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Advanced Therapies Treatment Centre

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

Edited by: Anne Black, Regional QA Specialist

With thanks to Pharmacists from CART-T Commissioned Centres

Version 3.0

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The first stop for professional medicines advice

Pharmacy Institutional Readiness for Marketed CAR-T Therapy: Guidance for Chief Pharmacists

1. Background

CAR-T Therapies are newly authorised medicines within Europe. They are currently undergoing review via the NICE Technology Appraisal process. CART-T therapies are classed as Advanced Therapy Medicinal Products (ATMPs) and as such, Chief Pharmacists are required to ensure that governance arrangements in line with the safe and secure handling of medicines are in place to manage these medicines within their organisations.

CAR-T is an individualised therapy. There are potentially disastrous consequences if the medicine is not administered to the patient for whom it was intended. There is a role for the chief pharmacist in ensuring that the risks, particularly around tracking and traceability, are minimised.

Whilst collaboration with colleagues who are experts in handling cellular products will be key operationally, this will be a new working relationship for many and, it may take time for this working relationship to develop and embed. Additionally, CAR-T therapies are associated with toxicities which must be well understood and managed in a timely fashion.

2. Purpose

The purpose of this document is to outline the key areas where chief pharmacists should focus pharmaceutical expertise prior to an organisation implementing CAR-T Therapy.

This document presents a flow diagram outlining a stepwise approach to implementing CART-T therapy. It is followed by a six checklists and a standard operating procedure (SOP) which relate to the various steps presented in the diagram. These are presented as appendices.

It is recognised that Pharmacy Services do not currently have the expertise to handle the products and that, routinely, Pharmacy Services may not come directly into contact with the product. However, it is important that where Pharmacy Services are not directly performing some of the outlined steps that the roles of those undertaking these steps are clearly documented in an overarching technical agreement with reference made to organisational approved SOPs.

In preparation for the implementation of NHS patient treatment an operational group consisting of representatives from the first wave of CART-T commissioned centres was convened in order to provide exemplar/templates for some of the key steps in the delivery of CART-T therapy (see appendices). This document provides the outputs from these discussions. The checklists may be used as appendices to local procedures as a way of documenting key steps or as an aid against which to check that local procedures are comprehensive.

Points for consideration by Chief Pharmacists

Governance

- Three levels of governance will be required for an NHS England-commissioned service. Chief pharmacists should ensure that governance for CAR-T's is documented as follows:

  1. Centres will need to be able to meet the requirements of the National Service Specification including being JACIE accredited.
  2. National approval re patient selection:
     - An approved centre will need to understand the national processes for patient selection.
  3. Local Governance:
     - As referenced in the "The Role of Pharmacy in the successful delivery of ATMPs - information for Chief Pharmacists, (Edition 1, Feb 2017)", organisational governance prior to providing any ATMP is advised. This may involve Drug & Therapeutics Committees, GMP Safety Committees and local requirements should be defined prior to implementation of a CAR-T therapy service and should be defined in an organisational policy.
     - Implementation sites will be asked to complete Commercial agreements with the relevant Pharmaceutical companies. These will require review by Pharmacy.
     - Due to the value of the Medicine, local financial governance requirements will need to be documented in an SOP. Financial approval should be gained prior to placing an order.
     - A centre wishing to provide CAR-T will define additional local governance requirements e.g. for private patients.

An exemplar medicines management checklist is available in appendix 1.

Approval of the Order

- Commercial operating systems (e.g. Cell Chain Platform and Kite Konnect) require a pharmacist's approval and/or the provision of a pharmacy purchase order. This will require an SOP to be defined. Companies may suggest that the approval required is little more than a data accuracy check, however, recognising that time pressures will exist, the pharmacy SOP should ensure that the process covers all governance aspects detailed above, and any appropriate clinical verification.
- Additionally, links with pharmacy purchasing systems, and prescribing systems will require definition and may form part of this SOP or be documented separately.

An exemplar pharmacy patient approval checklist is available in appendix 2.

Apheresis & Manufacture

- The Apheresis centre will procure the starting material for the CAR-T manufacture under their Human Tissue Authority licence. Where this is outsourced then the site should have undertaken supplier assurance.
- Local site documentation should be clear that during manufacture, GMP compliance is required and that the Qualified Person employed by the manufacturer has overall responsibility for release of the product, and what to do if a deviation is apparent.

Pharmacy may wish to understand these arrangements but is not responsible for them.

Product Receipt

- Receipt, storage, preparation & issue are pharmacy responsibilities, although CAR-T Therapies will routinely be received by Stem cell labs. The Chief Pharmacist should seek assurance re the governance of this.
- An SOP for receipt of the final (licensed medicinal) product is required to include integrity of the product, labelling and temperature compliance during transit. Certificate of Analysis / QP certificates detailing the dose in the bag check. This should be reviewed by an appropriately trained clinical pharmacist.

An exemplar product receipt checklist is available in appendix 3.

Storage

To note: -

- Kymriah requires storage at <-120^{o}C after receipt.
  Yescarta requires storage at <-150^{o}C after receipt.
  The SMPCs do not specify a timescale, however, transfer to Liquid nitrogen tank or suitable freezer should be within 24 hours of receipt.
- Continuous temperature monitoring and alarms are required. Actions in the event of an alarm should be specified.
- Deviation processes should be clarified e.g. if short period temperature out-of-specification occurs, the SOP should state actions to be taken. Pharmacy should be made aware of any on-site storage deviations.

The exemplar product receipt checklist available in appendix 3 covers aspects of storage.

Issue & Transportation to the clinical area

As part of the Chief Pharmacist's delegated responsibility to the stem cell laboratory to handle CAR-T therapy they should ensure that the following are included in the approved SOP.

- Confirmation that the system ensures that pre-conditioning is complete.
- Procedure for retrieval from Liquid nitrogen tank/freezer required or reference to SOP if no different to routine.
- Transportation on dry ice/vapour phase dewar to clinical area.
- Performed by /transported by stem cell lab staff (i.e. trained staff).
- Communication with pharmacy for booking out, and billing purposes, if required.
- Most sites have opted to provide supervision by implementing a pharmacist check.

An exemplar CAR-T product ship (to clinical area) checklist is available in appendix 4.

An exemplar pharmacy dispensing checklist is available in appendix 5.

Preparation

- Defrost will be undertaken in clinical areas by trained stem cell lab staff and this needs an SOP to detail methods, and define any additional labelling is required.
- Where multiple bags are supplied, sequential defrost is recommended immediately before administration of each bag, as the SMPCs limit the time allowed from defrost to administration to 30 minutes. It is advised that documentation for this process, i.e. a worksheet, be drafted.

An exemplar thaw checklist is available in appendix 6.

Administration & Monitoring

- The pharmacist with clinical responsibility for the patient need to be an expert on toxicity management e.g. Cytokine release syndrome and neurological adverse events.
- Management of cytokine release syndrome will include tocilizumab which must be available (4 vials/patient) at all times. NB There may be a requirement to use tocilizumab outside the terms of its licence (i.e. to patients below the age of 2). Use of IV human immunoglobulin may also be required
- Care should be taken to ensure that steroids are not inappropriately prescribed or administered. Corticosteroids should only be used as per SMPC recommendation, i.e. when other rescue therapies have failed.
- Close links with pharmacy aseptic service may be required in the event that parenteral nutrition or intrathecal therapies may be require to support management of patients who suffer major toxicities.

An exemplar clinical pharmacy SOP is available in appendix 7.

Pharmacy Aseptic Service

To prepare (or otherwise provide):

- Bridging Chemotherapy post order of CAR-T if required.
- Pre-conditioning prior to administration of CAR-T.
- Management of Toxicity (PN may be required). Where aseptic preparation is outsourced, written supplier assurances should be sought and logged by pharmacy.

Communication with aseptic unit is covered in the patient approval checklist available in appendix 2.

Practical Aspects of Medicines Management

- Governance aspects of medicines management are discussed above on page 1. An SOP will be required to ensure Pharmacy's involvement with the following process:
- Process cancellation
- Credit claims
- Deviations
- Pharmacist approvals may be required as part of the Commercial Operating System and the SOP should detail what this entails.

The exemplar medicines management checklist available in appendix 1 includes some of the practical aspects.

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Appendix 1

NEW CAR-T PRODUCT
PHARMACY MEDICINES MANAGEMENT CHECKLIST

Product Name			
Supplier			
Manufacturer (if different to above)			
Regulatory status	Licensed/Unlicensed/Clinical Trial		
Checking step	**Yes\No**	**Checker Initials**	**Date**
Treatment centre selected by NHSE to deliver CAR-T cell therapy	Yes/No		
Treatment centre accredited by JACIE to deliver CAR-T cell therapy	Yes/No		
Treatment centre qualified by manufacturer to deliver product	Yes/No		
Governance approvals in place for use of product as applicable: - Medicines Management/Formulary - ATMP Oversight Group/ (or similar) - Clinical trial approval	Yes/No		
Biological safety risk assessment completed / Genetically Modified Organism Safety Committee approval gained	Yes/No		
SMPC available	Yes/No		
Prescription added to electronic SACT prescribing system	Yes/No		
Product added to Pharmacy Ordering system	Yes/No		
Intravenous risk assessment completed	Yes/No		
Trust funding process approved	Yes/No		
Ensure product being tracked by Medicines Finance team and Contracts for Trust reimbursement	Yes/No		

Pharmacy product specific folder in place	Yes/No		
Pharmacy SOP in place for cancellation of order	Yes/No		
Pharmacy SOP in place for credit claims	Yes/No		
Pharmacy SOP in place for deviations	Yes/No		
Pharmacist Final Check (Print name, sign, date)			
Comments			

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Appendix 2

CAR-T PRODUCT PHARMACY PATIENT APPROVAL CHECKLIST

Product Name			
Supplier			
Manufacturer (if different to above)			
Patient name			
Patient Date of Birth (dd/Mmm/yyyy)			
Patient Hospital Number			
Checking step	**Yes\No\N/A\ Data**	**Checker Initials**	**Date**
Governance approval in place	Yes/No		
CAR- T treatment notified to GP.	Yes/No		
National patient selection approval	Yes/No		
Blueteq ID			
Trust funding approved	Yes/No		
Patient consent documented	Yes/No		
Pharmacist accuracy check on manufacturer's ordering portal completed	Yes/No		
Pharmacy order number issued	Yes/No		
Pharmacist approval documented on manufacturer's ordering portal	Yes/No		
Pharmacist Final Check (Print name, sign, date)			
Comments			

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Appendix 3

CAR-T PRODUCT RECEIPT CHECKLIST

Product Name			
Supplier			
Manufacturer (if different to above)			
Courier Job Number (& other ref no)			
Date & time received			
Received by			
Checking step\data	**Yes\No\N/A\ Data**	**Checker Initials**	**Date & time**
Tamper-evident ties intact? Outer Inner	Yes/No		
Transit Logger temperature checked on receipt as per requirement	Yes/No		
Data Logger Within specification (no alarms)	Yes/No		
All required documentation received: Shipping log, Returns documents Certificate of Analysis /QP release	Yes/No/NA Yes/No/NA Yes/No/NA		
Dose as prescribed and within range	Yes/No		
Quantity (no. of bags) received			
Product integrity visual check	Pass\Fail		
Lot/batch number			
Donation Identification Number or unique donation identifier correct	Yes / No		
Expiry Date	Yes / No		
Patient Name Correct	Yes / No		
Patient Date of Birth (dd/Mmm/yyyy) Correct	Yes / No		
Over wrap added (if locally agreed with company)	Yes / No		

Product placed into storage Storage location	Yes / No		
Receipt documented on portal	Yes / No		
1st Check (Print name, sign, date)			
2nd Check (Print name, sign, date)			
Completed receipt checklist sent to Pharmacy			
Comments			

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Appendix 4

CAR-T PRODUCT SHIP CHECKLIST

In stem cell lab - Drug/Product Details	
Product Name	
Supplier	
Manufacturer (if different to above)	
Storage Location	
Quantity (no. of bags) stored	
Confirm no temp deviations in storage	
Patient Details	
Patient Name	
Patient Date of Birth (dd/Mmm/yyyy)	
Patient Hospital Number	
Patient DIN Number	
Signed request/order	Dose/Time/Date/Ward/Approved Signatory
Subject is confirmed ready to receive	Yes / No
Pharmacist Checks undertaken	Yes / No
Removal from Storage	
Dry Shipper Checked prior to loading	Temperature/No evidence of LN/Temp logger active
Courier Booked	Yes/No / NA
Drug Removed from Storage	Time/Initials
Drug/Dose/Patient Details Check	x 2 persons
Placed in Shipper	Time

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Appendix 5

CAR-T PRODUCT PHARMACY PATIENT DISPENSING CHECKLIST

Product Name			
Supplier			
Manufacturer (if different to above)			
Patient name			
Patient Date of Birth (dd/Mmm/yyyy)			
Patient Hospital Number			
Treatment location			
Checking step	**Yes\No**	**Checker Initials**	**Date**
Lymphodepletion regimen administered to patient	Yes/No		
Screened prescription available for treatment date	Yes/No		
Certificate of analysis received with product	Yes/No/ NA		
Name on prescription matches product and certificate of analysis	Yes/No		
Patient identifier on prescription matches product and certificate of analysis	Yes/No		
Dose on prescription matches product and certificate of analysis	Yes/No		
CAR-T product receipt checklist is complete and signed for release by member of SCL	Yes/No		
Temperature deviations during storage on site	Yes/No		
Preparation worksheet issued for product for thawing and administration	Yes/No		
Record batch number/product identifier on prescription	Yes/No		
Receive and book out CAR-T product on Pharmacy Dispensing system	Yes/No		

Supportive medication e.g. tocilizumab x 4 doses prescribed and available on ward	Yes/No		
Pharmacist Final Check (Print name, sign, date)			

Once CAR-T cells administered to patient, file the following in the product specific folder which is kept in Pharmacy:

- Copy of completed patient prescription ☐
- Copy of certificate of analysis (if available) ☐
- Copy of completed "CAR-T product receipt checklist" ☐
- Original of this dispensing checklist ☐

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Appendix 6

CAR-T PRODUCT THAW CHECKLIST

In clinical area - Thaw	
Water Bath Preparation/Dry Heat	Local SOP
Prepare sterile field	Clean the trolley and/or tray surface with sterile alcohol. Apply a sterile absorbent sheet to surface, sterile gloves, sterile water
Confirm Water Bath Temp	##^{o}c
Confirm Shipper In Temp/Alarms	Yes/No
Confirm Ready to Proceed	Thawer/Admin/Patient
Single Bag Thaw	
Confirm drug/patient details against patient identifier/request/order	X 2 persons (Plus patient ID tag in front of patient)
Remove drug from shipper and insert in sterile overwrap	Unnecessary if overwrap applied upon receipt
Thaw process started (Local SOP)	Time
Thaw process completed	Time
Product integrity confirmed acceptable to administer	Yes/No
Product Handover/Administered	Time/Name
Product administered and line flushed	Time
Multiple Bag Thaw	
Confirm drug/patient details against patient identifier/request/order	X 2 persons (Plus patient ID tag in front of patient)
Confirm no of bags to be administered	Number
Remove drug 1 from shipper and insert in sterile overwrap	Unnecessary if overwrap applied upon receipt
Thaw process started (bag 1)	Time
Product integrity confirmed acceptable to administer	Yes/No
Product Handover/Administered	Time/Name
Thaw process started (bag 2)	Time
Product integrity confirmed acceptable to administer	Yes/No
Product Handover/Administered	Time/Name
Thaw process started (bag 3)	Time
Product integrity confirmed acceptable to administer	Yes/No
Product Handover/Administered	Time/Name
Thaw process completed (bag 3)	Time
All Product administered and line flushed	Time

Thawed by:

Checked By:

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Appendix 7

The role of the clinical pharmacist in managing patients receiving CAR-T cell therapy

Document & Version No **Authors Name** **Approved by** ***Approved by Programme Director*** ***Dr Ram Malladi***	

Keywords:	CAR-T cell, Cytokine Release Syndrome, Tocilizumab
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1.0				New policy

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Contents

Description:	To provide monitoring guidance for clinical pharmacists who are involved in the care of patients receiving CAR-T therapy
Document Scope:	All clinical pharmacists with responsibility for delivering and caring for patients undergoing CAR-T cell therapy. This also includes intensive care unit pharmacists.
Responsibility:	
Related Documentation	
Related JACIE Standard	
Acceptable end-points and the range of expected results	

- ## Introduction

CAR-T cell therapy is designed to treat high risk malignancies (mainly haematological). Infusion of the cell product is undertaken following lymphodepleting therapy to allow expansion of the infused T cells. This can lead to a number of life- threatening complications including cytokine release syndrome and neurological toxicity. These complications can develop rapidly and patients frequently become seriously ill and require admission to the Intensive Care Unit where they may require vasopressor support, renal replacement therapy and invasive ventilation.

Cytokine release syndrome (CRS), a well-known toxicity associated with CAR-T cell therapy, shows a wide range of clinical signs and symptoms because of markedly increased levels of various cytokines, including interleukin-6 (IL-6), IFN-g, TNF during the expansion of the infused cells. The symptoms usually occur within 1-14 days following infusion. Supportive care, tocilizumab, and corticosteroids have been used for the effective management of CRS. Tocilizumab is a recombinant humanised monoclonal antibody directed against IL-6, that binds to both soluble and membrane bound IL-6 receptors and inhibits IL-6 mediated signalling through these receptors. It has been shown to be an effective treatment for CRS.

Clinical pharmacists have an important role to play in identifying early signs of toxicity associated with CAR-T cells and ensuring that appropriate treatment modalities (e.g. tocilizumab) are promptly available for the management of such complications

- ## Objective

The aim of this SOP is provide monitoring guidance for clinical pharmacists who are involved in the care of patients receiving CAR-T therapy, including advice relating to accessing out of hours treatments for CRS.

- ## Method

3.1 Medication restrictions prior to CAR-T cell infusion

- Therapeutic doses of steroids must be stopped 5 days or 5 half-lives , whichever is greater, prior to cell infusion. However, the following physiological replacement doses of steroids are allowed: ≤ 40 mg/day hydrocortisone or equivalent.
- Steroids or other immunosuppressant drugs should NOT be used as pre-medication for CAR-T cell therapy or following CAR-T cell infusion, except as required for physiological glucocorticoid replacement therapy, or under life threatening circumstances.
- Steroids should NOT be used as pre-medication for blood product administration during the admission for CAR-T cell infusion unless approved by the Consultant Haematologist .
- Granulocyte macrophage-colony stimulating factor (GM-CSF) should be avoided due to its potential to worsen CRS symptoms. Short acting granulocyte colony stimulating factor (G-CSF) should not be given within 72 hours of cell infusion and long acting G-CSF should not be given within 10 days of cell infusion.

3.2 Patient monitoring

Clinical pharmacists will work with medical and nursing colleagues to monitor patients for toxicities associated with CAR-T cells, most commonly CRS and neurological toxicities. Patient should be monitored daily for the first 10 days following infusion for signs and symptoms of toxicities.

3.2.1 Monitoring for CRS

CRS is an expected toxicity of CAR-T cells, related to the mechanism of action of the therapy. In clinical trials, incidence has been reported as being as high as 93% with a median time to onset of 2-3 days (range 1-12 days). Any organ can be affected by CRS. Diagnosis is based on clinical signs and symptoms. The following table lists common signs and symptoms associated with CRS:

Table 1 - signs and symptoms associated with CRS	
Pyrexia	Chills
Tiredness	Renal Impairment
Cardiac failure	Headache
Tachycardia	Malaise
Cardiac arrhythmias	Transaminitis
Dyspnoea	Nausea
Hypoxia	Diarrhoea
Capillary leak syndrome	Hypotension

Based on existing algorithms for grading and management of CRS, patients with moderate-severe CRS will require urgent treatment with tocilizumab (refer to relevant SOP(s) for management of SOP / use of tocilizumab). See section 3.3 below.

3.2.2 Monitoring for neurological toxicity or CAR-T related encephalopathy syndrome (CRES)

Neurologic adverse reactions are commonly seen with CAR-T therapy and may occur on their own or alongside CRS. In clinical trials, incidence has been reported as being as high as 65% with a median time to onset of 5-7 days. The following table lists common signs and symptoms associated with neurologic adverse reactions:

Table 2 - signs and symptoms associated with neurologic adverse reactions	
Seizures	Ataxia
Somnolence	Memory impairment
Headache	Mental status changes
Confusion	Hallucinations
Agitation	Depressed level of consciousness
Speech disorders	Delirium
Tremor	Dysmetria
Encephalopathy	

Every patient should have a baseline CARTOX-10 neurological assessment. If neurotoxicity is suspected this will be increased to at least daily.

Based on existing algorithms for grading and management of neurologic toxicity or CRES, patients with moderate-severe toxicity will require treatment with corticosteroids, antiepileptics for seizures and consider tocilizumab if concurrent CRS (refer to relevant SOP(s) for management of neurological toxicity/CRES).

3.3 Availability of tocilizumab

Prior to any patient receiving their CAR-T infusion, pharmacy must ensure that at least four doses of tocilizumab are available on the ward where the treatment is to be administered. Consideration should also be given to ensuring that there is an additional supply of the drug available in a designated emergency/out of hours refrigerator.

All pharmacists providing an out of hours service must be aware of the potential need for tocilizumab out of hours and understand the requirement for the drug to be provided in a timely fashion.

3.4 Adverse events

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.

Consideration should also be given to reporting adverse events to the relevant manufacturer via their usual channels.

1. Training Implications

All staff should be made aware of this policy upon joining the unit. This is best achieved by signed confirmation that they have read the current version of the Policies & Procedures.

2. Monitoring, Audit and Evaluation Procedures

Audit of compliance with this policy can be performed against the responsibilities and content. Help is available within the department and from the divisional clinical governance team for the design and performance of audit.

- **References**

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