMPs may be autologous (starting material is from the intended recipient), **allogeneic** (starting material originates from a donor) or **xenogeneic** (starting material is of animal origin). ATMPS can also be classed as a Combined products; this is a combination of any of the above with a **medical device**

ADVANCE THERAPY TREATMENT CENTRES (2018- 2021)

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- **iMATCH: Manchester (MFT and Christies)**
- **MW-ATTC: Midlands – Wales: Birmingham, Nottingham and Wales**
- **NAATTC: Northern Alliance: Newcastle, Leeds and Scotland**

+ Universities and Industry partners

NHS and Industry are working to provide ready to use systems and solutions **to accelerate adoption of advance therapies**

- Institutional Readiness
- Increase recruitment into ATIMPs trials
- Increase number of patients treated with personalised medicine

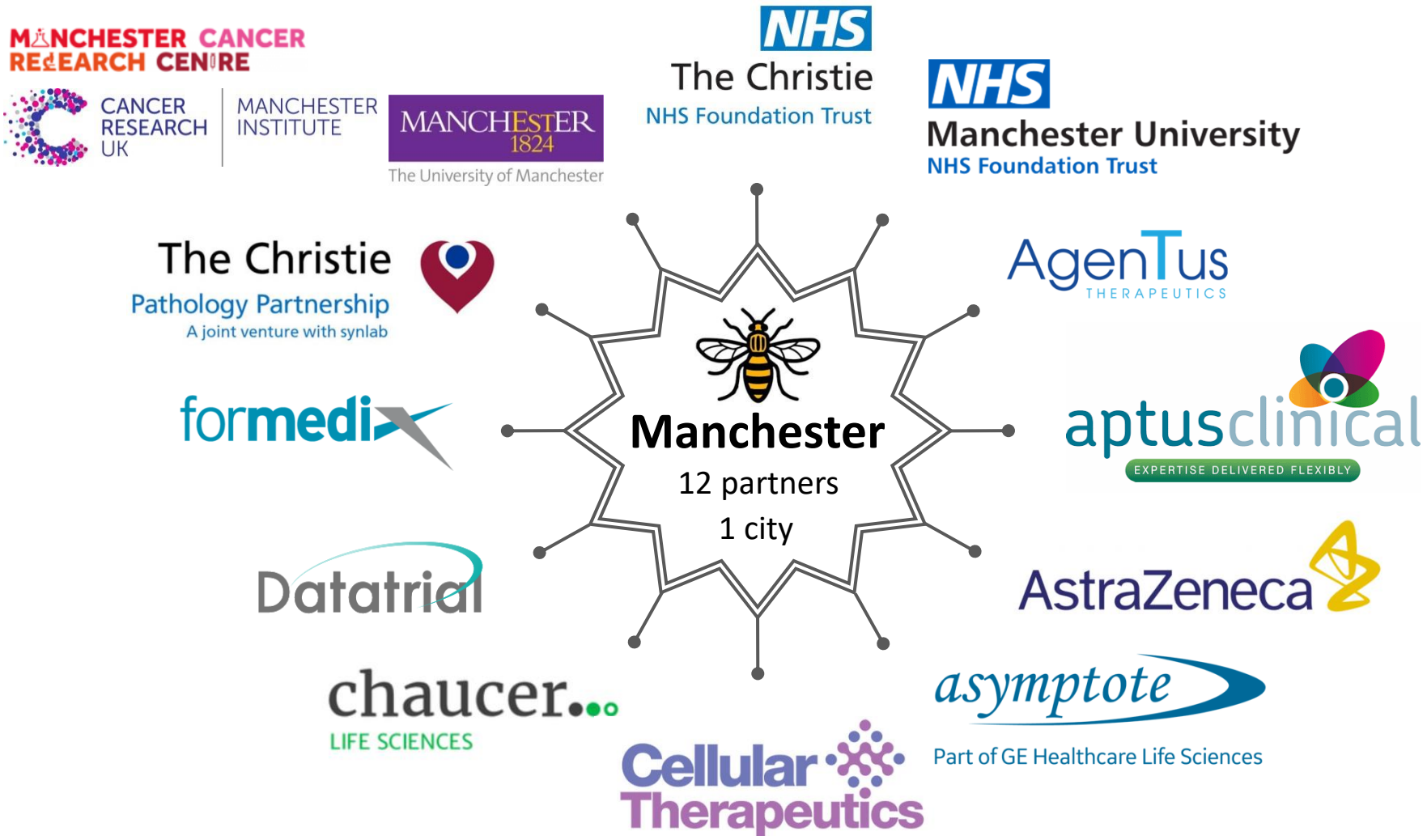
Potential Commercial and Economic Value of the sector
It could generate £10b in revenue for the UK
Create 18000 Industry jobs by 2035

Locally over the next 3 years:

- 50 high value jobs in industry and the NHS

Development of new therapies, products, services fit for deployment across the NHS

iMATCH
Innovate Manchester Advanced Therapy Centre Hub



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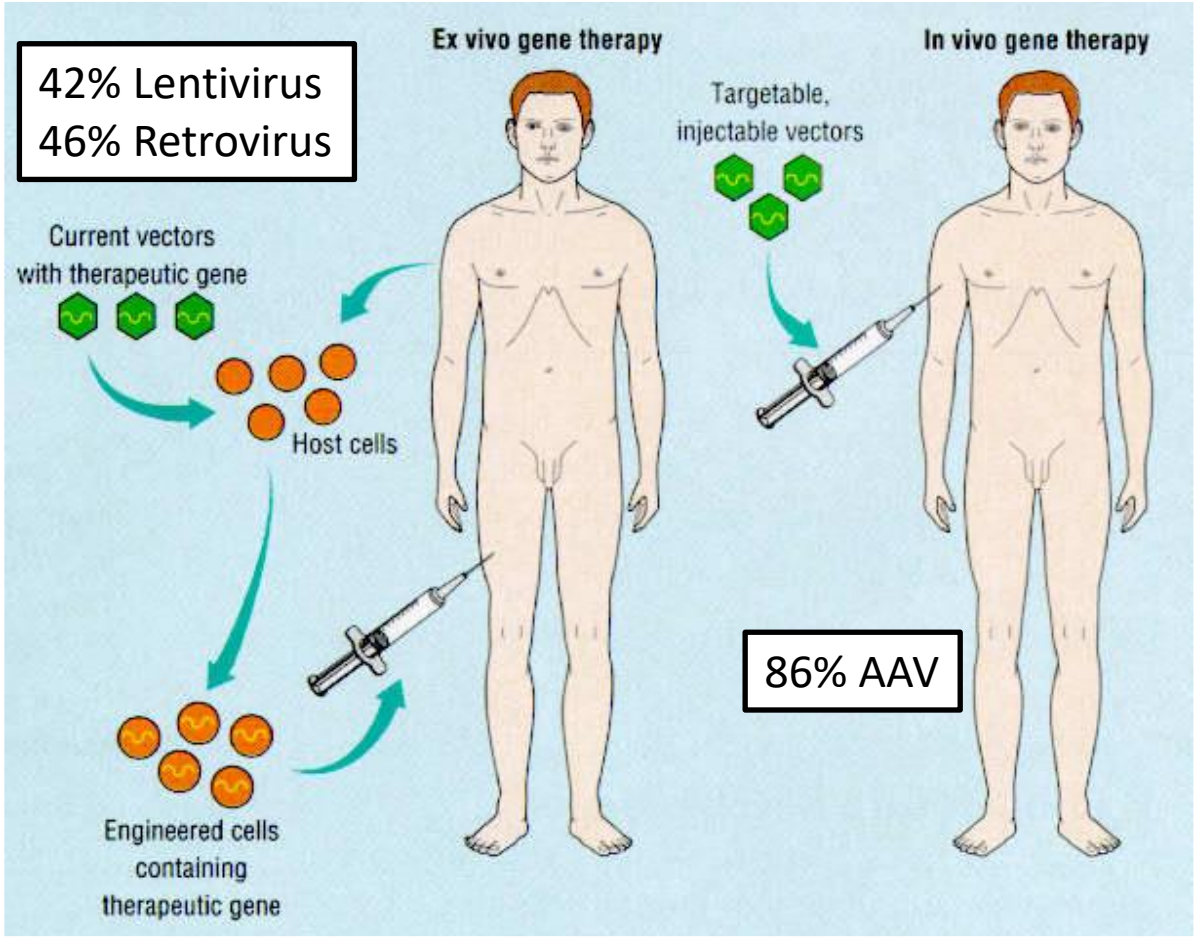
Gene Therapy

A gene therapy medicinal product (GT) is defined as 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;
- It's 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.

[Directive 2009/120/EC amending Directive 2001/83/EC]

"In vivo" vs "Ex vivo" Gene Therapy



Examples – Viral Vectors

		Adenovirus	Adeno-associated virus	Alphavirus	Herpesvirus	Retrovirus / Lentivirus	Vaccinia virus
Particle characteristics	Genome	dsDNA	ssDNA	ssRNA (+)	dsDNA	ssRNA (+)	dsDNA
	Capsid	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Icosahedral	Complex
	Coat	Naked	Naked	Enveloped	Enveloped	Enveloped	Enveloped
	Virion polymerase	Negative	Negative	Negative	Negative	Positive	Positive
	Virion diameter	70 - 90 nm	18 - 26 nm	60 - 70 nm	150 - 200nm	80 - 130 nm	170 - 200 X 300 - 450nm
	Genome size	39 - 38 kb	5 kb	12 kb	120 - 200 kb	3 - 9 kb	130 - 280 kb
							
	Family	*Adenoviridae*	*Parvoviridae*	*Togaviridae*	*Herpesviridae*	*Retroviridae*	*Poxviridae*
Gene Therapy Properties	Infection / tropism	Dividing and non-diving cells	Dividing and non-diving cells	Dividing and non-diving cells	Dividing and non-diving cells	Dividing cells*	Dividing and non-diving cells
	Host genome interaction	Non-integrating	Non-integrating*	Non-integrating	Non-integrating	Integrating	Non-integrating
	Transgene expression	Transient	Potential long lasting	Transient	Potential long lasting	Long lasting	Transient
	Packaging capacity	7.5 kb	4.5 kb	7.5 kb	> 30 kb	8 kb	25 kb

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Gene Therapy Legislation
- IMP: MHRA and HSE
- Licensed product: MHRA

- Medicines Act 1968
- Human Medicines Regulations 2012
- ATMP Regulation 1394
- **Health and Safety Executive (HSE) Genetically Modified Organisms (Contained Use) Regulations 2014**

- 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 as amended

Gene Therapy Local Governance

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- ATMP policy
- Gene Therapy Governance Considerations:
  - Organisational multidisciplinary committee: e.g. Medicines Management Committee, New Interventional Procedures Committee, ATMP assurance committee… etc
  - Biological Safety Officer (BSO) and Genetic Modification Safety Committee (GMSC) to advise the management of the notifying organisation on the adequacy of any risk assessments undertaken relating to GM activities.
  - Governance of preparation aspects

GMO Classification is Based on:

- The risk to human Health and
- The Environment

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Class 1 – well characterised agents not known to cause disease or affect health in humans and of minimal potential hazard **– *no or negligible risk.***

Class 2 – involves agents of moderate potential hazard **– *low risk.*** Class 2 agents are able to cause disease and affect health of humans. E.g. an organism classified as class 2 is a virus causing the common cold.

Class 3 – applicable to indigenous or exotic agents that may cause serious or potentially lethal disease in humans**– *moderate risk.*** E.g. an organism classified as class 3 is a virus causing HIV or Hepatitis C.

Class 4 – dangerous and exotic agents that may cause life threatening diseases in humans **– *high risk.*** E.g. an organism classified as class 4 is virus causing Ebola.

Risk Assessment

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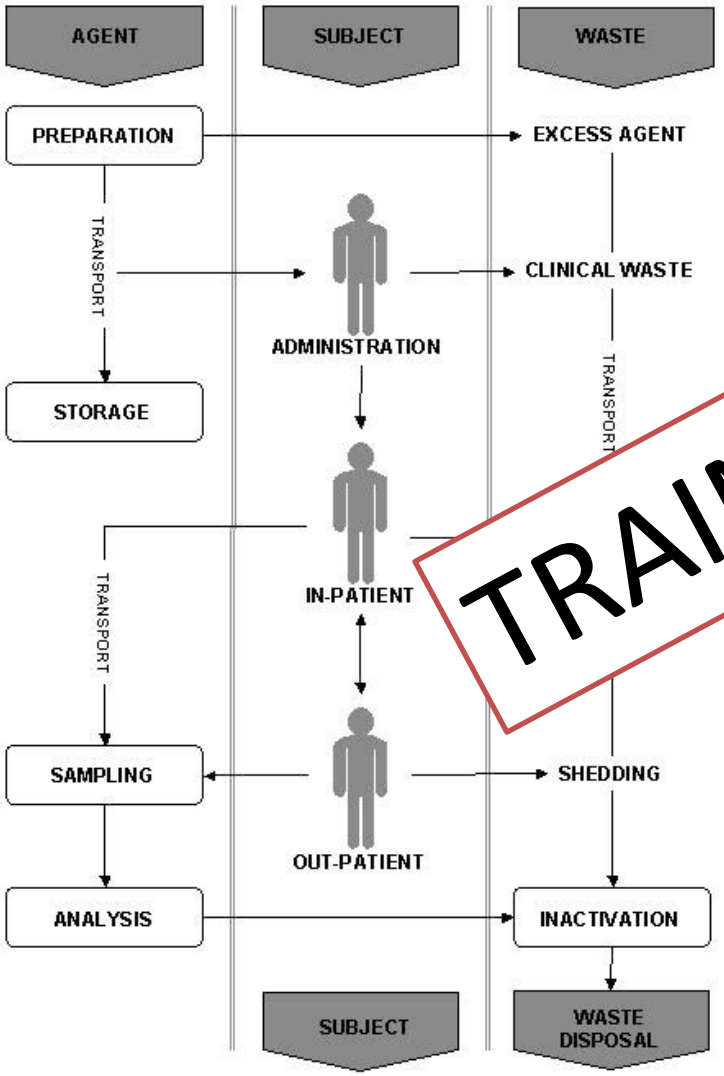

GMM pathway – considers all aspects relating to the GMM, including:
the properties of GMM;
receipt and storage of the GMM;
preparation of GMM for administration;
disposal excess GMM;
tra d containment of the GMM;
ient discharge post-trial;
ystem – from receipt through to

bject pathway – considers all procedures involving the subject, including:
administering the GMM;
patient handling and emergency procedures;
sampling and monitoring of shedding (if required);
interactions with other patients and staff, visitors and family.

Waste pathway – considers all GMM-contaminated waste, including:
stages at which contaminated waste is generated;
transport and containment of waste;
inactivation and disposal.

Ref: HSE-SACGM Compendium of guidance part 6

Gene Therapy Local Governance

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GMO Safety Committee is advised to be set up in organisations wishing to implement the use of gene therapies to assess risk assessments

Class 1: can be assessed by a Biological Safety Officer .
In organisations where there is no appointed biosafety/infection control officer, the responsibilities should be taken by a member of the infection control body.

Class 2: The HSE GMO Regulations for clinical trials defines that a GMSC assessment is an absolute requirement for a class 2 gene therapy medicine

References:
Guidance on the pharmacy handling of Gene Medicines. EJHP Practice, volume 13, 2007/5
HSE GMO Contained use regulations 2014. Regulation 8

Containment Level

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The HSE GMO Contained Use 2014 Requirements for GMSC

To ensure that risks to human health or the environment are minimised through the application of appropriate control measures.

- the establishment of a genetic modification safety committee (GMSC) to review any risk assessment carried out;
- notification of first use of premises; and
- notification of certain individual activities

Classification:

- Level of containment required to control the risk (4 levels: 1, 2, 3 and 4)
- GMO class 1 requires containment level 1
- GMO class 2 requires containment level 2

Containment level requirements

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Containment measures are ‘chemical or physical or biological barriers, or any combination of these’, designed to minimise contact with humans and release into the environment.

Containment measure	Level 1	Level 2
Autoclave	required on site	required in the building
Access restricted to authorised personnel only	not required	required
Specific measures to control aerosol dissemination	not required	required so as to minimise
Protective clothing	suitable protective clothing required	suitable protective clothing required
Gloves	not required	required where and to extent the risk assessment shows it is required
Specified disinfection procedures in place	required where and to extent the risk assessment shows it is required	required
Safe storage of GMMs	required where and to extent the risk assessment shows it is required	required
Inactivation of GMMs in contaminated material and waste	required by validated means	required by validated means

Ref: HSE-SACGM Compendium of guidance part 6

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Treating a Patient

Decontamination precautions and procedures in place **prior treatment** for:

- Needles and Sharps
- Work Surfaces
- Biohazard label for patient samples?
- Cleaning and decontamination of laundry
- Body Fluids

Transportation:

- Leak-proof biohazard container sealed in a plastic bag or other secondary container
- Transport kit should be marked on the outside showing that hazardous material is being transported
- Spill kit

Staff exposure log?

Staff health and safety: Is there a possibility that individual staff could be at increased risk? Accidental exposure

ATMP. The Role of Pharmacy

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The Role of Pharmacy is to oversee the governance arrangements and to ensure that ATMPs used are of appropriate quality for their intended use

NOTE: The use of some ATMPs may require specialist handling

- Recommended to work with HTA Designated individual

- Recommended to be assessed by appropriate multidisciplinary committee: MMC, New Interventional Procedures committee, GMO safety committee… etc.

ATMPs are medicines, they are subject to the same requirements as for other medicinal products and the **Chief Pharmacist is responsible for their governance and management**

- clinical trials
- licensed and
- unlicensed medicines

https://www.sps.nhs.uk/

Pharmacy aspects

Governance

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- Prescribed
- Prepared – **Labelling** requirements, storage
  - CT: Annex 13
  - Licensed products
- Release for administration – **QP Batch release certificate** for CT
- Handling: **Thawing**
  - **CT: Exemption 37**
    - Regulation 37 in Statutory Instrument 2004/1031 is an exemption from the requirement to hold a manufacturing authorisation for investigational medicinal products (IMPs). The regulation specifically applies to "assembly" carried out in a hospital or health centre by a doctor, a pharmacist or a person acting under the supervision of a pharmacist.
  - **Licensed products: Section 10 exemption**
- Administered
- Monitored
- ATMP Policy
- ATMP Assurance Group (MO)
- SOPs
- Audit
- Inspection
- Accreditation- JACIE
- GCP compliance
- Staff training
- Expert panel (Biological Safety Officer) approval

Technical Agreement

Licensed Products. CAR- T

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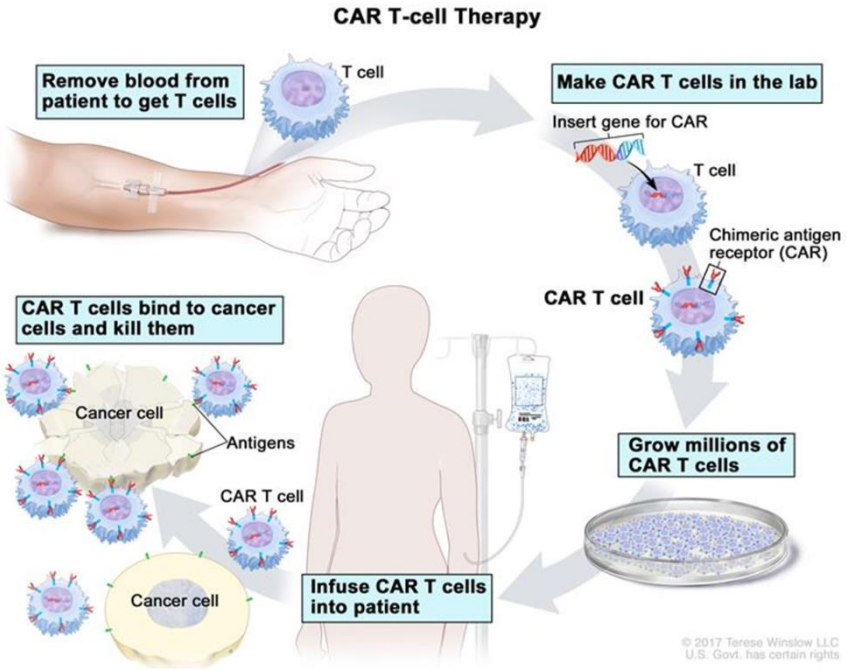
Combination of Cellular Therapy and Gene Therapy (ex-vivo)

Tisagenlecleucel- Kymriah® (Novartis)

- Relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years
- Relapsed or refractory diffuse large B-cell lymphoma in adults after 2 or more systemic therapies

Axicabtagene ciloleucel- Yescarta® (Gilead)

- Diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies



Zolgensma (previously known as AVXS-101). FDA approval by 31 May 2019?

- Spinal muscular atrophy is a progressive neuromuscular disease and the leading cause of genetic mortality in infants globally. Cause: single defective gene (SMN1 gene) SMA Type 1
- Gene replacement Therapy, designed to deliver a functional copy of the SMN1 gene to motor neurons in SMA patients. Zolgensma comprises the shell of a genetically engineered virus, the adeno-associated virus (AAV) 9, called a capsid, which delivers a normal copy of the *SMN1* gene to the target motor neurons.

Summary

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In summary:
Due to the nature of the viral vectors used in gene medicines, special consideration is necessary for their handling as biological agents in the clinical setting, as is the case for other infectious agents

In the majority of cases normal routine clinical procedures for preparing, transporting, and administering products to patients should be sufficient to ‘contain’ GMMs.

Clinical Trials. Horizon Scanning

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Is Gene editing the future of Gene Therapy?

2018: Catapult identified **3 trials** emerging in the UK

- Technology used:
  - Ex-vivo modification:
    - CRISPR being used for hematopoietic stem cells (HSCs)
    - TALEN being used for T cells
  - In vivo insertion of a zinc finger nuclease approach being used for factor IX (FIX) to treat Haemophilia B

Advantages? Gene editing using a non-viral gene delivery

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Pan UK Pharmacy Working Group for ATMPs

- Governance, Clinical Trials and Clinical subgroups
- Links with NPCTAG
- Is producing Gene Therapy Guidance… coming soon

Specialist Pharmacy Service

Hosting website for all documents

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Thank you for listening
Any Questions??