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NHS Foundation Trust

Clinical Application and Trial Process

Cell and Gene Therapy Symposium

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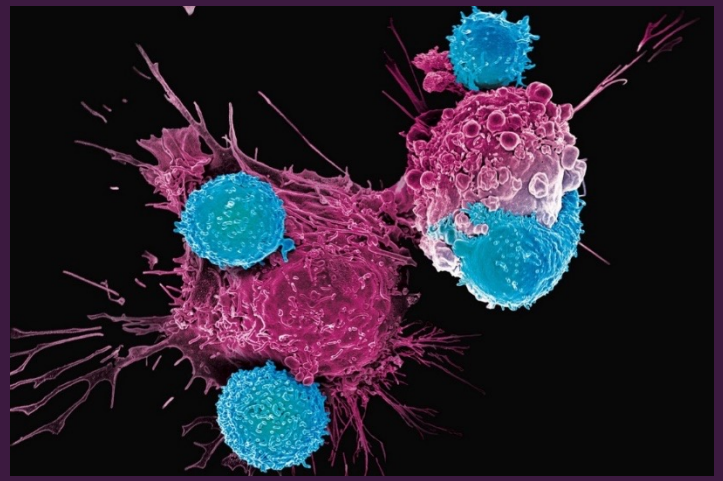

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Disclosures

- Educational grants: Kite Gilead, Novartis, Janssen

Outline

- Introduction
- Clinical application
  - Implementation
  - Patient pathway example
- Trial process
  - CTIMP requirements
  - Additional ATIMP requirements
- Summary

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Introduction

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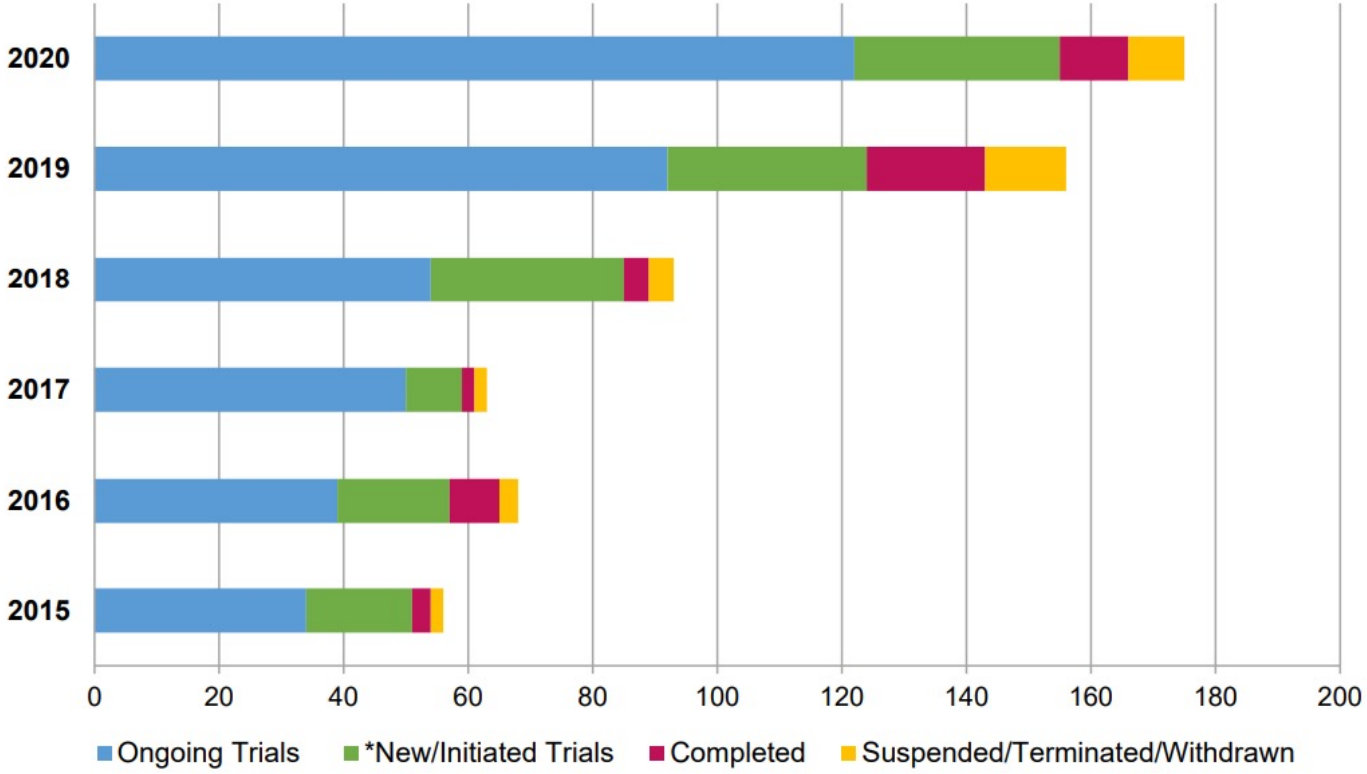
Expanding landscape

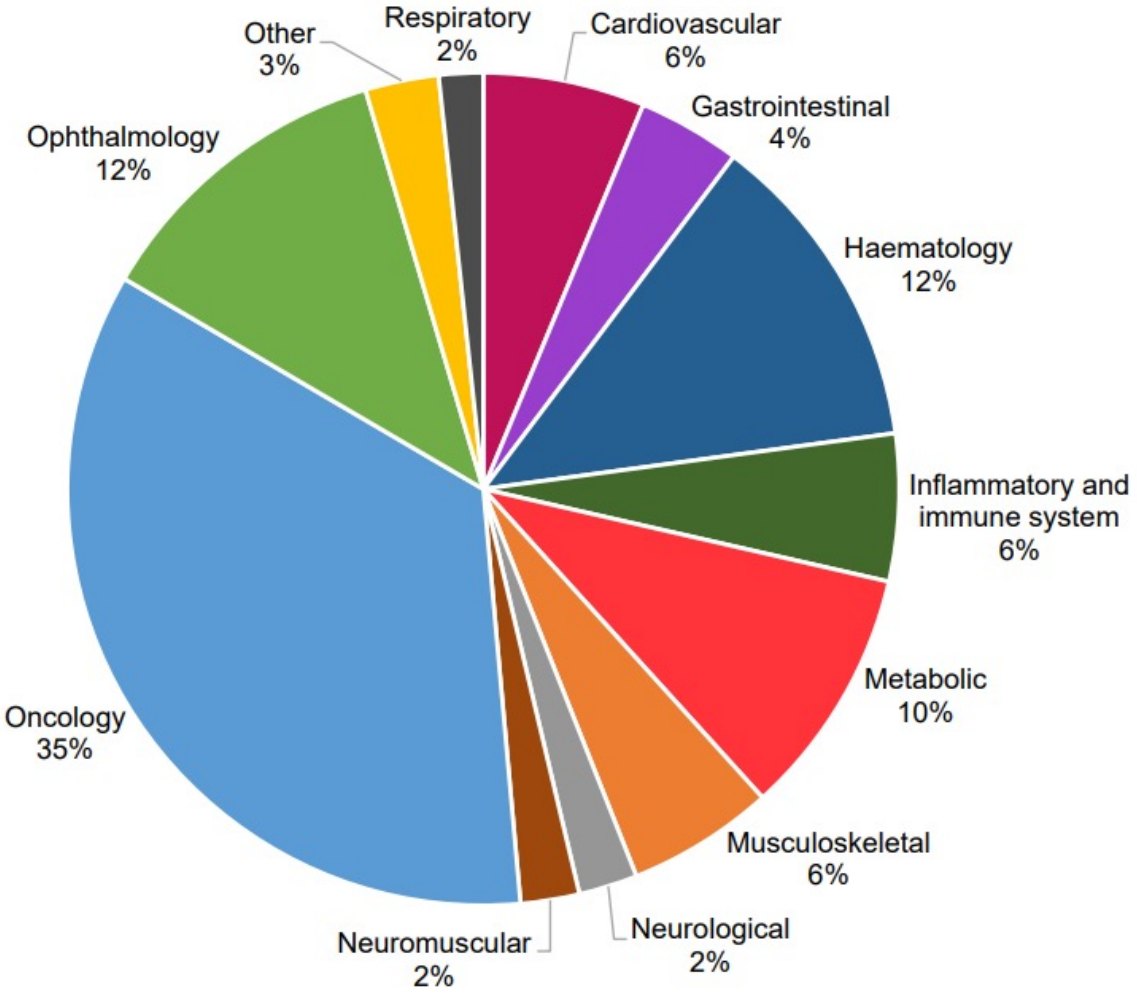
Figure 1: Number of ongoing, initiated, completed, and closed trials 2015-2020



*From 2019, trials shown in green are trials initiated during that year. For 2015-2018, the designation 'new' includes both trials registered and initiated each year.

Clinical Trials Database Commentary 2020.pdf (catapult.org.uk)

Figure 2: Distribution of UK ATMP clinical trials by therapeutic area in 2020



"Other" therapeutic areas, together representing approximately 3% of UK ATMP clinical trials, includes dermatological, infectious disease, oral, and renal/urogenital clinical trials.

Clinical Trials Database Commentary 2020.pdf (catapult.org.uk)

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Clinical Application

Implementation
Clinical pathway

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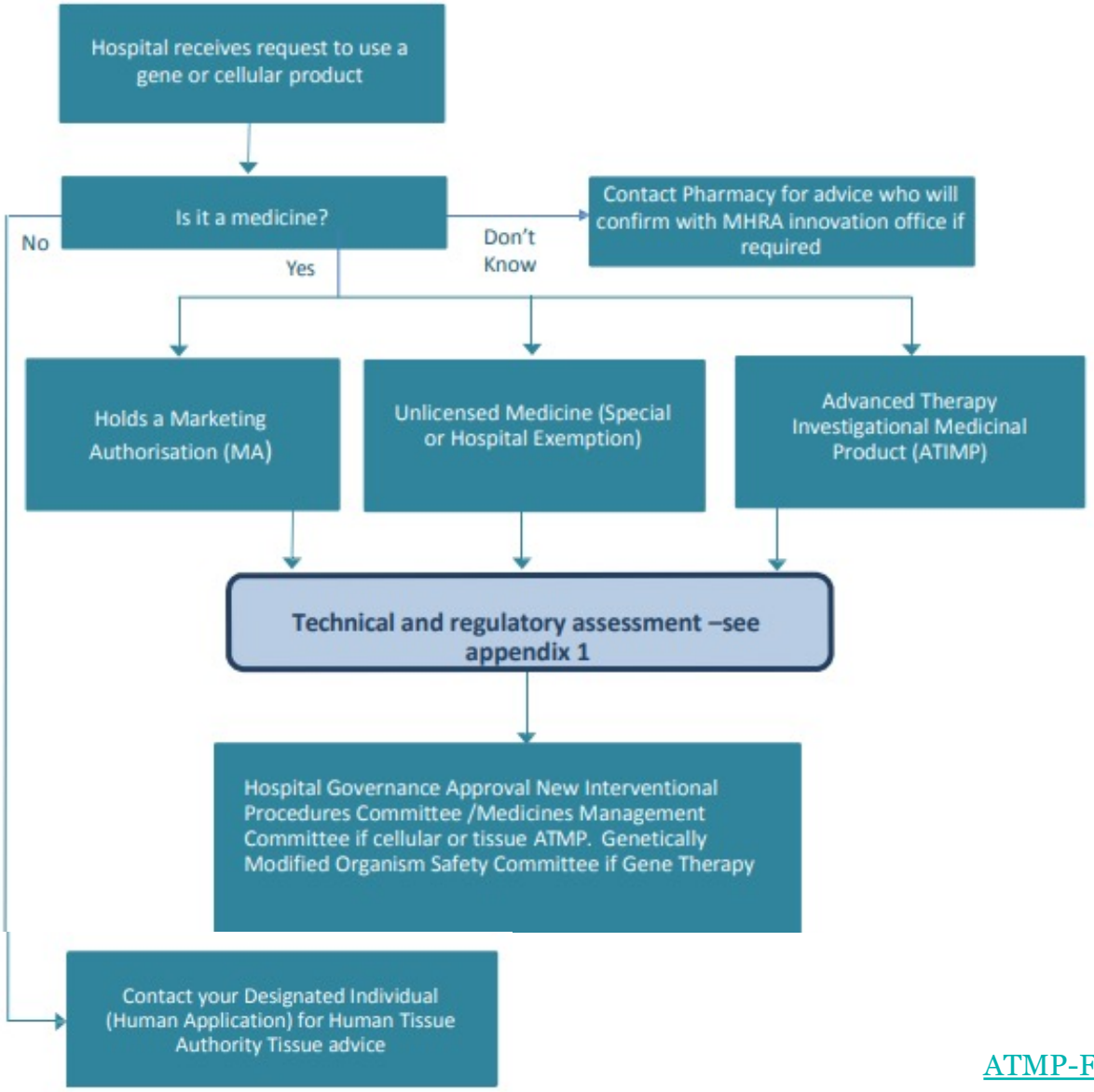
Different to traditional medicines



ATMP-Final-yellow.pdf (sps.nhs.uk)

Implementation

Specialist Pharmacy Service

Northern Alliance
Advanced Therapies Treatment Centre

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The Role of Pharmacy in the Successful Delivery of Advanced Therapy Medicinal Products (ATMPs)

Information for Chief Pharmacists

Edition 1

February 2017

N P C T A G
National Pharmacy Clinical Trials Advisory Group

ROYA PHAR SOCIE

Pharmacy Institutional Readiness for Marketed CAR-T Therapy: Checklists for Pharmacy Services

Edited by: Anne Black, Regional QA Specialist

With thanks to Pharmacists from CAR-T Commissioned Centres

Version 4.0

January 2020

Specialist Pharmacy Service

Pan UK Pharmacy Working Group for ATMPs

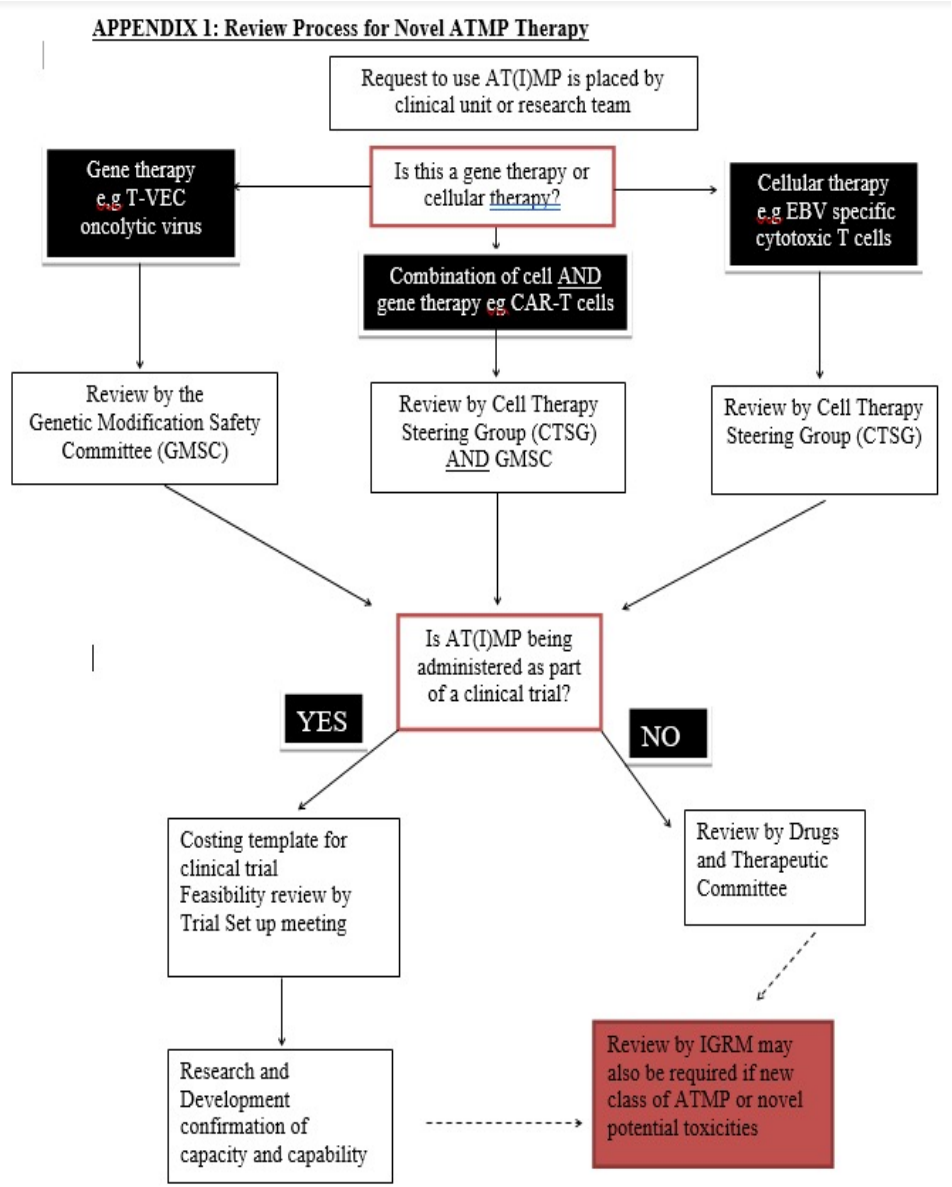
Gene Therapy Medicinal Products

Governance and Preparation Requirements

Version 2
October 2019

Governance requirements

- **Stakeholders**: pharmacy, nurses, clinicians, SCL
- **ATMP oversight group** (or equivalent)
- **GMSC** for GMO/gene therapy
- **Incident reporting** – eg ATMP governance
- **Policies and SOPs** for all processes
- Licensed and funded



Infrastructure

- **Facilities**
  - SCL or equivalent
  - Aseptic or gene therapy suite
  - Cold chain maintenance
  - ITU

- **Staffing**
- Nurses, pharmacists, quality team, doctors – each have own role in patient journey

- **Training and development**
- Management of product
- Management of patient, particularly toxicities

Governance:
CTSG
GMSC
R&D
DTC

Receipt & storage:
Specialist handling
SCL
Temp monitoring
QA of equipment

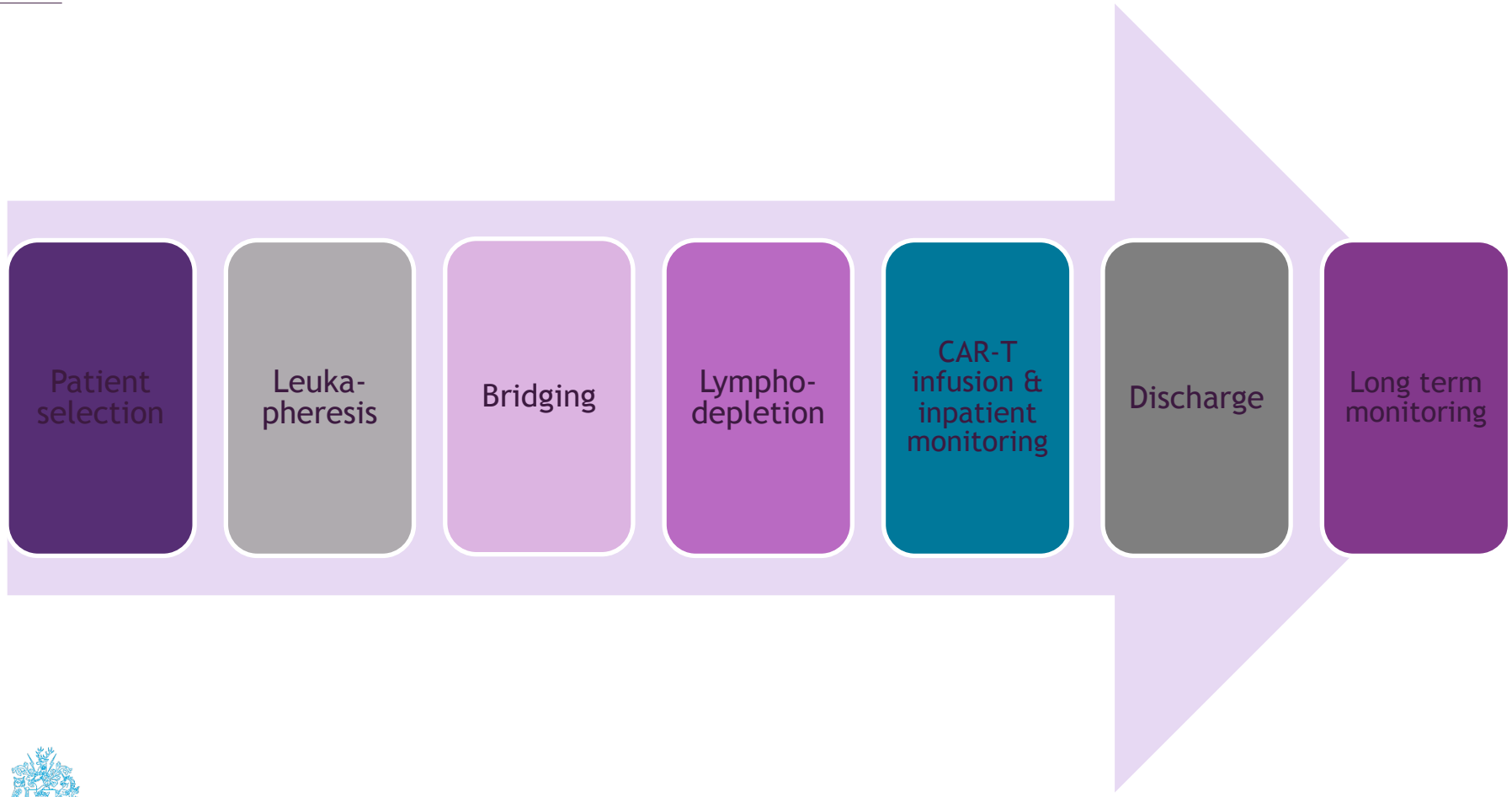
Dispensing:
Aseptic production
Supportive meds
Traceability

Set-up
Pathways
SOPs
Training
Resource
Finances

Procurement:
Ordering
Apheresis
Surgery
Preservation media

Clinical management:
Medication history
Restricted medicines
Lymphodepletion
Supportive medications
Patient counselling
Toxicity management
Long term effects

Clinical Practice – CAR-T patient journey



Patient selection

- Confirm patient eligibility
- Confirm funding
- Place orders with CAR-T manufacturer
  - Unique ID assigned

Leukapheresis

- Liaise with CAR-T manufacturer
- Medication history - ensure washout periods adhered to prior to leukapheresis

Bridging

- Screen chemotherapy
- Steroids reduced prior to lymphodepletion
- Liaise with local referral hospital
- Pre-treatment consultation and medication history

Lymphodepletion

- Ensure safe receipt of product prior to lymphodepletion
- Screen lymphodepletion
- Supportive medications

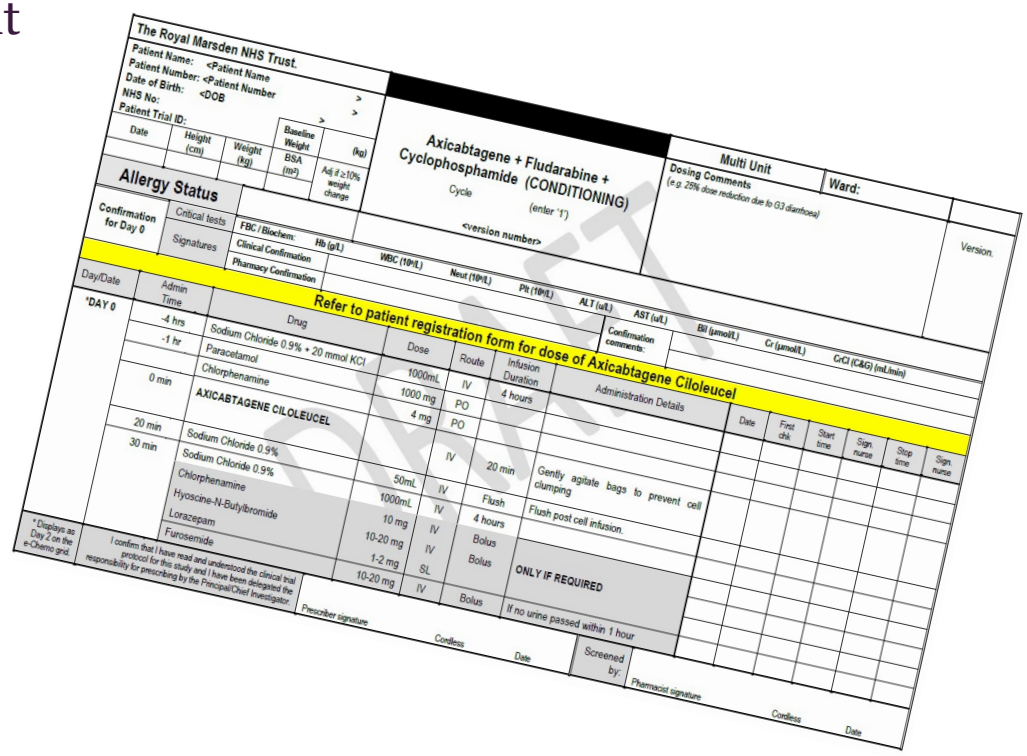
Lymphodepletion and supportive medications

Lymphodepletion:

- Usually combination of fludarabine and cyclophosphamide
- Regimen varies for each product
- Adjust for renal impairment

Supportive medications:

- Seizure prophylaxis
- TLS prophylaxis
- Antiviral
- Antifungal
- PCP prophylaxis
- Antibacterial prophylaxis
- PRN medication
- NO STEROIDS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Patient Name: <Patient Name>
Patient Number: <Patient Number>
Date of Birth: <DOB>
NHS No:
Patient Trial ID:

Axicabtagene + Fludarabine + Cyclophosphamide (CONDITIONING)
Cycle (enter '1')
<version number>

Multi Unit
Dosing Comments (e.g. 25% dose reduction due to G3 diarrhoea)
Ward:
Version:

Allergy Status

Refer to patient registration form for dose of Axicabtagene Ciloleucel

Day/Date	Admin Time	Drug	Dose	Route	Infusion Duration	Administration Details
*DAY 0	-4 hrs	Sodium Chloride 0.9% + 20 mmol KCl	1000mL	IV	4 hours	
	-1 hr	Paracetamol	1000 mg	PO		
		Chlorphenamine	4 mg	PO		
	0 min	AXICABTAGENE CILOLEUCEL		IV	20 min	Gently agitate bags to prevent cell clumping
	20 min	Sodium Chloride 0.9%	50mL	IV	Flush	Flush post cell infusion.
	30 min	Sodium Chloride 0.9%	1000mL	IV	4 hours	
		Chlorphenamine	10 mg	IV	Bolus	
		Hyoscine-N-Butylbromide	10-20 mg	IV	Bolus	ONLY IF REQUIRED
		Lorazepam	1-2 mg	SL		If no urine passed within 1 hour
		Furosemide	10-20 mg	IV	Bolus	

* Displays as Day 2 on the e-Chemo grid

I confirm that I have read and understood the clinical trial protocol for this study and I have been delegated the responsibility for prescribing by the Principal/Chief Investigator.

Prescriber signature | Cordless | Date

Screened by: | Pharmacist signature | Cordless | Date

DRAFT

CAR-T infusion & inpatient monitoring

- Tocilizumab available on the ward
- Dispensing of product from Stem Cell Lab
- Ensure traceability from 'vein to vein'
- Infusion on ward

- Daily monitoring and management of toxicity
  - Cytokine release syndrome
  - Neurotoxicity
- Any suspected adverse reaction to a CAR-T infusion should be reported. Reporting forms and information can be found at – www.mhra.gov.uk/yellowcard

Acute CAR-T cell toxicities

Cytokine Release Syndrome (CRS)

- Clinically manifests when large numbers of lymphocytes and/or myeloid cells become activated and release inflammatory cytokines into the blood
- Caused by expansion of CAR T cells, elevated IL-6 and other cytokines.
- Treated with tocilizumab and corticosteroids

IEC-associated Neurotoxicity Syndrome (ICANS)

- Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema."
- Treated with corticosteroids

Discharge

- Patient alert card
- Avoid driving
- Continue prophylactic medication
- Counselling on new medications and potential side effects

Long term monitoring

- B-cell aplasia/ hypogammaglobulinaemia (approved indication in updated DOH guidelines)
- Cytopenias
- Infections
- Delayed reactions

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Trial Process

GCP and CTIMP set-up

Additional ATIMP requirements

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Good Clinical Practice (GCP)

- Good Clinical Practice (GCP) is the international ethical, scientific and practical standard to which all clinical research is conducted
- Compliance with GCP assures patients and the public that the rights, safety and wellbeing of people taking part in studies are protected and that research data is reliable.
- Protection of rights, safety and well being and provisions of accuracy and credible data
- developed by the Health Research Authority for researchers conducting clinical trials of investigational medicinal products (CTIMPs)

Good Clinical Practice (GCP) | NIHR

CTIMP Trial Set-up

Site Qualification

- Initial feasibility
- Governance
- Infrastructure
- capacity

Site initiation

- Detailed review of protocol, pharmacy manual, lab manual
- Costings
- Approvals
- Labelling requirements

Trial open

- Follow protocol and SOPs
- Randomisation and dispensing
- Accountability logs
- Storage
- Administration and clinical monitoring

Additional ATIMP requirements

ATIMP trial
Additional approvals and license – clinical application, CTSG, GMSC, HTA
Traceability / labelling / confidentiality
Supply chain
Receipt, storage and handling
QP/CoA
Dispensing and accountability logs
Infusion requirements
Safety, rescue drugs etc
Staffing

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Summary

- Expanding area with complicated implementation into clinical practice
- Specific governance and infrastructure requirements for hospitals to deliver cell and gene products
- Collaborative working is essential

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Thank you!

Please contact me with any questions:

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