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Welsh Health Specialised
Services Committee (WHSSC)

Specialised Services

Service Specification: CP176

Interim specification for the delivery of tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) therapy for the treatment of:

- **B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-stem cell transplant or in second or later relapse in patients up to 25 years of age**
- **Diffuse large B-cell lymphoma (DLBCL) that is relapsed or refractory (r/r) after two or more lines of systemic therapy in adults.**

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Statement

Welsh Health Specialised Services Committee (WHSSC) will commission an interim service specification for the delivery of tisagenlecleucel chimeric Antigen Receptor T Cell (CAR T) Therapy for the treatment of (i) B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-stem cell transplant or in second or later relapse in patients up to 25 years of age and (ii) Diffuse large B-cell lymphoma (DLBCL) that is relapsed or refractory (r/r) after two or more lines of systemic therapy in adults, in accordance with the criteria outlined in this document.

In creating this document WHSSC has reviewed the requirements and standards of care that are expected to deliver this service.

Disclaimer

WHSSC assumes that healthcare professionals will use their clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply this document.

This document may not be clinically appropriate for use in all situations and does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

WHSSC disclaims any responsibility for damages arising out of the use or non-use of this document.

1. Introduction

This policy has been developed as the Welsh Specialised Services Committee (WHSSC) interim service specification for the planning and delivery of tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) Therapy for the treatment of (i) B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-stem cell transplant or in second or later relapse in patients up to 25 years of age and (ii) Diffuse large B-cell lymphoma (DLBCL) that is relapsed or refractory (r/r) after two or more lines of systemic therapy in adults, for people resident in Wales. The license for this product in the treatment of ALL is up to 26th birthday on day of apheresis.

This service will only be commissioned by the Welsh Health Specialised Services Committee (WHSSC) and applies to residents of all seven Health Boards in Wales.

1.1 Background

CAR T is a new medicine manufactured from the patient's own cells and reinfused to treat certain types of cancer. Close post-infusion management is required to manage toxicities.

Clinicians experienced in allogeneic stem cell transplantation, immunotherapy and in treating these cancers are best placed to deliver the service and this new service is being developed by building on the requirements for allogeneic Blood and Marrow Transplantation (BMT).

Clinical practice in CAR T has developed in 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 therapy is another innovative anti-cancer treatment. The NHS 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.

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. Indications for 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

where the treatment is administered. Therefore this and other interim specifications will remain under regular review.

The specification relates to commissioned clinical care, not research or trial activity.

1.1.1 About the therapy

Chimeric antigen receptor (CAR) T cell therapy is a promising approach for the treatment of refractory malignancies, but is associated with unique acute toxicities that need specialised monitoring and management. Cytokine-release syndrome (CRS) and CAR T cell-related encephalopathy syndrome (CRES) 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-IL-6 therapy, and/or corticosteroids for severe cases are required to reduce the morbidity and mortality associated with CAR T cell therapy¹.

Tisagenlecleucel (CTL019) is a CD19-directed genetically modified autologous T cell immunotherapy comprised of autologous T cells that are genetically modified using a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signalling domains for 4-1BB (CD137) and CD3 zeta. CD19 is expressed on B cells from early development until differentiation into plasma cells but is not present on pluripotent blood stem cells and most normal tissues other than B cells.

According to the EPAR for Tisagenlecleucel, in ALL the most common non haematological adverse reactions were cytokine release syndrome (77%), infections (65%), hypogammaglobulinaemia (47%), pyrexia (40%) and decreased appetite (39%). In DLBCL, the most common non-haematological adverse reactions were cytokine release syndrome (58%), infections (54%), pyrexia (35%), diarrhoea (32%), nausea (29%), hypotension (26%) and fatigue (26%). Hypogammaglobulinaemia may require immunoglobulin replacement therapy.

The European licence for the product was granted in August 2018² and NICE have now published the following two technology appraisals:

¹ Neelapu SS et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018 Jan;15(1):47-62. doi: 10.1038/nrclinonc.2017.148. Epub 2017 Sep 19.

² <https://www.medicines.org.uk/emc/product/9456>

- [Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years](#). NICE Technology Appraisal Guidance (TA554), December 2018.
- [Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies](#). NICE Technology Guidance (TA567), March 2019.

There is also a corresponding WHSSC interim service specification for the delivery of axicabtagene ciloleucel Chimeric Antigen Receptor T Cell (CAR T) therapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma after two or more lines of systemic therapies currently in development:

- CP175, Axicabtagene ciloleucel Chimeric Antigen Receptor T Cell (CAR T) therapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma after two or more lines of systemic therapies³

1.1.2 Patient eligibility issues

Adult patients with DLBCL

The relevant issues in determining the potential number of adult patients eligible to receive tisagenlecleucel CAR T therapy are:

- 5130 new patients diagnosed with DLBCL in the UK each year⁴ of which 4361 are in England. The median age of patients with DLBCL at diagnosis is 70 years.
- In the updated analysis of the JULIET trial⁵ of tisagenlecleucel treatment in DLBCL, the median age of the 111 patients treated was 56 years with an age range of 22-76 years and 23% were 65 years old or older. This bias towards selecting younger patients for CAR T cell therapies in this study reflects the need for patients to be very fit for a treatment with potentially severe and acute AEs which are manageable by skilled trained staff.
- 20% of patients with DLBCL do not receive any active treatment. This figure comes from the Haematological Malignancy Research Network (HMRN)⁴ for 2007 and is incorporated in a health economic model developed by the HMRN in conjunction with York University⁶. This 20% figure remains valid in view of the opposing trends that are evident: increasing diagnoses of DLBCL made since 2007, particularly so in older people (who due to assessment of fitness are less likely to receive active treatment) and the ability of greater numbers of

³ [Welsh Health Specialised Services Committee \(WHSSC\) | Specialised Services Commissioning Policies and Service Specifications](#)

⁴ Haematological Malignancy Research Network - [HMRN - Start](#)

⁵ [Novartis JULIET trial of Kymriah demonstrates more than one-year durability of responses in adults with relapsed or refractory DLBCL | Novartis](#)

⁶ (Eur J Health Economics 2017; 18: 255-267).

patients to undergo chemotherapy in 2018 that is better tolerated/supported than in 2007.

- 5% of the total patients diagnosed will receive radiotherapy only.
- 75% of the total patients diagnosed with DLBCL will receive chemotherapy, this equating to 3270 patients.
- Not all of these 3270 patients will receive optimal 1st line chemotherapy but 2nd line chemotherapy is only likely to proceed in relapsed patients treated with optimal 1st line chemotherapy.
- The HMRN/York economic model⁴ indicated that in 2007, 11.2% of all DLBCL patients proceeded to have 2nd line chemotherapy, 3.2% with subsequent Haematopoietic Stem Cell Therapy (HSCT) and 8% without SCT. Most but not all of this 8% in 2007 will have had aggressive 2nd line chemotherapy. Changes in practice since 2007 mean that more patients remain disease-free with 1st line chemotherapy and 2nd line salvage therapy is better tolerated and supported. Thus it is reasonable to assume similar percentages in 2018 to those in 2007 i.e. 3.2% of all DLBCL patients still have 2nd line chemotherapy plus HSCT (142 patients) and 8% of all patients have 2nd line chemotherapy without HSCT (349 patients).
- Of the 142 patients that have 2nd line chemotherapy and HSCT, approximately one quarter will remain disease-free. This therefore means that about 100 patients will relapse, often with very aggressive disease. Nevertheless, as these patients started 2nd line treatment as a fit group of patients, it is reasonable to assume that about 30-40 patients will subsequently be eligible for tisagenlecleucel.
- Of the 349 patients that receive 2nd line chemotherapy without HSCT, most will fail and a large proportion will be unfit for CAR T therapy either as a consequence of disease progression or because they lack the fitness required for CAR T therapy (see the trial selection criteria⁷). It is important to note that DLBCL that has progressed after 2 lines of therapy is often rapidly growing and thus can cause a steep and rapid decline in a patient's performance status and therefore contra-indicate CAR T therapy. This makes the likely number of eligible fit patients with relapsed DLBCL who have not had HSCT to be about a third of those that had 2nd line chemotherapy – 110-120 patients.
- In the axicabtagene ciloleucel study, 21% of patients had previously had HSCT. Thus the proportional estimate of patients eligible for CAR T therapy post HSCT in England (about 30-40 of such patients) is in broad accordance with the 110- 120 patients estimated to have not had HSCT.
- In total, NHS England estimates that approximately 135-150 patients with relapsed/refractory DLBCL will be eligible for tisagenlecleucel. This equates to approximately 7-8 eligible patients per year in Wales.

⁷ [Study of Efficacy and Safety of CTL019 in Adult DLBCL Patients - Full Text View - ClinicalTrials.gov](#)

However this may be an underestimate and the final figure may be closer to 15 patients per year once the NICE TA guidance⁸ has been fully tested.

- The numbers of children and teenagers with relapsed/refractory DLBCL will almost all be post HSCT and the number estimated to be potentially eligible in the event that off label CAR T cell therapy in future is permitted is 5-10, or 1 every 2-3 years in Wales.

Children and young people with ALL

Expert clinical opinion of the numbers of patients aged 1-24 years with B ALL who would fit the eligibility criteria for this product was sought. Based on data from current and previous national ALL trials⁹ for patients aged 1-24 years and activity of the national paediatric leukaemia MDT at which relapsed/refractory ALL patients are discussed, together with wider clinical opinion, it is estimated that there will be between 15-30 patients per year. This equates to approximately 1 patient per year in Wales, although there may be some years where 2-3 patients may be eligible.

In total, it is estimated that there will be about 150-180 patients per year eligible for treatment with tisagenlecleucel within its licensed indication, with approximately 7-9 eligible patients in Wales. There would be 5-10 children or teenagers who have diseases with similar biology to adults and who could also benefit from CAR T therapy in the event that off label use is available in future, with 1 patient every 2-3 years in Wales. At present, there is no data to support this use and it is not licenced for such use.

1.2 Aims and objectives

The aim of this service specification is to define the requirements and standard of care essential to deliver tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) therapy for the treatment of (i) B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-stem cell transplant or in second or later relapse in patients up to 25 years of age and (ii) Diffuse large B-cell lymphoma (DLBCL) that is relapsed or refractory (r/r) after two or more lines of systemic therapy in adults.

The objectives of this policy are to:

- detail the specifications required to deliver tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) therapy services for people who are resident in Wales
- ensure minimum standards of care are met for the use of tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) therapy

⁸ [Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years | Guidance and guidelines | NICE](#)

⁹ UKALL2003, UKALL2011 [AllTrials](#)

- ensure equitable access to tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) therapy
- identify centres that are able to provide tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) therapy for Welsh patients
- improve outcomes for people accessing tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) therapy services.

1.3 Relationship with other documents

This document should be read in conjunction with the following documents:

- **WHHSC Service Specification**
 - CP175, axicabtagene ciloleucel Chimeric Antigen Receptor T Cell (CAR T) therapy for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma after two or more lines of systemic therapies¹⁰.
- **NICE Technology Appraisals**
 - [Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years](#). NICE Technology Appraisal Guidance (TA554), December 2018.
 - [Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies](#). NICE Technology Appraisal Guidance (TA559), January 2019.
 - [Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies](#). NICE Technology Guidance TA567, March 2019
- **NHS Wales**
 - All Wales Policy: [Making Decisions in Individual Patient Funding requests](#) (IPFR).

1.4 Evidence

- **NICE Guideline**, Haematological cancers: improving outcomes, NG47. May 2016. <https://www.nice.org.uk/guidance/ng47>
- **The Joint Accreditation Committee (JACIE)** www.JACIE.org
- **European Society for Blood and Marrow Transplantation (EBMT)** <https://www.ebmt.org/Contents/Pages/Default.aspx>

¹⁰ [Welsh Health Specialised Services Committee \(WHSSC\) | Specialised Services Commissioning Policies and Service Specifications](#)

- **British Society of Blood and Marrow Transplantation (BSBMT)** <http://www.bsbmt.org/>

2. Service Delivery

The Welsh Health Specialised Services Committee will commission tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) therapy within its licensed indication¹¹ and in-line with the criteria identified in this service specification.

CAR T therapy is novel with remaining uncertainties about outcomes and complications. Therefore in the first instance there will be a phased approach to commissioning across the UK focused on beginning access at a small number of geographically spread JACIE accredited providers of haematopoietic stem cell transplantation (HSCT) who gain accreditation for Immune Effector Cell (IEC) therapy.

Accreditation and site qualification for the delivery of CAR T therapy must also be sought from Novartis in order to deliver this treatment. It is anticipated that Wales will have one centre based at the University Hospital of Wales that will be able to deliver this service.

The number of providers will increase as demand and capacity requires but is unlikely to be comparable with the number of commissioned allogeneic transplant centres due to the need to concentrate expertise in management at least in the early years of access. WHSSC will ensure that all eligible Welsh patients are appropriately referred to an accredited centre which may mean being treated in an NHS England hospital (see below). Full details of all NHS England providers can be found on their website¹².

NHS England have established two UK-wide CAR T Clinical Panels for the delivery of these treatments. Each Panel will prioritise access to accredited centres while capacity builds across the country. The Panels will be reviewing eligible patients to ensure they meet the clinical criteria as specified by the marketing authorisation and NICE as well as prioritising patients. Prioritisation of patients will be particularly important as providers' ramp up capacity across the UK. The Panels will be clinically led, with patient and public voice representation. Decisions will be made based on unanimous consent of the clinical and provider members. NHS Wales will refer all eligible patients to the UK-wide CAR T Clinical Panels in line with the access criteria described in this service specification. NHS Wales will also have a clinical representative on each Panel.

2.1 Access criteria

2.1.1 Population

This specification covers all ages, in line with the licence for the product.

¹¹ [Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years | Guidance and guidelines | NICE](#)

¹² <https://www.england.nhs.uk/cancer/cdf/car-t-therapy/>

2.1.2 Population needs

This is an innovative technology which will require phased implementation over the first 18-24 months. During the period that capacity is built, eligible patients may need to be prioritised and this priority will be determined by the UK-wide CAR T cell panels. Once full capacity is achieved, it is expected that all eligible patients will be treated

2.1.3 Expected significant future demographic changes

None as the specification has considered geographic distribution of centres administering CAR T therapy.

2.1.4 Decision to treat

Clinicians currently treating patients in the indicated population will consider their patient's eligibility for the treatment. At this stage they will:

- identify eligible patients who might benefit from CAR T therapy
- confirm patient eligibility in line with the manufacturer's licence with regard to age, fitness, disease and treatment stage
- confirm that patients have been informed and understand the potential benefits, risks and complications of treatment as part of shared decision- making
- refer such patients in line with agreed pathways (to be developed/provided separately) to the CAR T provider specialist Multi-Disciplinary Team (MDT) and then to the disease specific UK-wide national CAR T panel
- The UK-wide national CAR T panel is expected to meet weekly.

The UK-wide national CAR T panel will ensure that patients referred do meet the eligibility criteria, taking an overview of capacity planning and scheduling, and undertaking audit to ensure equity of access as well as outcomes.

Clinical decision making about individual patient treatment (assessment prior to treatment preparation, initiation and complications management) will be made by specialist MDTs operating at CAR T providers (and in the initial phase, with support from the disease specific national UK-wide CAR T MDT – see below). MDTs must operate in line with NICE IOG recommendations for MDTs¹³.

The primary clinicians overseeing the planned CAR T pathway will include transplant physicians/immunotherapy leads, including haematologists and haemato-oncologists. Other named specialists for pharmacy, critical care, neurology support and nursing will be part of the MDT available 24/7 to manage the planned and unplanned needs of CAR T patients. Psychology

¹³ [Haematological cancers: improving outcomes | Guidance and guidelines | NICE](#)

input into the MDT will also be required given the nature of the treatment, the need for high levels of patient awareness of symptoms and the side effects profile.

2.1.5 MDT role

The role of the provider centre MDTs will be to:

- identify eligible patients from their own and neighbouring Health Boards who may benefit for CAR T therapy in accordance with the criteria implemented by the national UK-wide CAR T panel. Referral to the national UK-wide CAR T panel would occur at this point. Once approved, the centre MDT would also do the following:
 - 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 and that psychological support is available. This should take place before the patient is referred to the national UK-wide CAR T panel
 - assess individual patients prior to treatment preparation and initiation. This should take place before the patient is referred to the national UK-wide CAR T panel
 - manage the treatment, post treatment management and follow up in line with the approved and accredited SOP
 - undertake reporting, data analysis and audit – this may include engagement with manufacturers as required
 - review cases 3 and 12 months after treatment from a learning perspective and feed results into audit/service evaluation and national learning processes
 - ensuring appropriate patient monitoring post treatment both within Wales and across the UK.

CAR T provider MDTs will demonstrate governance arrangements which meet the requirements for robust and effective quality management systems from a company accreditation, JACIE IEC therapy accreditation and NICE IOG perspective.

2.1.6 Requirements for a national MDT for patient selection

At the beginning of the phased implementation of the treatment, it may be necessary to have structures in place, such as a national UK-wide CAR T panel, to ensure selection of patients is not restricted to those patients treated at selected CAR T providers, but that equity of access is applied in considering all eligible, fit patients who are most able to benefit. Scheduling of patients will be required given that medicine manufacture can take about 1 month and clinical services will likely start by treating 1 patient per month expanding potentially to 1 per week over a period of time, based on the US experience. It is possible that depending on the number of providers deemed ready to provide CAR T that such arrangements may be in place for a limited period.

At the national level, this would mean establishing a newly adopted infrastructure. There is currently a national MDT for paediatric and TYA patients with ALL but no equivalent national MDT for patients with DLBCL.

The role of the site specific national UK-wide CAR T panel will be to:

- Produce, agree and implement criteria for patient selection for each: indication and prioritisation for this and other licenced and approved CAR T products and processes for receiving and prioritising referrals.
- Confirm patient eligibility in line with the manufacturer's licence and the trials on which the licence is based with regard to age (adult or paediatric population), fitness, disease and treatment stage, including direct review of tissue and radiological diagnostics and staging and fitness for treatment.
- Prioritise patients for treatment based on assessment of information regarding patient fitness, patient disease severity and available capacity.
- Provide expert advice for the management of complex cases.
- Work closely with UK JACIE to ensure compliance with relevant standards and the EBMT/BSBMT registries to support data submission for long term outcomes analysis.
- Provide a forum for learning, sharing experience, audit/service evaluation and research, which will support the expansion of CAR T centres over time.

The core members of a national UK-wide CAR T panel will also be in line with NICE IOG guidance¹⁴. Named representation covering adults and paediatrics and including deputising arrangements will be required. Membership will support delivery of the functions and therefore include:

- Independent clinical member (not a CAR T provider)
- Named clinical lead and deputy from each commissioned CAR T provider (Haematologists or other specialists meeting FACT-JACIE standards for BMT clinical programme director and/or physicians with tertiary level experience in the disease/age group).

Depending on experience over time, volume and geographical considerations the structures for patient selection, scheduling and audit may change. These structures would need to remain under review. Further information about the operation of the national UK-wide CAR T panel, provider MDTs and referral pathways will be produced.

¹⁴ [Haematological cancers: improving outcomes | Guidance and guidelines | NICE](#)

2.1.7 Initial Admission

Before administration of CAR T cells, patients are likely to require lympho-depleting chemotherapy (which should complete 2-14 days before infusion) and require an inpatient admission. Following infusion, patients are likely to remain as an inpatient for approximately 10 days (although this may be longer in some cases) and if the patient is stable, they can be discharged thereafter. If patients have low disease burden, patients may be discharged earlier on an individual basis. Following discharge from inpatient care, patients should then remain within about a 1 hour drive time of the administering unit for at least four weeks post infusion (note, company requirements are 2 hours). Adhering to these arrangements for safe clinical management can represent a significant burden for patients and their families. CAR T providers must ensure that patients and families are supported to secure the most appropriate arrangements to meet this. This may include signposting to forms of support including charities and benefits. For this period, principles of ambulatory care can be applied, as per the recommendations for ambulatory care for high intensity chemotherapy NICE Improving Outcomes Guidance for Haematological Cancer¹⁵.

A supportive care protocol for CAR T treatment in the US has been produced and published by Neelapu, et al.,¹⁶. Whilst this is pertinent to treatment in the US, in the absence of any other protocol, the clinical consensus is that this provides important contextual information on clinical presentations to help establish management of CAR T therapy patients in the UK. However it is not the case that all the investigations listed are mandated or commissioned in NHS Wales. In some cases, the treatments are not routinely commissioned e.g. baseline brain MRI or siltuximab.

Providers must note that this specification and the associated published NICE guidance sets out the commissioned position for NHS Wales. Treatments and interventions not included in these documents will not be supported or funded.

Where it relates to the regulatory requirements of the procurement, manufacture, storage and delivery of the product, the company requirements must be followed. In some cases, clinical consensus regarding the clinical management of the patient prior, during and after treatment and in relation to the management of toxicities may differ from the companies perspective and may be more stringent than those required by the company. These must be followed.

¹⁵ [Haematological cancers: improving outcomes | Guidance and guidelines | NICE](#)

¹⁶ [Neelapu SS](#) et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018 Jan; 15(1): 47-62. doi: 10.1038/nrclinonc.2017.148. Epub 2017 Sep 19

2.1.8 Product preparation/Manufacture

Please see commercially confidential Appendix C to be included in the contract of commissioned providers only.

2.1.9 Product delivery to patient

Receipt of the CAR T product will be by Pharmacy (Chief Pharmacist) or Pharmacy approved location (for example, in Cardiff this will be at the Stem Cell Processing Unit) and recorded in line with regulatory requirements.

The commissioned provider will follow the instructions for preparation of the product for infusion in accordance with manufacturer quality assurance (see below and Appendix C). Care provided will be in accordance with the SOP and JACIE 6.01 (or later) edition standards for IEC therapy delivery.

All staff involved in handling the tisagenlecleucel CAR-T product will be appropriately trained in the following areas and confirmation will be required:

- apheresis
- cell collection/processing
- handling and storage
- process
- product, administration and safety.

Tisagenlecleucel CAR T can only be administered in a certified clinical setting. 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. The product may be stored at the hospital in the vapour phase of liquid nitrogen until the patient is ready to receive the infusion. The hospital needs to confirm the patient identity and match the correct product at the time of treatment. If the patient is ready and has been conditioned as required, then the product is then transferred to the preparation area and is thawed according to manufacturer instructions. The member of staff has to be able to trace the product throughout the process.

The product is infused into the patient as per package instructions and by a trained member of staff. CAR-T therapy should be initiated under the direction of and supervised by physicians experienced in the treatment of haematological malignancies. In summary, the product must be prepared and delivered and patients monitored in line with the Summary of Product Characteristics (SMPC) and the company specific requirements about which all authorised providers must complete training and follow specific instructions provided.

The company requirements are that the patient must be monitored for at least 10 days at a certified clinical facility following infusion for signs and

symptoms of cytokine release syndrome (CRS) and neurologic toxicities (NT). The licence requires that patients should be instructed to remain within 2 hours travelling distance of a certified clinical facility for at least 4 weeks following infusion. Patients should be issued with relevant patient information to alert them to side effects and guide their action to seek medical attention.

In the initial phase, a more cautious approach to treatment will be undertaken with clinical opinion recommending patients remain within approximately 1 hour of the CAR T cell therapy centre and it is recommended this remains under review in the initial implementation phase. Providers must support patients and their families during this phase and ensure accurate and complete contact information is provided.

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 A and B to inform decision making with regard to ITU admission (grade 2 and above).

2.1.10 Management of Cytokine Release Syndrome (CRS)

Frequent daily monitoring is required at commissioned CAR T providers during the inpatient stay for at least 10 days for signs of CRS and for signs and symptoms of CRS for 4 weeks after infusion. The company will provide a Risk Management Programme with training and materials to be provided. Patients and their carers should be counselled to seek immediate attention should the signs or symptoms occur. CRS grading and action is set out in Appendix A and also further information from the company in Appendix C.

Cytokine Release Syndrome is a form of Systemic Inflammatory Response Syndrome and is characterised by elevated circulating levels of several cytokines, including interleukin IL-6. This side effect may occur with all CAR T products.

The product licence requires a grading system be used for assessment/description of CRS. Risk Management Plan materials are provided.

The purpose of using a grading system is to guide critical care management, which largely consists of supportive measures to reduce likelihood of further organ dysfunction/failure whilst recovery occurs and to determine timing of rescue therapy. There are 2 systems for grading CRS, National Cancer Institute Consensus criteria (Lee et al¹⁷) and the University of Pennsylvania (UPENN/CHOP¹⁸), with the main difference being in grades

¹⁷ [ASBMT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells - Biology of Blood and Marrow Transplantation](#)

¹⁸ [Cytokine Release Syndrome \(CRS\) after Chimeric Antigen Receptor \(CAR\) T Cell Therapy for Relapsed/Refractory \(R/R\) CLL | Blood Journal](#)

2 and 3 categories. Whilst the licence refers to the use of UPENN, the Lee system permits greater descriptors for grades 2 and 3 which are relevant for critical care management of adults and paediatric patients and therefore use of the Lee system is recommended by commissioned CAR T therapy providers (see Appendix A).

CAR T cell toxicities are familiar to those experienced in the delivery of allogeneic stem cell transplantation and immunotherapy although on a much smaller scale. These specialists, together with critical care and neurology specialists, are experienced in identifying immunologically-mediated toxicities early, to intervene in a timely manner and thus increasing the likelihood of managing side effects effectively.

2.1.11 Supportive drugs

Access to supportive treatments as set out in the SPC will require pharmacy facilities, expertise and capacity. Provision of immunoglobulin will be required for the management of CAR T complications. This is categorised as a blue indication and will need to be assessed through the Immunoglobulin Assessment Panel.

At least 4 doses of tocilizumab per patient must be available prior to infusion. The regulatory requirements for access to tocilizumab as part of CAR T therapy will be specified by the CAR T manufacturer. Further information will be included in the British National Formulary (BNF). In the US experience siltuximab has also been used in these patients.

2.1.12 Management of Neurologic Sequelae

Frequent daily monitoring is required at commissioned CAR T providers during the inpatient stay for at least 10 days for signs of CRS and for signs and symptoms neurologic toxicities for 4 weeks after infusion. Patients and their carers should be counselled to seek immediate attention should the signs or symptoms occur. CRES and U Penn grading and action is set out in Appendix B1 and B2 and further information from the company in Appendix C.

Neurotoxicity has been defined as CAR T cell related encephalopathy syndrome (CRES). Prevalence of encephalopathy varies and it is not possible to directly compare, for example, prevalence in DLBCL with B-cell ALL (34% in DLBCL Neelapu¹⁹ and 11% in ALL as per Maude et al²⁰). It can occur concurrently with or after CRS. Its pathophysiology remains incompletely understood, with possible roles for passive diffusion of cytokines into the brain and trafficking of T cells into the CNS. CSF protein levels are often increased compared with baseline measurements,

¹⁹ [Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. - PubMed - NCBI](#)

²⁰ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4119809/pdf/nihms607703.pdf>

suggesting disruption of the blood-brain barrier (BBB). Liver and kidney dysfunction as well as hypoxemia and infection can also contribute to the encephalopathy.

A CAR T cell therapy associated Toxicity (CARTOX) Working Group in the US has provided recommendations for monitoring, grading, and managing acute toxicities that can occur in patients treated with CAR T therapy²¹.

CRES typically manifests as a toxic encephalopathy, with the earliest signs typically including diminished attention, language disturbance, and impaired handwriting.

Other symptoms and signs include confusion, disorientation, agitation, aphasia, somnolence and tremor.

A grading system of CRES severity must be used. One example is the CARTOX 10-point neurologic assessment (CARTOX-10) tool²² (validated in adults, not validated in children) in which one point is assigned for each of the following tasks that is performed correctly: orientation to year, month, city, hospital, and Prime Minister of country of residence (total of 5 points), naming three objects (maximum of 3 points), writing a standard sentence (1 point), counting backwards from 100 in tens (1 point). Normal cognitive function is defined by an overall score of 10. The score can be used to define Grade 1 (CARTOX-10 score 7-9, mild impairment), Grade 2 (score 3-6, moderate impairment), Grade 3 (score 0-2, severe impairment), and Grade 4 CRES (patient in critical condition, and/or obtunded and cannot perform assessment tasks). From an equalities perspective, it is important to note that patients may not have English as a first language or may have cognition issues related to age or disability which need to be taken into account when using such tools.

Other parameters of CRES severity include raised intracranial pressure (stage 1-2 papilloedema or CSF opening pressure up to 27 cm H₂O in CRES Grade 3, stage 3-5 papilloedema or CSF opening pressure >27 cm H₂O or brain oedema in CRES grade 4), and seizures or motor weakness (partial seizure, or non-convulsive seizures on EEG with response to benzodiazepine in CRES Grade 3, generalised seizures, or convulsive or non-convulsive status epilepticus, or new motor weakness in CRES Grade 4).

Median onset time to CRES is 5 days (although this ranges 1-17 days) dependent on disease indication. It has been observed that clinical manifestation is often biphasic, with a first phase occurring concurrently

²¹ [Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. - PubMed - NCBI](#)

²² [Chimeric antigen receptor T-cell therapy — assessment and management of toxicities | Nature Reviews Clinical Oncology](#)

with high fever and other CRS symptoms, typically within the first 5 days after cell infusion, whereas a second phase occurs after the fever and other CRS symptoms subside, often beyond 5 days after infusion. However, delayed neurotoxicity has been observed in up to 10% of patients, with seizures or confusion occurring during the third or fourth week after CAR T therapy. Anti-IL6/IL-6R therapy has been reported to reverse CRES during the first phase, whereas corticosteroids are the preferred treatment for the second phase, possibly due to higher BBB permeability during the first phase enabling better diffusion of the therapeutic monoclonal into the CNS.

For tisagenlecleucel, the majority of neurological events occurred within 8 weeks following infusion and were transient. The median time to onset of neurological events was 7 days in ALL and DLBCL. The median time to resolution was 7 days for ALL and 12 days for DLBCL.

Other causes of neurologic symptoms should always be considered. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with ECG. Unhindered access to Critical Care should be available for severe or life threatening neurologic toxicities.

The typical duration of CRES can vary between a few hours to weeks. Rapid fluctuations in severity are possible and require close patient monitoring.

In patients with CRES, secondary cortical irritation is indicated by EEG findings of epileptiform discharges or non-convulsive electrographic seizures. The most common EEG findings are diffuse generalised slowing in keeping with encephalopathy, with or without triphasic waves at 1-2 Hz.

Treatment (anti-epileptics) should be administered as per British National Formulary (BNF).

2.2 Service description

In addition to the standards required within the Contract, specific quality standards and measures will be expected. The provider must also meet the standards as set out below.

2.2.1 Staffing

The primary clinicians for the delivery of this CAR T therapy (a cell infusion procedure) will be undertaken by consultants (haematologists/haemato-oncologists) and their teams with appropriate training and competency in DLBCL or ALL, immunotherapy and allogeneic HSCT according to quality managed policies and procedures. Support from medical oncology (immunotherapy / lymphoma) will be essential. In future and in relation to other CAR T therapies in other indications, the role of other clinicians in the delivery of treatment may evolve.

The core CAR T Team which will also include:

- immunotherapy
- ITU
- nursing
- psychology
- pharmacy
- laboratory.

The extended team would include as required:

- neuro-physiology
- neuromedicine +/-neurosurgery
- cardiology
- renal.

2.2.2 Providers

Commissioned providers will need to:

- evidence accreditation to JACIE standards for IEC therapy
- evidence previous experience of CAR T and other IEC therapy
- evidence effective implementation of standard operating procedures and risk management arrangements for successfully providing CAR T therapy and treating all complications including those that are severe and life-threatening
- evidence experience of managing serious toxicities associated with therapies such as CAR T therapy e.g. complex immunotherapy and allogeneic transplantation.

All necessary regulatory approvals and company accreditation are also pre-requisites for consideration for commissioning. This will include evidence of MHRA Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP).

This specification will be reviewed annually or at earlier intervals as service experience and patient need requires.

Training, competencies, policies and procedures are defined in the current FACT-JACIE standards (the 6.01 and 7th editions include IEC therapy standards). Commissioned providers must maintain full active JACIE accreditation and certification. JACIE reaccreditation occurs every four years.

The JACIE website provides two lists of providers and their accreditation status, updated monthly. List one includes those with valid accreditation (not yet expired). The second list includes those who have formally requested reaccreditation (applied, awaiting inspection, inspected awaiting report or in corrections phase). As the second makes no assessment of the centres' compliance with Standards, commissioners will seek evidence from

both the Health Board and JACIE to establish the circumstances of those awaiting reaccreditation.

The selected providers will need to demonstrate age appropriate disease specific expertise and immunotherapy experience, a level of training and competency in treating patients with the toxicities associated with the treatment (e.g. multi-organ failure managed in ITU and immediate access to neurological diagnostic and management interventions which are matched to the neurological toxicity profile associated with CAR T therapy).

Over time a number of commissioned CAR T therapy centres will be established across the UK. In order to develop that expertise, providers will be commissioned on the expectation that they will deliver all relevant CAR T therapy products which are licenced and approved. For example, where CAR T therapy products cover a similar patient group, providers 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.

All children and young people receiving CAR T cell therapy must be treated within designated CYP providers with full access to age-appropriate care as defined in the NHS Wales, National Standards for Teenagers and Young Adults with Cancer, aged 16-25 years²³. Commissioned providers for individual CAR T cell products will ensure that CYP will have access to CAR T cell products for which they are eligible.

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 those with JACIE accreditation for allogeneic HSCT and for all standards relating to IEC therapy. 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 interim specification.

2.2.3 Finance/Reimbursement

Managed entry agreements or managed access agreements may be developed between the manufacturer and NHS Wales with regard to the cost of the medicinal product and NHS Wales must ensure it also receives the same or similar agreements as recommended in the New Treatment Fund.

²³ http://www.wales.nhs.uk/sites3/Documents/322/Teenagers_and_Young_Adults_Cancer_Standards_-_Final_-_English.pdf

Approaches to reimbursement for service delivery are in development. It is anticipated that the pricing for allogeneic transplant will form the basis of the service reimbursement, with some uplifts to account for the additional MDT arrangements and treatment complexity in the initial implementation phase. Provider costing information will be required to be collected and submitted to commissioners to improve the approach to reimbursement for service costs as experience with CAR T improves. Bespoke activity reporting will be used.

The specification will remain under review as the CAR T therapy product pipeline develops.

Specialised allogeneic haematopoietic stem cell transplantation (HSCT) services are commissioned 30 days prior to and 100 days after transplant, after which commissioning responsibility returns to Health Boards. It is expected that in the first instance the same approach will be applied.

2.3 Interdependencies with other services or providers

All commissioned CAR T providers must 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 key requirements (2.3.1 to 2.3.7):

2.3.1 Regulatory

Compliance with Human Tissue Authority²⁴ (HTA) (for product procurement), JACIE - FACT HSCT standards²⁵ and Medicines and Healthcare Regulatory Agency (MHRA) standards²⁶.

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 relevant to CAR T. The Human Tissue Authority (HTA) in the UK and HPRA in Ireland are the Competent Authorities responsible for regulating TE registration.

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

2.3.2 JACIE accreditation

JACIE accreditation as a collection, storage and clinical centre for allogeneic transplantation. JACIE accreditation should be age appropriate i.e. cover

²⁴ [Find out what the HTA can do for you | Human Tissue Authority](#)

²⁵ <https://www.ebmt.org/sites/default/files/2018-06/FACT-JACIE%207th%20Edition%20Standards.pdf>

²⁶ [Welcome to our new MHRA website - GOV.UK](#)

paediatrics. 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 via a JACIE compliant 3rd party sub contracted arrangement.

2.3.3 Pharmacy

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. Pharmacy will need to collaborate with local experts e.g. stem cell laboratory colleagues, or third party colleagues, e.g. NHSBT to ensure that optimal arrangements are in place for the implementation site.

A facility (e.g. pharmacy/cell therapy laboratory) capable of receipt of the products with regard to suitable vapour phase liquid nitrogen Dewars and space for storage. Prolonged storage will require facilities capable of <-150 degrees centigrade temperature monitoring and 24 hour alarm system. This means having the required capacity, technology and expertise for handling, storage and non-manufacturing preparation steps of advanced therapy medicinal products (ATMPs) in line with MHRA GMP and GCP requirement. (Manufacturer QA process is set out in commercially confidential Appendix C).

Where the facility maybe part of a different organisation or hospital department, the local site Pharmacy are responsible for ensuring appropriate supplier approval assurances and technical agreements detailing the roles of both parties and ongoing monitoring are in place.

2.3.4 Specialist MDT for clinical management

An MDT led by the haematologist or equivalent specialist who meets JACIE standards for training and competency in allogeneic BMT and IEC therapy (including the ability to deal with safety issues such as CRS, TLS, GVHD and neurotoxicity), immunotherapy, disease specialist, critical care staff, nursing and a clinical pharmacist with ATMP knowledge. This MDT must have named members and clear agreements in place and operate in accordance with criteria set by the UK-wide CAR T therapy MDT for the appropriate selection of patients and management of complications.

The clinical team to include a role similar to a HSCT coordinator with sufficient seniority to negotiate and manage the significant logistical issues and interfaces involved in effective scheduling of cell procurement, product manufacture, storage and preparation, treatment delivery and clinical patient management.

Procedures for the appropriate clinical monitoring of patients immediately following CAR T therapy using Early Warning Scores (EWS) and minimum

of 4-hourly observations. Patients who develop grade 1 symptoms and signs should have monitoring escalated according to their EWS and admission to Critical Care should follow as indicated (Grade 2 and above).

Immediate access to specialised diagnostic services for assessment of potential complications is required. Electroencephalogram (EEG) must be available, with interpretation available during the working day of the working week. For grade 1 CRES, management will involve daily 30min EEG until toxicity symptoms resolve. For higher grades (i.e. worse encephalopathy) patients should be on ITU with neurological assessment including use of regular standard EEGs (up to daily) or other treatment as indicated. Co-location with neurosurgery is preferred but not a mandatory requirement. An evidenced referral pathway for neurosurgical input required.

Infrastructure for ambulatory care and rapid re-admission supported by Standard Operating Procedures (SOPs) must be in place as per NICE guidance²⁷ to safeguard patients in the 3-4 weeks following discharge from in-patient care. As patients may not recognise the onset of encephalopathy on their own, 24-hour availability of a carer is mandatory. Provision of appropriate patient and carer information is required.

2.3.5 Management of toxicities and critical care

Requirements:

- On-site critical care
- Age appropriate critical care which meets the NHS Wales service specification
- Capability to deliver the critical care needs of all CAR T patients at all times including those with the most serious side effects (e.g. level 3).

Risk management plans and documented evidence of experience in managing the types of toxicities associated with CAR T will be required e.g. sustained and frequent experience in the management of multi-organ failure. CAR T cell centres will need immediate and 24/7 access to a wide range of support specialists in intensive, renal, respiratory, cardiovascular and neurological medicine.

For cardiac support, echocardiography should be immediately available along with either cardiac monitoring by telemetry, or continuous ECG monitoring and pulse oximetry monitoring if patients develop CRS symptoms of grade 2 or above. This should be continued until cytokine-release syndrome (CRS) resolves, in order to detect arrhythmias.

There should be clear pathways, policies and SOPs in place for the diagnosis and management of complications and treatments.

²⁷ [Haematological cancers: improving outcomes | Guidance and guidelines | NICE](#)

The ICU facilities should be age-appropriate and should comply with either or both the draft service specification for adult critical care or Paediatric Critical Care service specification (5th edition PICS standards 2015)²⁸.

The ICU should have sufficient capacity to receive recipients of CAR T therapy and be able to demonstrate how that capacity is maintained throughout the year including at times of winter pressures.

2.3.6 Training

Completed all training for all staff as required by the regulators, the company and JACIE.

2.3.7 Patient/data registry

A written agreement is required to submit to or provide access for NHS Wales and WHSSC the long term follow-up data required by safety registries and a clear outline for how they will ensure the accuracy and sustainability of this data collection.

The Committee for Medicinal Products for Human Use (CHMP)²⁹ issued a draft opinion in July 2018 stating it considers that 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 draft opinion goes on to stipulate in detail the scope of the studies that may be performed based on the registry³⁰.

EBMT already have forms and data collection covering cell therapy including CAR T (Cell Therapy – MED-A). Wales already subscribes data to EBMT via BSBMT. Utilising an established and credible existing registry will ensure good quality data and access. There may be additional requirements to be added to Cell Therapy MED-A depending on regulatory requirements.

2.4 Acceptance Criteria

The service outlined in this specification is for patients ordinarily resident in Wales, or otherwise the commissioning responsibility of the NHS in Wales. This excludes patients who whilst resident in Wales, are registered with a GP practice in England, but includes patients resident in England who are registered with a GP Practice in Wales.

²⁸ <http://picsociety.uk/news/new-pics-standards-2016-now-available/>

²⁹ [Committee for Medicinal Products for Human Use \(CHMP\) | European Medicines Agency](#)

³⁰ [EMA draft qualification opinion on the EBMT cellular therapy registry for public consultation](#)

2.5 Care Pathway (Annex i)

Relapsed refractory DLBCL (diffuse large B cell lymphoma)

Chemo-immunotherapy remains the cornerstone of treatment for patients with DLBCL. If patients are to receive optimal therapy, they have to be medically fit to receive combination chemotherapy (cyclophosphamide, vincristine, doxorubicin and prednisolone) given in conjunction with rituximab. Such patients have a 70-80% chance of remaining free of disease progression.

Patients who relapse usually do so within the first 2 years after completing treatment and if fit for optimal (but toxic) chemo-immunotherapy have a low chance of remaining free of disease progression if just treated with conventional doses of chemotherapy. Patients who respond to 2nd line chemotherapy and who are sufficiently medically fit will usually be offered high dose chemotherapy and HSCT. Such consolidation of a response to 2nd line chemotherapy with HSCT is considered to be part of 2nd line chemotherapy. If not salvaged by 2nd line chemotherapy with or without HSCT, life expectancy is short and usually measured in terms of single numbers of months.

Salvage chemotherapy in DLBCL with new agents (e.g. B cell pathway inhibitors, checkpoint inhibitors, inotuzumab) have been disappointing and hence for relapsed/refractory DLBCL after 2 lines of chemotherapy, CAR T therapy is a novel and potentially efficacious treatment to improve outcomes in DLBCL.

Small numbers of children and teenagers are also diagnosed with DLBCL and a few of these will have relapsed/refractory disease after 2nd line therapy. These patients could benefit from CAR T therapy in the event that off label use is permitted in future.

B-cell acute lymphoblastic leukaemia (ALL) including refractory, in relapse post-stem cell transplant or in second or later relapse

According to the Children's Cancer and Leukaemia Group (CCLG)³¹ there are about 300 new cases of ALL each year. The aim of treatment is to destroy leukaemia cells and restore normal bone marrow function.

Chemotherapy is the main treatment for ALL. Induction therapy starts within days of diagnosis and continues for 4-6 weeks. Remission and prevention of spread into the brain and spinal cord is achieved usually through methotrexate lumbar puncture. If required, further drug and chemotherapy treatment is provided as indicated by the individual response to treatment. All patients have maintenance treatment involving 2-3 years of daily oral treatment and in some cases monthly injections of

³¹ [Children's Cancer and Leukaemia Group](#)

chemotherapy, oral pulses of steroids and three monthly intrathecal treatment.

Treatment is provided on an outpatient basis.

HSCT is only needed in a small minority of patients who experience relapse although it is used more often in the TYA age group as a higher percentage of older teenagers and young adults will relapse compared to younger children.

Relapsed ALL although only occurring in the minority of ALL patients, remains a leading cause of cancer death in children. Within children that relapse, it is possible to identify those with high risk features whose long term survival is dismal i.e. 20-30% even with standard intensive therapy including allogeneic stem cell transplantation (allo-SCT). Children with relapsed ALL often reach the ceiling of acceptable toxicity with standard chemo and radiotherapy. Allo-SCT comes with a potential burden of long term toxicity in the form of chronic graft versus host disease and absolute treatment related mortality (TRM) of 5-20% depending on procedural and factors relating to the donor/recipient. For those who relapse post allo-SCT, outcomes are even poorer, especially for those who relapse early (<1year) post-transplant.

In some cases, boys may require testicular radiotherapy and both boys and girls may require additional intrathecal administration of methotrexate chemotherapy if leukaemia cells are detected in the CNS at diagnosis.

2.6 Service provider/Designated Centre

Interim phase 1 commissioned providers to be confirmed – Q1 and Q2 2019.

Interim phase 2 process for commissioned providers to be confirmed following phase 1

2.7 Exceptions

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If the patient wishes to be referred to a provider outside of the agreed pathway, an IPFR should be submitted.

Further information on making IPFR requests can be found at: [Welsh Health Specialised Services Committee \(WHSSC\) | Individual Patient Funding Requests](#)

3. Quality and Patient Safety

The provider must work to written quality standard and provide monitoring information to the lead commissioner. The quality management systems must be externally audited and accredited.

The centre must enable the patients, carers and advocates informed participation and to be able to demonstrate this. Provision should be made for patients with communication difficulties.

The aim is to commission providers who will oversee the clinical delivery of AR T Therapy to eligible patients.

The specification will ensure:

- Patient access is secured at a national level.
- Best practice for the safe and effective delivery of CAR T therapy.
- Clinical dependencies are addressed and secured.
- Traceability and tracking and best practice for patient follow-up and data capture is secured.

The main aim of this service specification is to support the introduction and delivery of this CAR T as a clinically and cost effective 3rd line treatment for the conditions set out in its licence.

As novel treatment, commissioned centres will support research activity and where appropriate be willing to support future phased adoption across the NHS in England and Wales working closely with designated Advanced Therapies Treatment Centres supported by Innovate UK and Cell and Gene Therapy Catapult. There is a need for shared learning between teams regarding these new technologies and their toxicities. This will also need to include how teams involved in cell therapies for non-malignant and malignant conditions collaborate and share resource, expertise and learning.

3.1 Quality Indicators (Standards)

Indicators include the following (Table 1), Novartis will also have indicator requirements as part of their regulatory arrangements and all efforts will be taken to harmonise these to ensure key data are collected without duplication. Complete and timely data collection, reporting and submission will be a mandatory requirement for commissioned providers as will agreements for data sharing. Data to be collected and reported separately for each indication.

Table 1

Number	Indicator	Data Source
Clinical Outcomes		
101	Proportion of patients who complete treatment and are alive 30 days after infusion.	Provider / Specialised services quality dashboard NHS England (SSQD)
102	Proportion of patients who complete treatment and are alive one year after first infusion.	Provider / SSQD
103	Proportion of patients who complete treatment and are alive two years after first infusion.	Provider / SSQD
104	Total number of Incidences of CRS and CRES at grades 2 and above requiring level 3 critical care or PICU.	Provider / SSQD
105	Median duration of admission for patients where an incidence of CRS and/or CRES at grades 2 and above has occurred.	Provider / SSQD
106	30 day mortality rate	Provider / SSQD
107	3 month mortality rate	Provider / SSQD
108	Average length of stay of patients following treatment	Provider / SSQD
Patient Experience		
201	There is patient information available.	Self- declaration
202	A patient feedback exercise is undertaken at least annually.	Self- declaration
203	Disease free survival	Self- declaration
204	Undertake family and caring activities at a level similar to that previously undertaken (adults only)	Self- declaration
205	Undertake work activities at a level similar to that previously undertaken (adults only)	Self- declaration
206	Undertake leisure and social activities at a level similar to that previously undertaken	Self- declaration
Structure and Process		
301	There is a centre MDT as per the service specification.	Self declaration
302	All relevant patients applicable for CAR-T are discussed at the local haematological cancer MDT	Self declaration
303	The service participates in the national / regional CAR-T MDT, with named representatives attending.	Self declaration
304	All members of the MDT undertake training as per the service specification.	Self declaration
305	There is an infrastructure to support being a specialist provider of this service as detailed within the service specification.	Self declaration

306	Where cellular therapy products are received via a third party there is a written agreement in place.	Self declaration
307	There are agreed clinical guidelines as per the service specification.	Self declaration
308	There are commissioner agreed patient pathways.	Self declaration
309	The service participates in local and national audits as required.	Self declaration
310	The service submits EBMT / other registry information for Cell Therapy (via MED-A	Self declaration

Commissioned providers are required to participate in annual quality assurance and collect and submit data to support the assessment of compliance with the service specification.

3.2 Applicable Obligatory National Standards

All commissioned providers must meet the standards and be JACIE accredited for age appropriate delivery of allogeneic HSCT, including standards covering immune effector cell (IEC) therapy as set out in the 6.01 (or later) edition of the FACT-JACIE International Standards for Haematopoietic Cellular Therapy Product Collection, Processing, and Administration. Over the next 4 years, all cellular therapy providers are expected to complete reaccreditation against the 7th edition of the standards published in 2018.

Commissioned providers for adult patients must meet the mandatory requirements set out in WHSSC's service specifications for Haematopoietic Stem Cell Transplantation (Adult).

Commissioned providers for paediatric patients must meet the mandatory requirements set out in WHSSC's service specification for Haematopoietic Stem Cell Transplantation (children).

All providers must hold HTA licenses as well as the current version of the FACT- JACIE International Standards for Haematopoietic Cellular Therapy Product Collection, Processing, and Administration.

3.3 Other Applicable National Standards to be met by Commissioned Providers

- CCLG, Children and Young People with Cancer, Acute Lymphoblastic Leukaemia (ALL) guide³²

³² [PGFSALL - Acute lymphoblastic leukaemia ALL - pgfactsheets - publications](#)

3.4 Other quality requirements

- The provider will have a recognised system to demonstrate service quality and standards.
- The service will have detailed clinical protocols setting out nationally (and local where appropriate) recognised good practice for each treatment site.
- The quality system and its treatment protocols will be subject to regular clinical and management audit.
- The provider is required to undertake regular patient surveys and develop and implement an action plan based on findings.

4. Performance monitoring and Information Requirement

4.1 Performance Monitoring

WHSSC will be responsible for commissioning services in line with this policy. This will include agreeing appropriate information and procedures to monitor the performance of organisations.

For the services defined in this policy the following approach will be adopted:

- Service providers to evidence quality and performance controls
- Service providers to evidence compliance with standards of care

WHSSC will conduct performance and quality reviews on an annual basis

4.2 Key Performance Indicators

The providers will be expected to monitor against the full list of Quality Indicators derived from the service description components described in Section 3.1.

The provider should also monitor the appropriateness of referrals into the service and provide regular feedback to referrers on inappropriate referrals, identifying any trends or potential educational needs.

4.3 Date of Review

This document is scheduled for review before 2022 where we will check if any new evidence is available.

If an update is carried out the policy will remain extant until the revised policy is published.

5. Equality Impact and Assessment

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (Welsh).

This policy has been subjected to an Equality Impact Assessment.

The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

6. Putting Things Right: Raising a Concern

6.1 Raising a Concern

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided.

The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern.

If a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be guided to the LHB for [NHS Putting Things Right](#). For services provided outside NHS Wales the patient or their representative should be guided to the [NHS Trust Concerns Procedure](#), with a copy of the concern being sent to WHSSC.

6.2 Individual Patient Funding Request (IPFR)

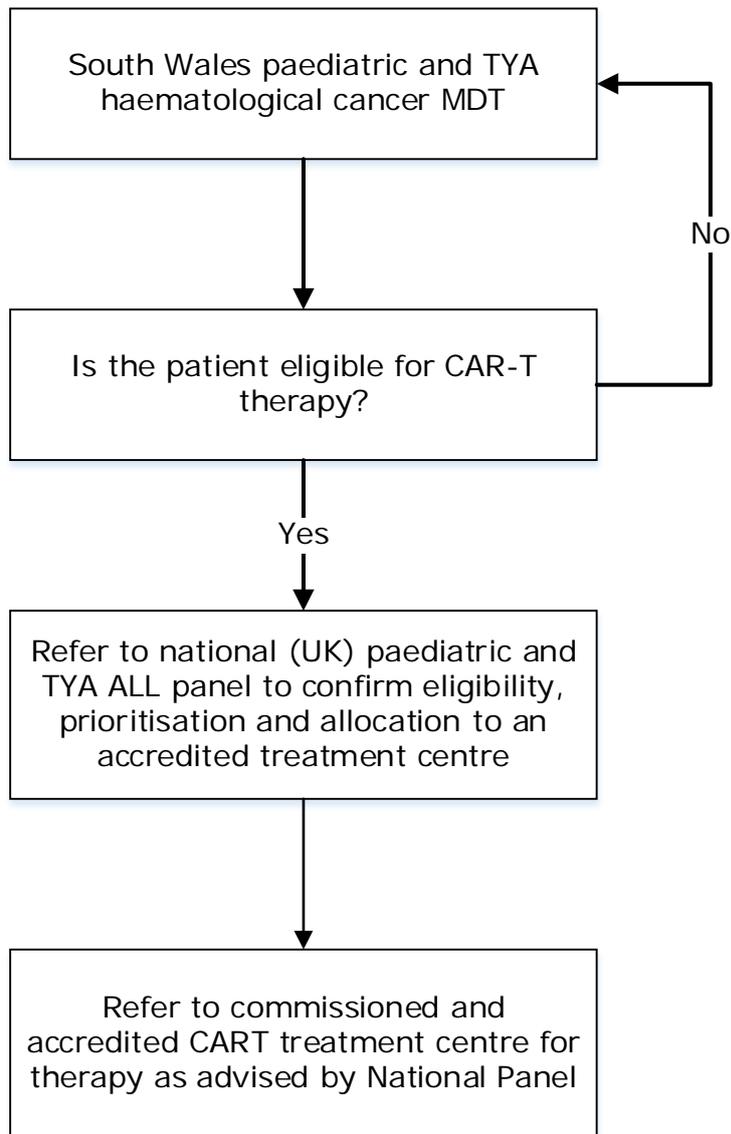
If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If an IPFR is declined by the Panel, a patient and/or their NHS clinician has the right to request information about how the decision was reached. If the patient and their NHS clinician feel the process has not been followed in accordance with this policy, arrangements can be made for an independent review of the process to be undertaken by the patient's Local Health Board. The ground for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated

If the patient wishes to be referred to a provider outside of the agreed pathway, and IPFR should be submitted.

Further information on making IPFR requests can be found at: [Welsh Health Specialised Services Committee \(WHSSC\) | Individual Patient Funding Requests](#)

Annex i Interim Patient Pathway



Annex ii Abbreviations and Glossary

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

AE	Adverse Event
BMT	Blood and marrow transplantation, which is used interchangeably with HSCT (see below)
CAR T	Chimeric antigen receptor T-cell: Artificial receptor that combines an antigen specificity domain coupled with an intracellular signalling domain typically expressed by an immune effector cell (e.g., T cell or natural killer cell)
CCLG	Children's Cancer and Leukaemia Group
DLBCL	Diffuse Large B-Cell Lymphoma
FACT	Foundation for the Accreditation of Cellular Therapy (North American Counterpart of JACIE, who collaborate to produce the FACT-JACIE standards).
HSCT	Haematopoietic stem cell transplantation
ICU	Intensive Care Unit – critical care level 3
IEC Therapy	Immune effector cell therapy - A cell that has differentiated into a form capable of modulating or effecting a specific immune response
JACIE	The Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT)
LN2	Liquid nitrogen
MED - A/B	Minimal Essential Data-A/B (EBMT data collection forms). MED-A are short and generic and MED-B are more detailed and disease specific
MDT	Multi-disciplinary team
OS	Overall survival
PICU	Paediatric Intensive Care Unit
PMBCL	Primary Mediastinal B-cell Lymphoma
SOP	Standard operating procedure

Appendix A – Lee Grading System for CRS

Grade	Assessment	Additional critical care treatment
Grade 1	Symptoms not life threatening and require symptomatic treatment only	Vigilant supportive care, assess for infection. Critical care outreach /critical care to be notified of patient. NEWS with escalation process in place to detect deterioration and respond. 4 hrly observations.
Grade 2	Symptoms require and respond to moderate intervention e.g. Hypotension: responds to fluids or one low dose vasopressor required Hypoxia: Requires < 40% oxygen	Admitted to critical care (level 3) with enhanced monitoring.
Grade 3	Symptoms require and respond to aggressive intervention e.g. Hypotension: requires multiple vasopressors or high dose single agent vasopressor Hypoxia: Requires \geq 40% oxygen Other organ toxicity: renal/hepatic/neurological	Echocardiography (Transthoracic) immediately available with ability to deliver optimal advanced cardiovascular and basic respiratory support
Grade 4	Life threatening symptoms Requirement for advanced respiratory support (intubation) and other organ support. (excludes transaminitis)	Advanced respiratory support immediately available and experience in management of ARDS patients. Renal support available on site (CVVHF and haemodialysis). EEG available on site.
Grade 5	Death	

Appendix B1 – CRES grading system

Grading Assessment of CRES	No concurrent CRS	Concurrent CRS
Grade 1	<ul style="list-style-type: none"> • Neurology consultation • Vigilant supportive care, aspiration precautions, intravenous (IV) hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause central nervous system depression • Low doses of lorazepam or haloperidol (in accordance with BNF) can be used, with careful monitoring, for agitated patients • Fundoscopic exam to assess for papilloedema • MRI of the brain with and without contrast, diagnostic lumbar puncture with measurement of opening pressure, MRI spine if the patient has focal peripheral neurological deficits, CT scan of the brain can be performed if MRI of the brain is <ul style="list-style-type: none"> • not feasible • Daily 30 min electroencephalogram (EEG) until toxicity symptoms resolve, if no seizures are detected on EEG, continue levetiracetam (in accordance with BNF) • If EEG shows non-convulsive status epilepticus, treat as per institutional algorithm ** 	<ul style="list-style-type: none"> • Consider anti-IL-6 therapy with tocilizumab/siltuximab (in accordance with BNF)
Grade 2	<ul style="list-style-type: none"> • Supportive care and 	<ul style="list-style-type: none"> • Tocilizumab/siltuximab

	<p>neurological work-up as described for grade 1 CRES</p> <ul style="list-style-type: none"> • Dexamethasone or methylprednisolone (in accordance with BNF) <p>Consider transferring patient to intensive- care unit (ICU) if CRES associated with grade ≥ 2 CRS</p>	<p>(in accordance with BNF)</p> <ul style="list-style-type: none"> • Dexamethasone or methylprednisolone (in accordance with BNF) if refractory to anti-IL-6 therapy
Levetiracetam in accordance with BNF		
Grade 3	<ul style="list-style-type: none"> • Supportive care and neurological work-up as indicated for grade 1 CRES • ICU transfer required • Corticosteroids as outlined for grade 2 CRES, continue corticosteroids until improvement to grade 1 CRES and then taper • Stage 1 or 2 papilloedema with cerebrospinal fluid (CSF) opening pressure • < 20 mmHg should be treated as per algorithm presented in BOX 4 <p>Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥ 3 CRES</p>	<ul style="list-style-type: none"> • Anti-IL-6 therapy, as described for grade 2 CRES and if not administered previously • Corticosteroids as outlined for grade 2 CRES if symptoms worsen despite anti-IL-6 therapy, continue corticosteroids until improvement to grade 1 CRES and then taper
Levetiracetam in accordance with BNF		
Grade 4	<ul style="list-style-type: none"> • Supportive care and neurological work-up as outlined for grade 1 CRES • •consider mechanical ventilation for airway protection • Anti-IL-6 therapy and repeat neuroimaging as described for grade 3 CRES • High-dose corticosteroids continued until improvement to grade 1 CRES and then taper, for example, • methylprednisolone IV (in accordance with BNF), followed by rapid taper • For convulsive status 	<ul style="list-style-type: none"> • Anti-IL-6 therapy, as described for grade 2 CRES and if not administered previously • Corticosteroids as outlined for grade 2 CRES if symptoms worsen despite anti-IL-6 therapy, continue corticosteroids until improvement to grade 1 CRES and then taper

	epilepticus, treat as per algorithm in BOX 3 <ul style="list-style-type: none">• Stage ≥ 3 papilloedema, with a CSF opening pressure ≥ 27 cm H₂O cerebral oedema, should be treated as per institutional algorithm **	
Levetiracetam in accordance with BNF		

** Detailed protocols available in Neelapu et al., 2018; Nat Rev Clin Oncol 15:47-62

For CRES grading see page 11 -

<https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf>

Clinical opinion to NHS England is for critical care admission for Grade 2 CRS and CRES.

Appendix B2 – U Penn

The U Penn/CHOP grading scale was used to grade CRS in the tisagenlecleucel pivotal studies and is provided here for information:

Penn/CHOP CRS Grading Scale³³

³³ Porter DL, et al. *Sci Transl Med.* 2015; 7(303):303ra139

Appendix C – Product Preparation and Manufacture

Redacted. Commercially Confidential