NCCP Service Specification for the Provision of Chimeric Antigen Receptor-T Cell (CAR-T) Therapy Services

Commissioner Lead: NCCP

NCCP-designated CAR-T Centres: St. James's Hospital (SJH), Children's Health Ireland (CHI) at Crumlin and University Hospital Galway (UHG)

Version	Date	Amendment	Approved By
1	28/07/2023		NCCP Haemato-oncology Clinical Leads Group
2	02/10/2024	Minor wording and format changes throughout for readability Change of terminology from 'commissioned CAR-T Providers' to 'NCCP-designated CAR-T Centres' Removal of section 'Population Covered and Population Needs' Changes to section 'Outcomes and Applicable Quality Standards'	NCCP Haemato-oncology Clinical Leads Group

All comments and feedback are welcome at oncologydrugs@cancercontrol.ie

Contents

1 Background

CAR-T is a new medicine manufactured from the patient's own T cells and reinfused to treat certain types of cancer. Close post-infusion management is required to manage toxicities. Clinicians experienced in stem cell transplant, immunotherapy and in treating these cancers are best placed to deliver the service. Clinical practice in CAR-T developed initially in the haematology and Stem Cell Transplant Units with Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT) (hereafter JACIE) accreditation for cellular therapy, building on the services for transplant / immunotherapy and clinical trial and academic research activity.

CAR-T cell therapy is an innovative anti-cancer treatment. CAR-T cell therapies are amongst the first of a pipeline of cell therapies transitioning from 'bench to bedside' for both malignant and non-malignant diseases. They are considered to be highly innovative, personalised treatments offering potentially effective therapy with severe but manageable adverse events (AEs), which require specialised monitoring and management. Cytokine-release syndrome (CRS) and CAR-T cell-related encephalopathy syndrome (also referred to as immune effector cell-associated neurotoxicity syndrome [ICANS]) are the most common toxicities observed after CAR-T-cell therapy and, rarely, CRS can evolve into fulminant haemophagocytic lymphohistiocytosis (HLH). Intensive monitoring, accurate grading and prompt management of toxicities with aggressive supportive care, anti-interleukin(IL)-6 therapy, and/or corticosteroids for severe cases are required to reduce the morbidity and mortality associated with CAR-T cell therapy (1, 2).

The HSE has experience of developing and / or introducing novel and toxic anti-cancer treatments e.g. complex immunotherapy, and the need to concentrate and develop expertise is key. The NCCP designated St. James's Hospital (SJH) and Children's Health Ireland (CHI) at Crumlin as the initial sites for the treatment of adult and paediatric patients with CAR-T for those indications that have been approved for reimbursement by the HSE. In 2022, an additional hospital, University Hospital Galway (UHG), was also designated as a CAR-T centre for the treatment of adult patients.

In order to implement a CAR-T therapy programme into a healthcare system, there are a number of requirements including regulatory, accreditation, technical and logistical. Clinical considerations include the location of the service, the Multidisciplinary Team (MDT) available and the specialised training of staff. Some of the requirements in terms of infrastructure and workforce are outlined in the NCCP Service Specification Document for Haemato-oncology Services (3) and align with the requirements for a NCCP-designated Type 1 Cancer Centre (4). Service development requirements are considered through the national service planning process.

2 Scope and Purpose

This purpose of this specification document (and any associated NCCP National SACT [systemic anti-cancer therapy] regimens / guidance) is to set out the service requirements for hospitals designated as sites for the provision of CAR-T therapy in Ireland.

This specification relates to the provision of clinical care for CAR-T therapy indications that have been approved for reimbursement by the HSE. This specification does not relate to the use of CAR-T in research or clinical trial activity.

Licensed and reimbursed indications for other Advanced Cell Therapies are expected to expand beyond current indications, which are largely haematological malignancies. This will have implications for the teams involved and also for where the treatment is administered. This and other future specifications are beyond the scope of this document.

3 Principles underpinning the NCCP Service Specification for the delivery of CAR-T Therapy

The principles underpinning the service specification are:

1. The CAR-T product has been approved for reimbursement by the HSE through the Oncology Drugs Management System (ODMS).
2. CAR-T therapy is novel with remaining uncertainties about outcomes and complications. Therefore, in the first instance, access will be provided at NCCP-designated Type 1 Cancer Centres that also fulfil the qualification requirements of the pharmaceutical company providing the relevant CAR-T product.
3. The number of hospitals providing CAR-T therapy may increase as demand and capacity requires.
4. All necessary regulatory approvals and company accreditation are pre-requisites for service provision at the selected providers.
5. The primary clinicians involved in the delivery of CAR-T therapy will be:
    a. Consultants (haematologists / haemato-oncologists) and their teams with appropriate training and competency in the relevant indications, immunotherapy and allogeneic HSCT according to quality managed policies and procedures.
    b. The core CAR-T Team will include haematology / nursing / pharmacy / laboratory.
    c. The extended team will include the intensive care unit (ICU) department, neuro-physiology and neuromedicine +/- neurosurgery, cardiology, renal, psychology, etc. as required.

   d. In future and in relation to CAR-T therapies in other indications, the role of other clinicians in the delivery of treatment may evolve.

6. If required to fulfil pharmaceutical company qualification requirements, JACIE training, competencies, policies and procedures are defined in the current Foundation for the Accreditation of Cellular Therapy (FACT)-JACIE standards[1] (the 6.01, 7th and 8th editions include IEC therapy standards). JACIE reaccreditation occurs every four years.
7. NCCP-designated CAR-T centres will need to demonstrate:
   a. Age appropriate disease specific expertise and immunotherapy experience
   b. A level of training and competency in treating patients with the toxicities associated with the treatment (e.g. multi-organ failure managed in the ICU)
   c. Immediate access to neurological diagnostic and management interventions which are matched to the neurological toxicity profile associated with CAR-T therapy
8. The aim is to develop NCCP-designated CAR-T Centres in Ireland. In order to develop that expertise, centres will be designated on the expectation that they will deliver all relevant CAR-T therapy products which are licensed and approved for reimbursement by the HSE. For example, where CAR-T therapy products cover a similar patient group, centres will be expected to be able to deliver all products available. This will include training and accreditation by each individual company providing the relevant CAR-T therapy.
9. All young people receiving CAR-T cell therapy must be treated within NCCP-designated CAR-T Centres with full access to age-appropriate care. Centres for individual CAR-T cell products will ensure that paediatrics and Adolescents and Young Adults (AYA) will have access to CAR-T cell products for which they are eligible within the HSE reimbursement assessment process.
10. Although the initial wave of CAR-T therapies will be directed at haematological cancers, the indications are expected to expand and are likely to include solid tumours. The nature of the CAR-T technology means that it is expected that such future indications will also be commissioned to be delivered by NCCP-designated CAR-T Centres that fulfil the qualification requirements of the pharmaceutical company providing the relevant CAR-T product. Such centres will also be responsible for the necessary aftercare of patients following CAR-T therapy, including rapid admission pathways and treatment of complications. Over time, it is expected that developments in CAR-T and associated therapies will require further consideration of the future workforce requirements for such treatments. This is out of scope of this specification.

[1] https://www.ebmt.org/jacie-accreditation

4 Care Pathway and Clinical Dependencies

4.1 Current Care Pathways

Current care pathways for indications will be outlined in the relevant NCCP Patient Pathway, where available.

4.2 Decision to Treat

1. Clinicians currently treating patients in the indicated populations will consider their patient's eligibility for treatment in line with the eligibility criteria detailed in the NCCP National SACT regimen (link to NCCP regimens page) and HSE reimbursement status. At this stage they will:
   a. Identify eligible patients who might benefit from CAR-T therapy
   b. Confirm patient eligibility in line with the manufacturer's licence with regard to age, fitness, disease and treatment stage
   c. Confirm that patients have been informed and understand the potential benefits, risks and complications of treatment as part of shared decision-making
   d. Refer such patients in line with agreed pathways to the NCCP-designated CAR-T Centre specialist tumour conference
2. Clinical decision making about individual patient treatment (assessment prior to treatment preparation, initiation and complications management) will be made by specialist tumour conferences operating in NCCP-designated CAR-T Centres.

4.2.1 Tumour conference considerations:

1. The primary clinicians overseeing the planned CAR-T pathway will include transplant physicians / immunotherapy leads.
2. Representation from specialists in pharmacy, critical care, neurology and nursing.
3. Psychology input into the tumour conference may also be required given the nature of the treatment, the need for high levels of patient awareness of symptoms and the side effects profile.
4. NCCP-designated CAR-T Centre tumour conferences will demonstrate governance arrangements which meet the qualification requirements for robust and effective quality management systems from a company accreditation perspective and which align to the NCCP Tumour Conference SOP Guidance.

4.2.2 Role of patient's treating hospital /NCCP-designated CAR-T Centre

1. The role of the patient's treating hospital is to:
   - Identify eligible patients from their own and neighbouring hospitals who may benefit from CAR-T therapy in accordance with the agreed criteria. Referral to the NCCP-designated

CAR-T Centre tumour conference would occur at this point. Refer to the NCCP National CAR-T Adult Patient Referral Pathway (for patients identified as potentially eligible for CAR-T outside of NCCP-designated CAR-T Centres), in Appendix 2. The treatment of paediatrics with cancer is centralised to Children's Health Ireland (CHI) at Crumlin and follows a separate referral pathway.

2. The role of the NCCP-designated CAR-T Centre is to:

- Confirm patient eligibility in line with the HSE reimbursement process, the NCCP National SACT regimen eligibility as well as the manufacturer's licence and the trials on which the licence is based with regard to age, fitness, disease and treatment stage, including direct review of tissue and radiological diagnostics and staging and fitness for treatment.
- Confirm that patients (and / or their carers) have been informed and understand the potential benefits, risks and complications of treatment as part of shared decision-making.
- Assess individual patients prior to treatment preparation and initiation.
- Manage the treatment, post treatment management and follow-up.
- Undertake reporting, data analysis and audit – this may include engagement with manufacturers as required.
- Review cases three months after treatment from a learning perspective and feed results into audit / service evaluation and national learning processes.
- Ensure appropriate patient monitoring post treatment.

4.3 Initial Admission

1. Before administration of CAR-T cells, patients will require chemotherapy (which should be completed two to 14 days before infusion). Following infusion, patients are likely to remain as an inpatient for 10 to 14 days and if the patient is stable, they can be discharged thereafter. Patients may be discharged earlier, on an individual basis, depending on toxicities.
2. Patients should then remain within two hours of the administering unit for approximately four weeks post infusion.
3. Published supportive care guidelines are available (1, 2). As CAR-T therapies evolve, these guidelines will be refined. It is the responsibility of the NCCP-designated CAR-T Centre to ensure that the most up to date supportive care guidelines, reflecting best practice, are followed.

- For supportive care guidelines published in other jurisdictions, not all the investigations listed are recommended, mandated or commissioned in Ireland. In some cases, the treatments listed are not routinely commissioned e.g. baseline brain MRI.
- In relation to published supportive care guidelines, centres must note that the NCCP Service Specification for the Provision of CAR-T Therapy Service and any associated NCCP National SACT regimens/guidance sets out the service requirements for Ireland. Treatments and interventions not included in these documents will not be supported or funded. Where published supportive care guidelines relate to regulatory requirements of the procurement, manufacture, storage and delivery of the product, the company requirements must be followed. In some cases, clinical consensus regarding clinical management of the patient prior, during and after treatment and in relation to the management of toxicities may differ from the company's perspective and may be more stringent than those required by the company.

4.4 Product Preparation / Manufacture

As per product Summary of Product Characteristics (SPC) and as per details provided by the company.

4.5 Product Delivery (to patient)

1. Receipt of the CAR-T product will be by Pharmacy (Chief Pharmacist) or Pharmacy approved location and recorded in line with regulatory requirements.
2. The NCCP-designated CAR-T Centre will follow the instructions for storage and preparation of the product for infusion in accordance with manufacturer quality assurance (QA). Care provided will be in accordance with the SOP and qualification requirements of the pharmaceutical company providing the relevant CAR-T product.
3. All staff involved in handling the relevant CAR-T product will be trained in the following areas:
   a. Final product unpacking / storage
   b. Monitoring the product temperature at the time of the receipt
   c. Traceability
   d. Identification and reporting of product complaints
4. A trained, named individual will receive the product at the hospital and sign for the receipt of the product. The individual will document the temperature of the product upon receipt.
5. The product is then transferred to the preparation area. The member of staff must be able to trace the product throughout the process. The hospital must confirm the patient identity and match the correct product at the time of treatment.
6. If the patient is ready and has been conditioned as per previous information, then the product is prepared according to manufacturer instructions.

7. The product is infused into the patient as per package instructions and by a trained member of staff.

In summary, the product must be prepared and delivered and patients monitored in line with the SPC and the company specific requirements. All NCCP-designated CAR-T Centres must complete training and follow specific instructions provided.

4.5.1 Monitoring for toxicities

1. As per the company requirements, the patient must be monitored at the NCCP-designated CAR-T Centre, for at least ten days following infusion, for signs and symptoms of cytokine release syndrome (CRS) and neurologic toxicities (NT).
2. The licence requires that patients should be instructed to remain within two hours travelling distance of a certified clinical facility for at least four weeks following infusion and issued with relevant patient information to alert them to side effects and guide their action to seek medical attention.
3. Relevant members of staff will receive training on all aspects of the above and in particular on CRS and NT side effect management and will receive a mandated adverse drug reaction guide that they will need to follow.
4. Clinical consensus is that at the introduction of CAR-T cell therapy, treating centres will need to follow the grading systems set out in Appendix 4 and in Appendix 5 to inform decision making with regard to ICU admission (grade 2 and above).

4.5.2 Management of Toxicities

Each NCCP-designated CAR-T centre should develop and approve guidance for the management of toxicities including CRS. These should be collaborated on as appropriate to the patient cohort and the relevant information.

This document should include recommendations on:

1. Supportive care
2. Management of CRS
3. Management of neurologic sequelae

4.6 Interdependence with other Services

All NCCP-designated CAR-T Centres must have the required capacity, technology and expertise for handling, storage and non-manufacturing preparation steps of advanced therapy medicinal products (ATMPs). Manufacturer QA processes must be adhered to. NCCP-designated CAR-T

Centres must also be able to demonstrate they have the required protocols, clinical facilities, staffing, medical supervision and care, training and education, accreditation and governance to address the following:

1. Regulatory

a. Compliance with the Human Tissue Authority (HTA) (for product procurement) and Health Products Regulatory Authority (HPRA) / Irish National Accreditation Board (INAB) standards is required.

b. Approval as a Tissue Establishment (TE) site that is authorised under the EU Tissue and Cells Directive (EUTCD) to perform procurement, testing, processing, storage, distribution and import / export of human and tissue cells as relevant to CAR-T is required. The HPRA in Ireland are the Competent Authorities responsible for regulating TE registration.

c. A Quality Management System, SOPs and Protocols and Risk Evaluation and Mitigation Strategy capable of demonstrating a high quality, safe treatment pathway for effectively managing all side effects, including those that are life threatening, is required.

2. Pharmaceutical company qualification

a. All NCCP-designated CAR-T Centres must fulfil the qualification requirements of the pharmaceutical company providing the CAR-T product as a collection, storage and clinical centre for allogeneic transplantation.

b. As patients may be unstable and / or recovering from chemotherapy during harvest, accredited collection facilities (leukapheresis and/or bone marrow harvest procedures) should be on-site or provided via a company-approved third party sub contracted arrangement.

3. Pharmacy

a. CAR-T therapy is a medicine and therefore its governance (via medicines management / clinical effectiveness committees) and operational management i.e. receipt, storage, preparation, prescription and issue are the responsibility of pharmacy.

b. Pharmacy will need to collaborate with local experts e.g. stem cell laboratory colleagues, or third party colleagues as appropriate to ensure that optimal arrangements are in place for the NCCP-designated CAR-T Centre.

c. An appropriate facility (e.g. pharmacy / cell therapy laboratory) capable of receipt and storage of the product in line with the Manufacturer QA processes including temperature monitoring and 24 hour alarm systems should be in place.

d. Where the facility may be part of a different organisation or hospital department, the NCCP-designated CAR-T Centre Pharmacy are responsible for ensuring appropriate supplier

approval assurances and technical agreements detailing the roles of both parties and ongoing monitoring, are in place.

4. Specialist tumour conference for clinical management by NCCP-designated CAR-T Centres

Specialist tumour conferences at NCCP-designated CAR-T Centres (SJH, CHI at Crumlin and UHG), are to be established for all patients referred for CAR-T (as detailed earlier). Note that these tumour conferences may be incorporated into appropriate existing tumour conferences where the patient numbers are small.

5. Clinical management

The clinical management of patients should be detailed in the NCCP-designated CAR-T Centre's SOPs and should include procedures for clinical monitoring of patients (toxicity monitoring), requirement for access to specialist diagnostic services and ambulatory care procedures.

6. Management of toxicities and critical care

These should be detailed in the NCCP-designated CAR-T Centre's SOPs and should include reference to toxicities, critical care and cardiac support requirements.

7. Training

Training should be completed by all staff as required by the regulators and pharmaceutical company providing the CAR-T product.

8. Patient / data registry

Currently, the EBMT have a requirement in relation to data collection which should be adhered to.

The Committee for Medicinal Products for Human Use (CHMP) issued an opinion in February 2019 stating that it considers the cellular therapy module of the EBMT registry may be used as a data source for regulatory purposes in the context of CAR-T cell therapies authorised for haematological malignancies. The opinion stipulates in detail the scope of the studies that may be performed based on the registry:

https://www.ebmt.org/sites/default/files/2019-03/EMA%20qualification%20opinion%20on%20Cellular%20therapy%20module%20of%20the%20EBMT%20Registry-28022019.pdf

5 Outcomes and Applicable Quality Standards

5.1 Quality Statement – Aim of Service

The aim is to detail the expected requirements of NCCP-designated CAR-T Centres who will oversee the clinical delivery of CAR-T therapy to eligible patients.

The specification will ensure that:

- Patient access is secured at a national level.
- Best practice for the safe and effective delivery of CAR-T therapy is secured.
- Clinical dependencies are addressed and secured.
- Traceability and tracking and best practice for patient follow-up and data capture is secured. NCCP-designated CAR-T Centres are required to submit data on the outcome of patients progressing through the service (see Section 5.4 below).

As it is a novel treatment, NCCP-designated CAR-T Centres will support research activity and where appropriate be willing to support future phased adoption across the HSE. There is a need for shared learning between teams regarding these new technologies and their toxicities. There should be mechanisms for teams involved in cell therapies for non-malignant and malignant conditions to collaborate and share resources, expertise and learning.

5.2 Quality Assurance (QA)

NCCP-designated CAR-T Centres are required to participate in annual QA and collect and submit data to support the assessment of compliance with the service specification.

5.3 Quality Indicators for CAR-T Service

There are a number of quality indicators for CAR-T services which are to be collected / adhered to by the NCCP-designated CAR-T Centres. These are outlined in Table 1.
These quality indicators should be used by the NCCP-designated CAR-T Centres to evaluate their service and develop quality improvement programmes as required. These quality indicators are not required to be submitted to the NCCP.

Table 1: Quality indicators for CAR-T Services

1.	**Clinical outcomes**
1.1	The number of patients who complete treatment and are alive 28 days after infusion
1.2	The number of patients who complete treatment and are alive one year after infusion
1.3	The number of patients who complete treatment and are alive two years after infusion
1.4	Total number of incidences of CRS at grade 2 and above requiring ICU / PICU
1.5	Total number of incidences of ICANS at grade 2 and above requiring ICU/ PICU
1.6	Mortality rate at 3 months, 6 months, 1 year and 2 years
1.7	Average length of stay of patients following treatment
1.8	Number of patients who are discussed at tumour conference and proceed to CART
1.9	Number of patients within defined treatment timeframes for; • Tumour conference discussion to initial review • Review to apheresis • Apheresis to infusion Any reasons for delays / non-achievement of targets to be recorded and audited for trend analysis.
2.	**Service requirements**
2.1	There is a tumour conference as per the service specification
2.2	All relevant patients applicable for CAR-T are discussed at the relevant tumour conference
2.3	All members of the tumour conference undertake training as per the service specification
2.4	There is an infrastructure to support being a NCCP-designated CAR-T Centre provider as detailed within the service specification
2.5	There are written agreements in place for the receipt of the cellular therapy products
2.6	There are agreed clinical guidelines in place
2.7	The service participates in local and national audits as required including patient selection in line with the approved indication
2.8	The service submits EBMT / other registry information for Cell therapy (via Med-A forms)

5.4 Data Submission (Patient Outcomes and Quality Indicators)

The NCCP should be provided with regular data submissions from NCCP-designated CAR-T Centres.

- NCCP-designated CAR-T Centres are required to submit patient outcome data on a **quarterly** basis. This quarterly update is to be provided to the NCCP using a standard format to ensure that all required data is captured.

6 Applicable Service Standards

6.1 Applicable Obligatory National Standards

All NCCP-designated CAR-T Centres must meet the qualification requirements of the pharmaceutical company providing the relevant CAR-T product, for the appropriate delivery of CAR-T. All centres must hold the relevant HPRA licenses, and adhere to the relevant INAB standards.

7 NCCP-designated CAR-T Centres

The NCCP has designated SJH and UHG as the designated adult CAR-T Centres and CHI at Crumlin as the designated paediatric CAR-T Centre in Ireland. This will be kept under review. Additional centres may be designated in time.

8 References

1. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. New England Journal of Medicine. 2017;377(26):2531-44.

2. Hayden PJ, al. e. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Annals of Oncology. 2022;33(3):259-75.

3. National Cancer Control Programme. Service Specification for Haemato-oncology Services. 2022.

4. NCCP. Systemic Anti-Cancer Therapy Model of Care. 2022.

Appendix 1. Abbreviation and Acronyms

The following abbreviations and acronyms have been used in this document:

Abbreviation/Acronym	Detail
AE	Adverse Event
ALL	B-cell acute lymphoblastic leukaemia
ATMPs	Advanced therapy medicinal products
BMT	Blood and marrow transplantation, which is used interchangeably with HSCT (see below)
CART	Chimeric antigen receptor T-cell
CCLG	Children's Cancer and Leukaemia Group
CHI	Children's Health Ireland
CHMP	Committee for Medicinal Products for Human Use
CRS	Cytokine release syndrome
EBMT	European Society for Blood and Marrow Transplantation
EEG	Electroencephalogram
EPAR	European Public Assessment Report
EUTCD	EU Tissue and Cells Directive
FACT	Foundation for the Accreditation of Cellular Therapy (North American Counterpart of JACIE, who collaborate to produce the FACT-JACIE standards).
HLH	Haemophagocytic lymphohistiocytosis
HPRA	Health Products Regulatory Authority
HSCT	Haematopoietic Stem Cell Transplantation
HTA	Human Tissue Authority
IEC Therapy	Immune effector cell therapy - A cell that has differentiated into a form capable of modulating or effecting a specific immune response
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICU	Intensive Care Unit
IL-6	Interleukin-6
INAB	Irish National Accreditation Board
ISCT	International Society for Cellular Therapy
JACIE	The Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT)
MDT	Multidisciplinary team
NT	Neurologic toxicities
ODMS	Oncology Drugs Management System
OS	Overall survival

Abbreviation/Acronym	Detail
PICU	Paediatric Intensive Care Unit
QA	Quality Assurance
SJH	St James' Hospital
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
TE site	Tissue Establishment site
TFL	Transformed Follicular Lymphoma
UHG	University Hospital Galway

Appendix 2. National CAR-T Adult Patient Referral Pathway for patients identified as potentially eligible for CAR-T outside of designated CAR-T centres

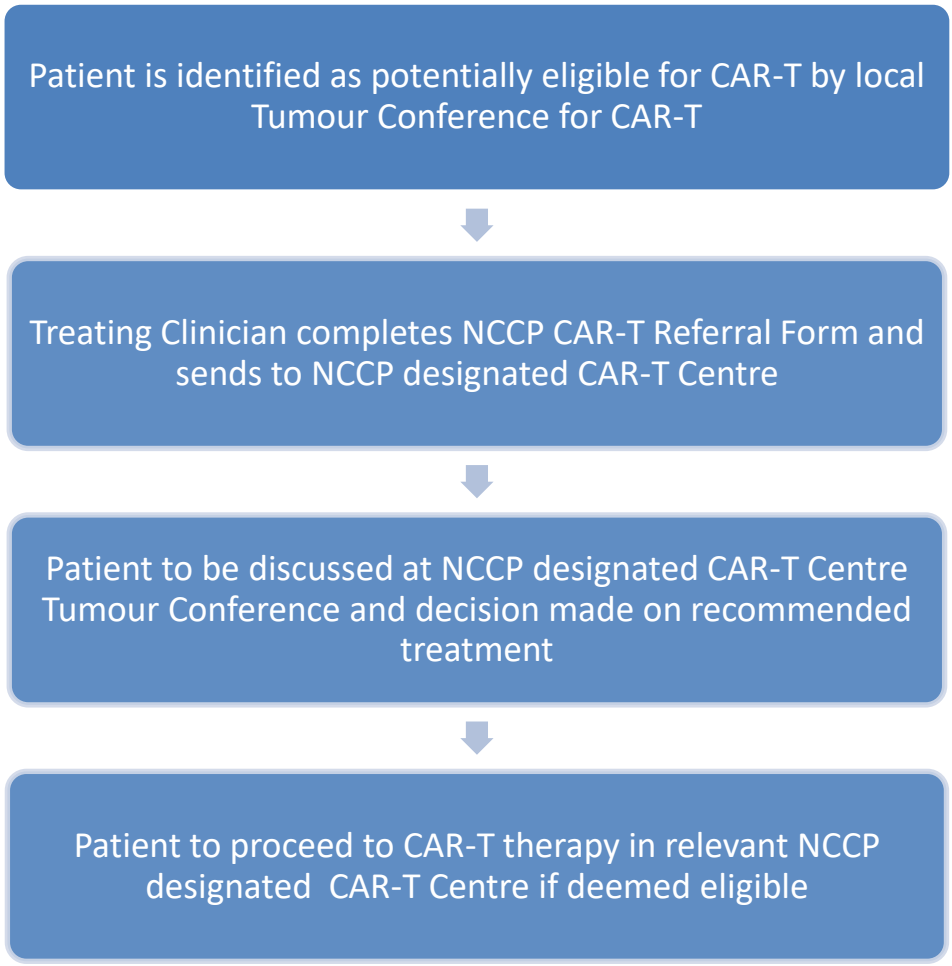
National CAR-T Adult Patient Referral Pathway for patients identified as potentially eligible for CAR-T outside of NCCP-designated CAR-T centres

	Patient Referral Pathway	Roles and Responsibilities	Clinician Responsible for patient's care
1.	Patient is identified as potentially eligible for CAR-T by local Tumour Conference* for CAR-T	Patient to be referred to NCCP designated CAR-T Centre Tumour Conference for discussion by treating clinician.	Treating clinician at patient's local hospital
2.	Treating Clinician completes NCCP CAR-T Referral Form and sends to relevant NCCP designated CAR-T Centre		Treating clinician at patient's local hospital
3.	Patient to be discussed at NCCP designated CAR-T Centre Tumour Conference and decision made on recommended treatment	CAR-T Centre Tumour Conference including the designated CAR-T Centre Lead Clinician and treating clinician, as appropriate, to consider patients and decide if patient is to progress for CAR-T	Treating clinician at patient's local hospital together with designated CAR-T Centre Lead Clinician
4.	Patient to proceed to CAR-T therapy in relevant NCCP designated CAR-T Centre if deemed eligible	CAR-T Centre to take over care of patient for duration of CAR-T therapy	Designated CAR-T Centre Lead Clinician in conjunction with treating clinician at patient's local hospital

** As appropriate to the disease (for example; lymphoma, leukaemia) and the local Tumour Conference referral processes.*

Note: *This pathway is not intended to disrupt existing referral pathways (e.g. transplant)*

Figure 1: National CAR-T Adult Patient Referral Pathway Flowchart



Appendix 3. CAR-T Toxicities and management (as reported by manufacturers)

Pease refer to individual SPCs for each CAR-T drug.

Appendix 4. Grading System for CRS

Please refer to local hospital SOPs.

Appendix 5. Grading system for ICANS

Please refer to local hospital SOPs.