GIG CYMRU NHS WALES

Pwyllgor Gwasanaethau Iechyd Arbenigol Cymru (PGIAC)

Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Policy Position: PP185

Chimeric Antigen Receptor (CAR) T-cell therapy

April 2023

Version 2.1

Document information	
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Description	NHS Wales routinely commission this specialised service in accordance with the criteria described in this policy
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Update information

This policy is an update to the previous published Policy Position Statement published in 2021.

Treatments are marked to indicate the year of the last publication of the NICE Technology Appraisal Guidance:

[2018], [2019], [2021] No change made since first publication of the NICE Technology Appraisal Guidance. **[Updated 2023]** Publication of revised NICE Technology Appraisal Guidance.

Contents

Policy Statement

The Welsh Health Specialised Services Committee (WHSSC) commission Chimeric Antigen Receptor (CAR) T-cell therapies identified in this document within their licensed indications in accordance with the criteria outlined in this policy position statement.

In creating this policy position statement WHSSC has reviewed all relevant technology appraisal (TA) guidance issued by National Institute for Health and Care Excellence (NICE) (see section 2.1).

Welsh Language

WHSSC is committed to treating the English and Welsh languages on the basis of equality, and endeavour to ensure commissioned services meet the requirements of the legislative framework for Welsh Language, including the Welsh Language Act (1993), the Welsh Language (Wales) Measure 2011 and the Welsh Language Standards (No.7) Regulations 2018.

Where a service is provided in a private facility or in a hospital outside of Wales, the provisions of the Welsh language standards do not directly apply but in recognition of its importance to the patient experience the referring health board should ensure that wherever possible patients have access to their preferred language.

In order to facilitate this WHSSC is committed to working closely with providers to ensure that in the absence of a welsh speaker, written information will be offered and people have access to either a translator or 'Language-line' if requested. Where possible, links to local teams should be maintained during the period of care.

Decarbonisation

WHSSC is committed to taking assertive action to reducing the carbon footprint through mindful commissioning activities. Where possible and taking into account each individual patient's needs, services are provided closer to home, including via digital and virtual access, with a delivery chain for service provision and associated capital that reflects the WHSSC commitment.

Disclaimer

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

This policy 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 policy position statement.

1. Introduction

This Policy Position Statement has been developed for the planning and delivery of Chimeric Antigen Receptor (CAR) T-cell therapy for people resident in Wales. These treatments 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 Aims and objectives

This Policy Position Statement defines the commissioning position of WHSSC on the use of CAR T-cell therapy, identifies the specific treatments and specifies the indications for which their use is licensed and commissioned.

This Policy Position Statement includes the following CAR T cell therapies:

- axicabtagene ciloleucel
- tisagenlecleucel
- autologous anti-cd19-transduced cd3+ cells

The objectives of this policy are to:

- ensure commissioning for the use of CAR T cell therapy is evidence based
- ensure equitable access to CAR T cell therapy across Wales
- define the criteria for people to access the therapies listed in this policy
- improve outcomes for people receiving the treatments listed in this policy.

1.2 Treatment

CAR T therapy

Chimeric Antigen Receptor (CAR) T-cell therapy is specifically developed for each individual patient. The treatment involves reprogramming the patient's own immune system cells which are then used to target their cancer. It is a highly complex and potentially risky treatment.

CAR T-cell therapies contain the patient's own T cells that have been modified genetically in the laboratory so that they make a protein called chimeric antigen receptor (CAR). Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion. CAR can attach to another protein on the surface of cancer cells called CD-19. When this treatment is given to the patient, the modified T cells attach to and kill cancer cells, thereby helping to clear the cancer from the body.

Tisagenlecleucel is licensed for the following two indications:

- paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia that is refractory, in relapse post-transplant or in second or later relapse
- adult patients with relapsed or refractory diffuse large B-cell lymphoma after 2 or more lines of systemic therapy.

Axicabtagene ciloleucel is licensed for the following indication:

- adult patients with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more lines of systemic therapy.

Autologous anti-cd19-transduced cd3+ cell therapy is licensed for the following indication:

- adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

1.3 Background

Acute lymphoblastic leukaemia (ALL)

Acute lymphoblastic leukaemia (ALL) is a cancer of lymphocyte-producing cells. In ALL there is an excess production of immature lymphocyte-precursor cells, called lymphoblasts or blast cells, in the bone marrow. This affects the production of normal blood cells and there is a reduction in the numbers of red cells, white cells and platelets in the blood. ALL can be classified into 3 different subtypes:

- pre (precursor) B cell ALL, this is the most common type in adults
- pre (precursor) T cell ALL, this is more likely to affect young adults and is more common in men
- mature B cell ALL, this type is identified by particular genetic changes

Mature B cell ALL is sometimes called Burkitt type ALL because it is similar to another cancer called Burkitt lymphoma.

ALL in children and TYA patients has high cure rates with intensive modern combination chemotherapy regimens. When patients fail to achieve a remission or their disease relapses, outcomes are very poor with conventional treatments.

Patients with B cell disease can access inotuzumab[1] and blinatumomab[2] as a bridge to transplant.

[1] Overview | Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia | Guidance | NICE
[2] Overview | Blinatumomab for treating acute lymphoblastic leukaemia in remission with minimal residual disease activity | Guidance | NICE

CAR T provides a curative option for patients with relapsed / refractory CD19+ B cell ALL.

Diffuse large B-cell lymphoma

Non-Hodgkin lymphomas (NHL) are a diverse group of conditions which are categorised according to the cell type affected (B-cell or T-cell), as well as the clinical features and rate of progression of the disease. Diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma (PMBCL) are aggressive subtypes of non-Hodgkin lymphoma. Both of these express CD-19 antigen on the cell surface. PMBCL is a rare sub-type of NHL which develops in the mediastinum and has distinct clinical, pathological, and molecular characteristics from other subtypes.

Relapsing patients and those refractory to induction therapy are treated with salvage chemotherapy followed by consolidation with an autologous stem cell transplant in responders. Approximately 25% of younger, fitter patients eligible for this approach will experience long term survival (see data from the CORAL study). Those who are unfit for or do not respond to salvage treatment, or relapse following autologous transplantation, have a poor chance of long term survival.

The most widely used first-line treatment for DLBCL (including mediastinal large B-cell lymphoma) is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). Sometimes etoposide is added to this regimen. NICE guideline CG52 recommends salvage therapy with rituximab in combination with chemotherapy for relapsed or refractory disease followed by stem cell transplantation. If stem cell transplantation is not suitable chemotherapy or immunotherapy may be used alone. NICE TA306 recommends pixantrone monotherapy for people who have multiply relapsed, been treated previously with rituximab and are on the third or fourth line of treatment.

There is no standard treatment for relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies and so there is an obvious unmet need for these patients. Salvage chemotherapy is the most common treatment option.

Mantle cell lymphoma

Mantle cell lymphoma is a subtype of non-Hodgkin lymphoma and can have debilitating symptoms. Rates of relapse after initial treatment are high, and it has a huge effect on quality of life. Mantle cell lymphoma is considered incurable with current treatment. Outcomes for people with refractory or relapsed disease are poor. Treatment options after relapse are not well established and normally associated with lower responses and rapid disease progression.

1.4 Epidemiology

ALL is most common in children, adolescents and young adults, with 68% of cases diagnosed in people aged under 25 years. A second increase in incidence is observed in people aged over 60 years [CRUK]. ALL is rare with 25 people being diagnosed in Wales in 2017[3]. The age group with the highest incidence is young children aged 0-4 years[4].

There were around 14,095 new cases of non-Hodgkin lymphoma (NHL) in the UK in 2017 (654 in Wales). Each year approximately 40% of the patients are diagnosed with diffuse large B cell lymphoma (DLBCL)[5]. Approximately 3% of lymphomas in the UK are primary mediastinal large B-cell lymphoma (PMBCL) and 10-70% of low grade lymphomas transform into a high grade form [CRUK].

Most people diagnosed with DLBCL are 65 or over[6]. Survival rates at 5 years for DLBCL are around 65-70% for stage I and II and around 50% at stages III and IV[7]. Diffuse large B cell lymphoma is more common in males than females.[8]

MCL is a rare type of B cell lymphoma. Each year around 75 people are diagnosed with MCL in the UK. Out of all people with NHL in the UK, less than 1 in every 100 people (1%) have MCL.

[3] Welsh Cancer Intelligence and Surveillance Unit
[4] What is acute lymphoblastic leukaemia (ALL) | Cancer Research UK
[5] Cancer Research UK https://www.cancerresearchuk.org/
[6] Diffuse B-cell lymphoma. Lymphoma association [accessed March 2018]
[7] Cancer Research UK https://www.cancerresearchuk.org/
[8] https://www.cancerresearchuk.org/about-cancer/non-hodgkin-lymphoma/types/high-grade

2. Criteria for Commissioning

The Welsh Health Specialised Services Committee will fund the use of axicabtagene ciloleucel, tisagenlecleucel and autologous anti-cd19-transduced cd3+ cells in line with NICE technology appraisal guidance TA554, TA872 **[2023]**, TA567 and TA677 as set out in section 2.1 of this policy position statement.

2.1 Inclusion criteria

- Tisagenlecleucel therapy is recommended for use within the Cancer Drugs Fund[9] as an option for treating relapsed or refractory diffuse large B-cell lymphoma in adults after 2 or more systemic therapies, only if the conditions in the managed access agreement are followed[10]. **[2019]**

- Axicabtagene ciloleucel is recommended, within its marketing authorisation, as an option for treating relapsed or refractory diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma in adults after 2 or more systemic therapies. It is recommended only if the company provides axicabtagene ciloleucel according to the commercial arrangement. [11]. **[updated 2023]**

- Tisagenlecleucel therapy is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years, only if the conditions in the managed access agreement are followed[12]. **[2018]**

- Treatment with autologous anti-CD19-transduced CD3+ cells is recommended for use within the Cancer Drugs Fund as an option for treating relapsed or refractory mantle cell lymphoma in adults who have previously had a Bruton's tyrosine kinase (BTK) inhibitor. It is only recommended if the conditions in the managed access agreement for autologous anti-CD19-transduced CD3+ cells treatment are followed[13] **[2021]**

The patient eligibility criteria for each of the above indications is presented within the relevant managed access agreement.

[9] Please see WHSSC Policy for New Treatment Fund
[10] TA567: Overview | Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies | Guidance | NICE
[11] TA872: Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies | Guidance | NICE
[12] TA554: Overview | Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years | Guidance | NICE
[13] TA677: Overview | Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma | Guidance | NICE

2.2 Acceptance criteria

The service outlined in this policy 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.

2.3 Patient Pathway (Annexes i and ii)

CAR T therapy is novel with several uncertainties about long term outcomes and adverse treatment events. This is a rapidly developing field and enrolment into a clinical trial (if open) should be encouraged. There will be a phased approach to commissioning CAR T across the UK in the first instance beginning with 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. Further details can be found in the WHSSC service specifications for CAR T therapies published by WHSSC in May 2019[14,15].

The number of providers will increase with demand but is unlikely to be comparable with the number of commissioned allogeneic transplant centres due to the need to concentrate expertise in a few centres. 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).

Lymphoma (Annex i)

NHS England has established a UK-wide CAR T clinical panel[16] for the delivery of CAR T treatments for adults with the lymphoma indications specified in 2.1 above. The Panel prioritises access to accredited centres while capacity builds across the UK. The Panel reviews eligible patients to ensure they meet the clinical criteria as specified by the marketing authorisation and NICE as well as prioritising patients. The Panel is clinically led, with patient and public representation. Decisions are based on unanimous consent of the clinical and provider members. NHS Wales will refer all eligible patients to the UK-wide lymphoma CAR T Clinical Panel in line with the access criteria described in this document. NHS Wales will also have a clinical representative on the Panel.

[14] WHSSC, Service Specification: CP175 Axicabtagene Ciloleucel Chimeric Antigen Receptor T-Cell (CAR T)
[15] WHSSC, Service Specification: CP176 Tisagenlecleucel Chimeric Antigen Receptor T-Cell (CAR-T)
[16] https://www.england.nhs.uk/cancer/cdf/car-t-therapy/

Clinicians currently treating patients in the indicated population will consider their patient's eligibility for the treatment at the appropriate local lymphoma CAR T MDT[17]. At this stage they will:

- identify eligible patients who might benefit from CAR T therapy
- confirm patient eligibility in line with the relevant manufacturer's marketing authorisation 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 to the UK-wide lymphoma CAR T Panel.

The UK-wide lymphoma 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.

Acute Lymphoblastic Leukaemia (Annex ii)

Please see annex ii.

2.4 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, 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

2.5 Clinical Outcome and Quality Measures

The Provider must work to written quality standards and provide monitoring information to the lead commissioner. Please refer to the WHSSC Service Specifications _Axicabtagene Ciloleucel Chimeric Antigen Receptor T Cell (CAR T) (CP175) and _Tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) (CP176) for details.

[17] For patients in North Wales this will be the CAR T MDT at the Christie in Manchester and for patients in South Wales this will be the CAR T MDT at the University Hospital of Wales in Cardiff

The centre must enable the patient's, carer's and advocate's informed participation and to be able to demonstrate this. Provision should be made for patients with communication difficulties and for children, teenagers and young adults.

2.6 Responsibilities

Referrers should:

- inform the patient that this treatment is not routinely funded outside the criteria in this policy, and
- refer via the agreed pathway.

Clinicians considering treatment should:

- discuss all the alternative treatments with the patient
- advise the patient of any side effects and risks of the potential treatment
- inform the patient that treatment is not routinely funded outside of the criteria in the policy, and
- confirm that there is contractual agreement with WHSSC for the treatment.

In all other circumstances an IPFR must be submitted.

3. Documents which have informed this policy

The following documents have been used to inform this policy:

- **WHSSC policies and service specifications**
  - CP175, Axicabtagene ciloleucel Chimeric Antigen Receptor T Cell (CAR T) therapy
  - CP176, Tisagenlecleucel Chimeric Antigen Receptor T Cell (CAR T) therapy, Service Specification
  - Children with cancer service specification CP86

- **National Institute for Health and Care Excellence (NICE) guidance**
  - Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies. NICE Technology Appraisal Guidance (TA567), December 2018.
  - 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 large B-cell lymphoma after 2 or more systemic therapies. NICE Technology Appraisal Guidance (TA872), February 2023.
  - Autologous anti-CD19-transduced CD3+ cells for treating relapsed or refractory mantle cell lymphoma, NICE Technology Appraisal Guidance (TA677), 24 February 2021

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

- **NHS Wales**
  - All Wales Policy: Making Decisions in Individual Patient Funding requests (IPFR).

4. Date of Review

This document will be reviewed annually or when information is received which indicates that the policy requires revision.

5. Putting Things Right: Raising a Concern

5.1 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.

5.2 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

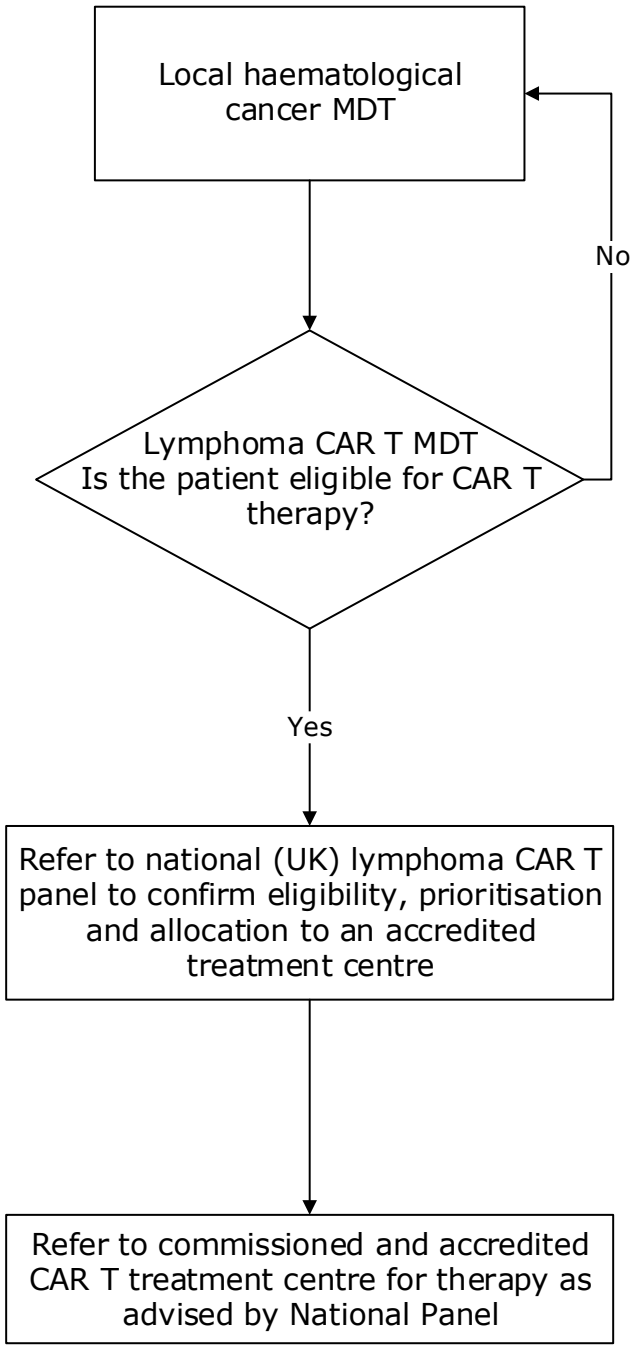
6. Equality Impact and Assessment

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.

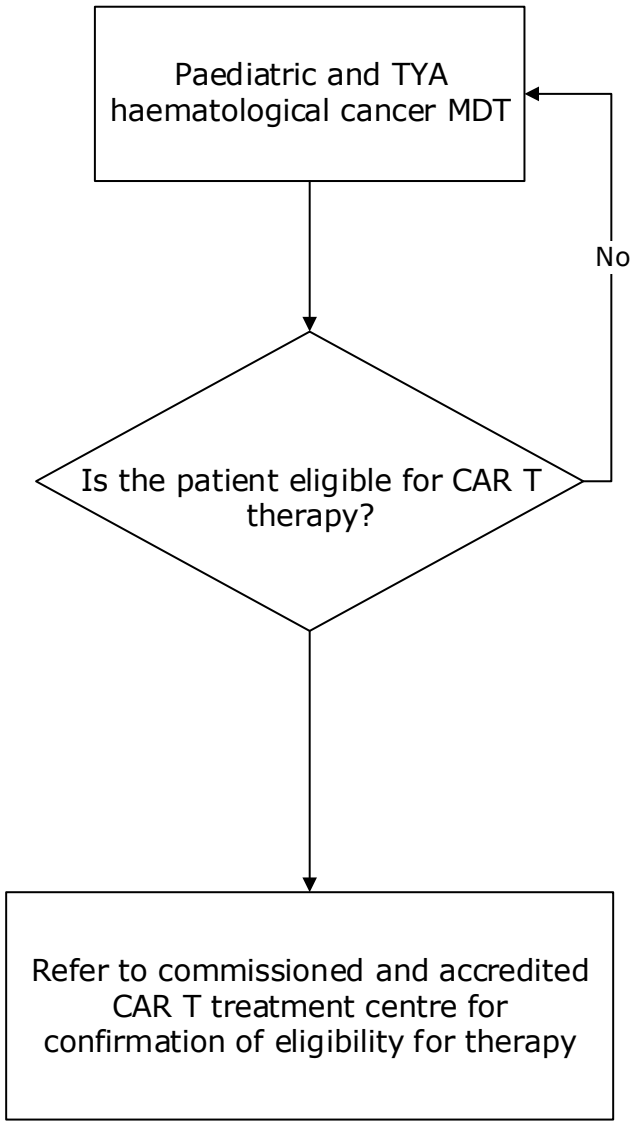
The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

Annex i Patient Pathway: Lymphoma[18]



[18] See section 2.1 for indications included

Annex ii Patient Pathway: Leukaemia[19]



[19] See section 2.1 for indications included