Future-proofing the UK CAR-T patient referral pathway

White Paper 2023

Cell and Gene Therapy Catapult, The Advanced Therapy Treatment Centre Network, NHS Blood and Transplant, The Christie NHS Foundation Trust, Autolus Limited, Gilead Sciences Ltd, Janssen-Cilag Limited.

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Explanation of funding / funders

This has been a collaborative project between the UK pharmaceutical industry and the National Health Service (NHS). It was developed and has been delivered under a collaborative working agreement as set out in Clause 20 of the Association of British Pharmaceutical Industry (ABPI) Code of Practice for the Pharmaceutical Industry,[1] and as such has complied with all Code requirements. The project was initiated by Advanced Therapy Treatment Centre Network (ATTC) coordinated by The Cell and Gene Therapy Catapult (CGTC). Funding and contribution in kind toward deliverables were provided by Autolus Limited (Autolus), Gilead Sciences Ltd (Gilead) and Janssen-Cilag Limited (Janssen).

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Executive summary

Chimeric Antigen Receptor T-Cell (CAR-T) therapy has been available in England for five years for patients with some types of blood cancer, after the NHS in England became the first public health system in Europe to make the therapy available. In 2019 CAR-T was also made available in Scotland, ensuring eligible patients in every devolved nation in the UK had access to CAR-T. It is now available to some adults with Diffuse Large B-Cell Lymphoma (DLBCL), Mantle Cell Lymphoma (MCL) and children, young people and adults with Acute Lymphoblastic Leukaemia (ALL).

Significant progress has been made in the last five years in expanding patient access to CAR-T: centre expansion means it is now available across sixteen adult specialist sites in the UK as of October 2023; patient referrals have increased; and CAR-T is now approved via routine commissioning for some blood cancer patients. Whilst progress has been made in scaling up the delivery of CAR-T, the referral pathway for patients remains the same now as it was in 2018, with referrals reliant on local and/or regional networks feeding into national panels to confirm eligibility.

The Cell and Gene Therapy (CGT) Catapult and the Advanced Therapy Treatment Centre (ATTC) network developed this report to identify and analyse CAR-T patient referral pathways in the UK and make recommendations about how improvements could be made. If implemented, these reforms will help to ensure that referral pathways remain appropriate for the next five years of CAR-T therapy and beyond in delivering equitable access to CAR-T for eligible patients. It has been drafted based on surveys and interviews with referral and CAR-T treatment centres in England - who also receive referrals from the devolved nations - engagement with patient groups, and informed production of detailed mapping of patient referral pathways from referral sites to treatment centres.

Based on the findings from this engagement, the report sets out a series of recommendations linked to the predominant four themes that arose from it.

Key recommendations include:

Streamlining patient identification and referral

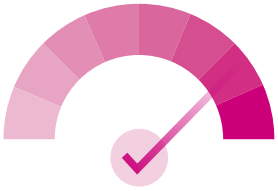
Formalised referral processes should be established from secondary care to CAR-T treatment centres, to support streamlined patient referrals across the UK, with mechanisms to ensure referrals are received at the earliest time to minimise delay

Addressing inequalities in access to CAR-T

Work should be carried out to identify causes of variation in access to CAR-T, with targeted measures then implemented to support access for underrepresented demographics

Overcoming barriers in capacity and infrastructure

A review of the capacity and infrastructure across the system required to deliver CAR-T should be carried out, both now and in anticipation of future demands, to ensure the system is ready for expected increases in CAR-T patient numbers and approved indications



Delivering reforms aimed at workforce training and communication

Reforms aimed at delivering improvements in training and communication within the CAR-T workforce should be implemented, to increase awareness of CAR-T and the patient referral pathway

Introduction

The NHS was one of the earliest health services in Europe to adopt CAR-T therapy, and it has now been available on the NHS to some blood cancer patients for five years. Since 2018, the number of CAR-T treatment centres has continued to increase, with a treatment centre now in every region in England and in Scotland and Wales, supporting increases in the number of patients receiving CAR-T. Whilst these changes have helped to facilitate improved patient access, the CAR-T patient referral pathway has remained the same, relying on local and/or regional networks feeding into national panels to confirm eligibility.

As the spread and scale of access to CAR-T widens, with the treatment now available in more indications, and with the growing expectation that all specialist stem cell allograft centres could deliver CAR-T within the coming years, it is important to review the appropriateness of existing processes and consider reforms that will help to ensure they are effective in ensuring equitable patient access to standard of care CAR-T therapy.

This project was initiated and developed by the CGT Catapult and the ATTC network, to identify and analyse CAR-T patient referral pathways in the UK and make recommendations about how this might be improved. Its findings are informed by a series of surveys and interviews carried out with referral and CAR-T treatment centres in England, who also receive referrals from the devolved nations, and patient groups involved in supporting patients undertaking CAR-T. Detailed mappings of patient referral pathways from referral sites to CAR-T treatment centres were also carried out.

The key aims/objectives of the project were to:

- Review patient referral pathways for access to standard of care and clinical trial CAR-T treatment options
- Acquire a picture of the current and future landscape by critically analysing bottlenecks, best practice, and preferences of key opinion leaders across North West and South West referral centres (England) and UK wide CAR-T treatment centres
- Produce an outline business case for change of delivery at CAR-T treatment centres

Following a review of survey and interview findings, the report identifies the following four themes that capture the key barriers across the pathway:

Streamlining patient identification and referral

Addressing inequalities in access to CAR-T

Overcoming barriers in capacity and infrastructure

Delivering reforms aimed at workforce training and communication

Linked to these themes, the report then makes a series of justified recommendations for change with the aim of supporting improvements in the patient referral pathway.

The project was delivered under the Association of British Pharmaceutical Industry (ABPI) collaborative working framework,[1] and was funded and received input from Autolus Limited (Autolus), Gilead Sciences Ltd (Gilead) and Janssen-Cilag Limited (Janssen).

Summary of recommendations

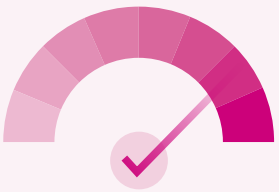
Streamlining patient identification and referral

1. Formalised referral processes should be established from secondary care to CAR-T treatment centres, to support streamlined patient referrals across the UK, with mechanisms to ensure referrals are received at the earliest time to minimise delay.
2. Mechanisms should be established to ensure referrals are received at the earliest time point to minimise delay in the patient pathway – with clear expectations set on timelines at each stage.

Addressing inequalities in access to CAR-T

3. Work should be carried out to identify causes of variation in access to CAR-T, with targeted measures then implemented to support access for underrepresented demographics. This should include a review of patient information, gaps in support required, and the establishment of regional patient support networks.

Overcoming barriers in capacity and infrastructure



4. A review of the capacity and infrastructure across the system required to deliver CAR-T should be carried out, both now and in anticipation of future demands, to ensure the system is ready for anticipated increases in CAR-T patient numbers and approved indications.

Delivering reforms aimed workforce, training, and communication

5. Reforms aimed at delivering improvements in training and communication within the CAR-T workforce should be implemented, that includes the development of a dedicated CAR-T education programme for stakeholders at all points of the CAR-T referral and treatment pathway.

Problem statement

Overview of CAR-T

CAR-T therapy is one of the most successful immunotherapies identified in the past decade, demonstrating notable efficacy in relapsed or refractory (R/R) haematological malignancies.[2] This technology combines T-cell characteristics such as self-renewal and lytic ability with the binding properties of monoclonal antibodies to make a living drug.

In current CAR-T cell therapy protocols, a patient's own (autologous) T cells are collected from patients by apheresis and are then genetically engineered to express the CAR construct. The modified cells are cultured and allowed to expand until they reach an appropriate clinical dosage. Infusion of the manufactured cells back to the individual patient then takes place following lymphodepletion with an appropriate conditioning chemotherapy regimen.

The UK was one of the first in Europe to approve CAR-T therapy in 2018 with NHS England (NHSE) authorising the use of Axicabtagene Ciloleucel and Tisagenlecleucel within licenced indications. This has now expanded to three CAR-T-cell therapy products in routine clinical use across five indications.[3,4,5,6,7,8] Whilst CAR-T therapy for myeloma is currently only available in the UK within clinical trials, it has the potential to be the next CAR-T indication to be approved here for standard-of-care use.

CAR-T is a type of advanced therapy medicinal product (ATMP), a group of products based on genes, tissues or cells. Both CAR-T and ATMP research continues to grow, and there more than 900 CAR-T clinical trials[9] currently recruiting worldwide. As demonstrated by the CGT Catapult annual audit of UK CAR-T clinical trials,[10] the number continues to increase year-on-year, with 178 trials reported as ongoing in 2022, up from 168 in 2021. This contrasts with a global 13% decline in ongoing ATMP clinical trials observed worldwide,[10] reflecting the challenges of delivering these therapies – including cost and complexity.

The many challenges that exist in delivering CAR-T include the need to effectively manage potentially life-threatening toxicities that can be associated with CAR-T treatments. Key toxicities include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[11] These occur when inflammatory cytokines are elevated due to activation of the immune system, resulting in a variety of clinical findings including constitutional symptoms and organ failure. Early recognition of CRS and ICANS alongside prompt intervention ensure that the effects can be adequately managed and are generally reversible. In addition, since CAR-T offers a potentially life-saving treatment, cost effective analysis and identification of other factors restricting access are required, to ensure equity of access to this therapy.[12]

The CAR-T referral pathway

Currently patient referrals for CAR-T rely on local or regional networks feeding into national panels, to confirm eligibility for access to CAR-T treatments. The National CAR-T Clinical Panels (NCCP) for lymphoma and Acute Lymphoblastic Leukaemia (ALL) were established in November 2018, when these treatments became available through the Cancer Drug Fund (CDF). The remit of these panels is to:

- Provide general advice on the use of CAR-T for the recommended cohort of patients
- Provide assurance of patient clinical eligibility
- Prioritise patients for treatment to match centre capacity and the distribution of patients

As the number of approved CAR-T products and indications has grown, and the number of eligible patients increased, it is important a review is carried out of the effectiveness of current processes for referring patients, to ensure patients have equitable access to existing and future products.

Justification for project and project plan

Justification

The CGT Catapult coordinates the ATTC network, which operates within the NHS framework, to address the complex challenges of bringing pioneering ATMPs to patients.

To consider how the CAR-T patient referral pathway can be improved, CGT Catapult entered a collaboration with Autolus Limited (Autolus), Gilead Sciences Ltd (Gilead) and Janssen-Cilag Limited (Janssen), who provided funds and input to two project delivery sites – The Christie NHS Foundation Trust (The Christie) and NHS Blood and Transplant (NHSBT) – to identify and analyse current CAR-T patient referral pathways in the UK and define future best practice.

Please note this report uses a series of common abbreviations in describing the CAR-T pathway. Appendix 1 includes a breakdown of abbreviations used.

Methods

Project aims

1. To review the current patient referral pathways for access to standard of care and investigational CAR-T treatments
2. Following critical analysis of the current and future landscape, to identify best practice and service improvement recommendations to maintain patient access to these treatments going forward, in the form of a white paper
3. Produce an outline business case for change

Project methodology

This project generated a consolidated view of current CAR-T therapy patient referral pathways through surveys, follow-on interviews, and detailed mappings of patient referral pathways at two CAR-T treatment centres. The survey reached a broad range of CAR-T treatment centres, secondary care referral centres in the North West and South West of England, and it was also shared with patient advocacy groups who support patients undertaking CAR-T.

Critical analysis of referral pathways was completed to identify any ineffective practice and suggest future developments. A range of real-world metrics within the current referral pathway were assessed at the project delivery sites to aid analysis and discussion. An outline business case for change was also developed.

A breakdown of the methodology is as follows:

1. Surveys were sent to ten CAR-T treatment centres across England and all secondary care referral centres across the North West and South West to identify each stakeholder's perspective of the existing CAR-T referrals process for both standard of care and clinical trials across DLBCL, MCL, ALL and MM. Responses were received from seven CAR-T treatment centres,13 North West and six South-West referral centres. Surveys were also sent to seven patient advocacy groups or representatives with responses from four of these.
2. Follow-on interviews were conducted with eleven key opinion leaders, based on their survey responses, to further interrogate their perspectives to capture in the white paper.
3. The patient referral process from secondary care to CAR-T treatment centre was mapped, utilising data from the surveys and interviews. Based on the data, the extent to which these processes can be generalised across the UK was assessed.
4. A critical analysis of referral practices was undertaken to highlight best practice; evaluate the root causes for ineffective processes; define patient and health care professional requirements for a high-quality referral process; and explore equity of access and how current processes can account for anticipated changes in the CAR-T environment. A range of metrics within the current referral pathway was analysed, generated by the two project delivery teams (The Christie and NHSBT).
5. The white paper was developed with recommendations for service improvement and an outline business case for CAR-T treatment centres, describing the formal referral process from secondary care to treatment centre.

Project plan

CGT Catapult led the creation and development of this collaborative working project by identifying the relevant parties for involvement. All parties were brought together as a Working Group, to steer progress against the project aims and methodology. Each project delivery site created a small team of specialists to undertake the required activities, report progress and challenges and receive direction from the Working Group. Project delivery site teams included a range of clinicians, project coordinators and administrators.

An online survey platform was required to run the surveys of CAR-T treatment centres, secondary care referral centres and patient advocacy groups. Following research and advice, the 'SmartSurvey' platform was identified as the most suitable software to meet NHS Data Protection and Governance requirements. This platform was used to create and distribute the surveys and to analyse the results.

A series of virtual interviews were conducted via Microsoft Teams, to further probe and test the survey responses. These interviews were held to gain more qualitative feedback from a cross section of key opinion leaders, to identify improvements which could be made to these referral pathways.

Each project delivery site conducted a thematic analysis of the survey and interview results, to then produce:

- Maps of the current CAR-T referral pathways for patients with lymphoma and ALL, across England
- A white paper that included a set of service improvement recommendations for the CAR-T referral pathway and an outline business case

Results

Findings

Key themes that emerged from the surveys and interviews include:

- Most but not all sites had access to a CAR-T Multi-Disciplinary Team (MDT) meeting on a local (≥91%) or regional level (71%) and fed into this via email/electronic portal
- Whilst communication and guidance on referrals was in place across centres, this was not uniform or consistent
- Inequality of access to CAR-T was deemed to be present, with particular inequalities within certain population groups, mainly as a result of travel costs, expenses incurred, and additional support required
- Whilst referral and treatment timelines were generally in line with what was felt to be ideal for CAR-T treatment centres, barriers were identified across the pathway and there was a lack of spare capacity should indications increase

Key areas of potential delay in the referral pathway were also raised, including:

- Timelines for transfer of information (for example, scan images or reports)
- Apheresis scheduling
- Stem cell laboratory capacity
- Workforce limitations, inpatient capacity and manufacturing timelines

While there were many similarities between standard of care (licensed therapy) and clinical trials, a lack of awareness of trial opportunities was detailed, highlighting the importance of awareness and communication, as well as having both pathways running in parallel.

Patient advocacy groups largely mirrored the opinions from sites, focusing on inequality of access to CAR-T in general and specific access limitations, for example to adequate patient information materials.

A range of metrics within the current pathway were produced by the project delivery sites and compared to data provided by key opinion leaders, with discrepancies highlighted around varying bridging therapy regimes and a lack of inpatient capacity. In conjunction with the above findings, process maps were generated for lymphoma and ALL to demonstrate the forums and patient flow through the referral process, from initial identification to long term follow up.

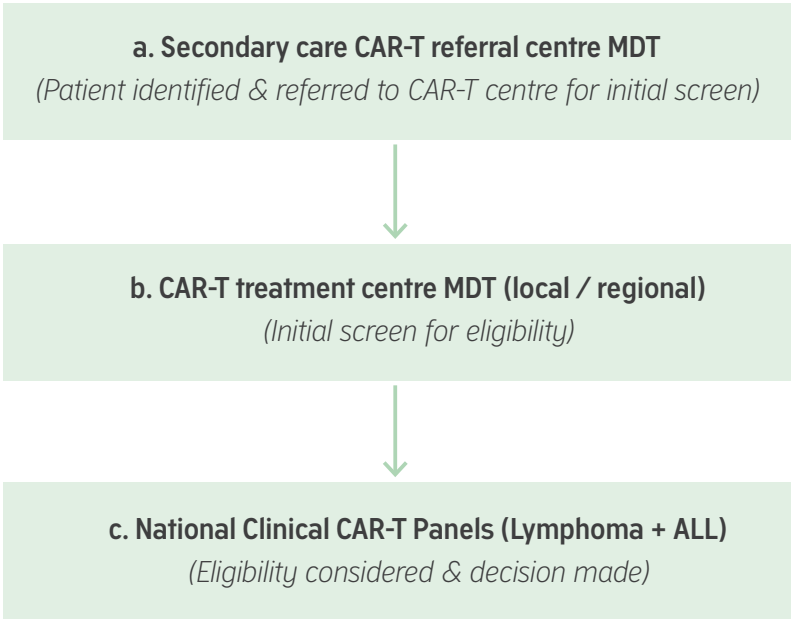
The project results are presented as follows:

1. CAR-T pathway meetings
2. Process maps
3. Outputs from surveys and interviews

1. CAR-T pathway meetings

The meetings included in the CAR-T referral pathway and the steps taken in them are outlined in Figure 1.

Figure 1:



NOTE: In the South-West regional disease specific CAR-T MDTs are not established, however Bone Marrow Transplant planning meetings occur where these discussions take place.

Please see Appendix 2 for an overview of the role and membership of the secondary care CAR-T referral centre MDT, the CAR-T treatment centre MDT (local / regional), and the National Clinical CAR-T Panels (Lymphoma + ALL).

Section findings

We asked for feedback on membership of the above MDTs and the results were compared with NICE recommendations on the makeup of MDTs in haematological cancers.[13] Generally, 'Core' members were included in the MDTs, but a Haemato-pathologist was only mentioned as an attendee at one secondary care site.

Some meetings in the pathway may not require a formal MDT, or sites may utilise parts of other planning meetings to discuss cases, which may not include all staff required in a diagnostic MDT. A more detailed evaluation of Haemato-oncology MDT core and extended membership across the UK is required to assess compliance.

2. Process maps

Please see Appendix 3 for the following maps outlining the different stages of the referral pathway and a more detailed overview of the process at each step:

Process map: This provides a key to the symbols, steps and decision points in the pathways, with colour coding for the different forums.

An overview of the CAR-T referral process: Potentially eligible patients are identified for CAR-T; referral is then made to a CAR-T centre-led MDT for initial screening and eligibility assessment; before the NCCP determine eligibility to progress to treatment.

Patient identification to initial eligibility screen at CAR-T centre: A process map is included for first identification of a potentially eligible patient in a healthcare setting before the MDT assesses potential eligibility.

CAR-T centre initial screen to NCCP eligibility decision: The CAR-T centre accepts a referral and completes the initial eligibility screen to determine whether the patient is suitable for CAR-T.

Approval of CAR-T treatment to patient discharge: Following a positive NCCP eligibility decision, the CAR-T centre led MDT discusses if the patient continues to be well enough to receive treatment. The following steps then occur:

- CAR-T treatment plan and consent is confirmed
- Apheresis is undertaken, and cells are sent for manufacture
- Bridging therapy is undertaken where appropriate
- A post-bridging therapy assessment takes place
- An inpatient stay (at least 14 days) is scheduled
- Once the medicinal product is manufactured, CAR-T infusion takes place, alongside monitoring for toxicities
- Ongoing assessment and monitoring

Indicative long term follow up patient pathway: (note: practice may vary across the UK)

Alternative treatment options: Due to the progressive nature of diseases presented, if it is no longer appropriate for a patient to remain on the CAR-T pathway, alternative treatment options are discussed with the patient.

Appendix 4 provides an overview of the CAR-T referral process for ALL. The indications for CAR-T in ALL cover paediatric, teenage and young adult and adult services. Steps followed on identification of a patient as potentially eligible for CAR-T are outlined. Due to subspecialist care and relatively small patient numbers, national MDTs work as panels on an age specific basis and are used to discuss all management options for the patient.

3. Outputs from surveys and interviews

3.1 Survey and interview metrics

Response rate

Surveys were sent to all adult haematology centres who refer patients for CAR-T in the North West and South West of England , adult CAR-T treatment centres in England and patient advocacy groups, to identify each stakeholder's perspective of the CAR-T referrals process.

In the North West, 15 trusts were approached and 16 responses were received across 13 trusts (87% trust response rate). Of these, 14 responses were received for lymphoma, one for myeloma and one for ALL. In the South West, nine trusts were approached with six completed responses (66% response rate). Of these, four responses for lymphoma and five for myeloma were received.

Nationally, ten CAR-T treatment centres were approached, with responses received from seven (70% response rate). Surveys were sent to six patient advocacy groups and one patient representative with four responses received from this grouping (57%).

Interviews were held with 11 referral and CAR-T treatment centres taking referrals from across the UK in order to supplement the information gained from the surveys.

3.2 Local & regional MDTs

The survey found that:

- A high proportion of centres have access to a relevant local MDT (all survey responders in South West, 91% of those in North West and all CAR-T treatment centres)
- The North West CAR-T centres have a local MDT which is also used as a regional MDT and covers the trusts without their own local MDT
- In total, 71% reported access to a regional MDT. In the South West, whilst there is no specific regional MDT, there are proposals to start these, focussing on high-risk cases of lymphoma and myeloma
- Interviews in the South West indicated differing opinions about what constituted an MDT in this setting, with 33% reporting an existing regional meeting despite none being setup as of yet. It was noted by some respondents that the governance of the referral process would be enhanced by having a regional MDT, particularly if more than one CAR-T centre was represented. One respondent stated:

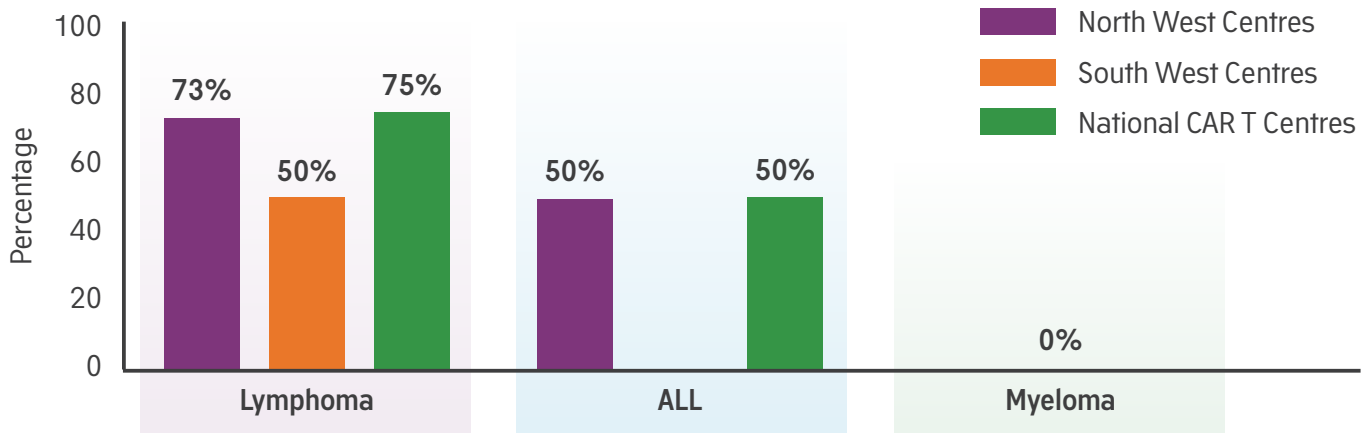
> **"It would be very helpful to have a regional MDT for ensuring best practice care, also to identify patients for high dose therapy and clinical trials."**

Nationally, practice is variable according to the disease group. 50–75% of sites treating lymphoma and ALL patients have a regional MDT (Graph 1) and a local MDT, which meets for one to two hours from twice a week through to monthly. Two respondents (treating ALL and lymphoma) suggested they did not require a regional MDT in addition to the local MDT because it would cause duplication and was not required as the NCCP is in place.

Feedback from CAR-T treatment centres also indicated that having a separate CAR-T MDT was more beneficial than adding this function to an existing disease specific MDT. In addition, it was recommended that referring centres should follow NICE guidance[8] on Haemato-oncology MDTs – which sets out core and extended team membership and issues that should be discussed.

These results highlight the need for standardised processes to formalise MDT attendance and establish a clear flow of decision making from a local to national level.

Graph 1: Access to regional MDTs by disease group and by region



Note National CAR T centre data made up of NW / SW + national CAR T centre data
Note no ALL responses from SW
Note some 'formal' regional MDT takes form of regional transplant MDT rather than dedicated disease subspeciality MDT

3.3 The NCCPs

Most respondents found NCCPs (lymphoma and ALL) to be valuable, as they:

- Provide a helpful and quick process to approve eligibility
- Enable discussion on borderline and more complex cases, bridging therapy and toxicity management
- Facilitate knowledge sharing between more experienced sites and newer sites
- Support the development of new research and the production of publications in this field
- Enable direct discussion with NHS England on updates and changes to eligibility

"It has built an incredibly helpful and close professional network."

The future role of the panels was also discussed with interviewees, who identified that:

- The NCCP could potentially delegate eligibility decisions to CAR-T MDTs for cases where they clearly satisfy all eligibility criteria; this would mirror the Blueteq approval process for other therapies. Blueteq is used by NHSE as a high cost drugs database. Clinicians are required to complete proformas for each patient receiving CAR-T to document that requirements for funding have been met.
- Determining patient fitness to receive treatment, based on information presented, remains challenging for NCCPs as panel members may have not met the patient themselves. Some participants also questioned the future role of the panel and highlighted possible alternative models
- It was important to have a CAR-T pathway coordinator in post, to support and manage the administration process required
- The current workload of the NCCP was felt to be acceptable but ongoing monitoring of its increasing case load is needed to ensure it does not exceed capacity

Opinion differed on whether the current NCCP set up should be continued and used for future indications (50% thought it should continue, 25% thought not and 25% were unsure).

3.4 Treatment timescales

Ideal and current timelines were assessed in the North West and South West regions (Table 1).

Table 1	Lymphoma			ALL	
	Current (approx.) (CAR-T treatment centre*)	**Ideal** (CAR-T treatment centre)	**Ideal** (Referring sites)	**Current** (approx.) (CAR-T treatment centre)	**Ideal** (CAR-T treatment centre)
	No. of days			**No. of days**	
Referral to appointment at CAR-T treatment centre	5	7	5-14	2	2
Patient seen at CAR-T treatment centre to apheresis	22	14	7-14	12	7
Apheresis to CAR-T infusion	40	35	14	25	20
Infusion to discharge	**17 (SW) and 28 (NW)	28	10-28	18	14

'Ideal' and 'current' timelines for pathways for lymphoma (from referral and treatment centres in the North West and South West) and ALL treatment (North West only). 'Ideal' timelines for lymphoma and ALL pathways and 'current' timelines for ALL were based on survey returns. 'Current' timelines for lymphoma referrals were based on patient record assessment of 57 referrals over a 12-month period at the two project delivery sites to give a more accurate picture. Median days are documented to account for outliers where patient specific factors affected timelines.

** This reflects the two project delivery sites*

***South West discharges on day 17 (median) after infusion unless significant toxicity but are then moved for an additional time to near hospital accommodation where appropriate.*

Table 1 demonstrates that time from referral to apheresis was approximately a week longer than the ideal, and that time from apheresis to infusion is also longer than ideal ranges. It was commented during interviews that capacity constraints in both apheresis and inpatient wards contributed to some delays in the pathway, although patient specific reasons behind any delays were not explored. The role of the NCCP was considered by some as extending the timeline for some patients. In ALL, timings following appointment at the CAR-T treatment centre were all longer than the ideal stated.

Ideal and current timelines were also surveyed for the CAR-T centres nationally (Table 2).

Table 2	**Lymphoma**		**ALL**	
	Current (approx.)	**Ideal**	**Current** (approx.)	**Ideal**
	No. of days (Range)		**No. of days** (Range)	
Referral to appointment at CAR-T treatment centre	2-7	5-7	1-2	2-5
Patient seen at CAR-T treatment centre to apheresis	14-21	14-21	12-14	7-14
Apheresis to CAR-T infusion	21-40	21-40	25-28	20-28 (Depends on patient)
Infusion to discharge	10-28	10-28	10-18	14-28 (Depends on toxicity)

National CAR-T centre feedback on current and ideal referral and treatment timescales (lymphoma and ALL) Data based on survey returns received. Timescales were approximated by the centre by CAR-T treatment centres nationally with relatively large ranges.

Table 2 illustrates ALL patients appear to be seen and apheresed marginally quicker than those with lymphoma. Similarly, ALL patients appear to be discharged more quickly than those with lymphoma. The length of in patient stay likely depends on the product received and the individual's response to that product, particularly if complications are experienced, such as ICANs and CRS. Ideal timescales were in line with the reported current timelines throughout.

CAR-T centres who treat lymphoma and ALL patients were asked how satisfied they are with the current process, and we heard that:

- 33% were very satisfied
- 50% were satisfied
- 16.5% were dissatisfied

3.5 Causes of delays in the referral pathway

Survey feedback across the country noted a range of perceived delays along the pathway (delays were reported by 75% of CAR-T treatment centres). Table 3 documents the reasons for the delays noted in survey results and interviews as well as improvements suggested by respondents. The results revealed a regional difference that whilst in the North West referrals are made directly to the CAR-T treatment centre, in the South West initial delays had been caused by referrals being triaged through an allograft centre which does not deliver CAR-T.

As more allograft centres are commissioned to deliver CAR-T in future, this picture is likely to evolve. In the case of myeloma, there is not an existing pathway as CAR-T is only available in clinical trials and respondents had little to no experience of the lymphoma pathway.

Table 3

Cause of delay	Improvements to the pathway suggested by survey respondents or at interview
• A lack of capacity in: – Apheresis – Clinical trial teams – Inpatient wards and ITU – Manufacturing • When transfer of imaging, organ function and histopathology reports are not provided in time for the initial consultation • Timing of biopsies / re-biopsies	• Earlier receipt of referrals • Referral centres to have sight of NCCP referral/Blueteq form • Introduction of a standardised electronic referral system (with an accompanying e-form) which would allow safe and secure file sharing, and help ensure necessary data is available to all stakeholders and coordinators (although one interviewee noted electronic forms may not be beneficial) • Mandatory early transfer of imaging, organ function and histopathology reports, in time for the CAR-T led centre MDT meeting • Availability of re-biopsies at the correct point in the pathway, to avoid delays

3.6 Referrals and pathway communications

Referral to MDT occurs by several different routes, as shown in Graph 2. For local MDTs, there was a high rate of electronic portal usage (41%), with emailed proformas/referrals used by 53%. For regional MDT referrals there was higher use of electronic proforma (59%). Paper proformas were rarely used.

Graph 2: Modes of referral to local MDTs for both the SW and NW responses by percentage of the total responses

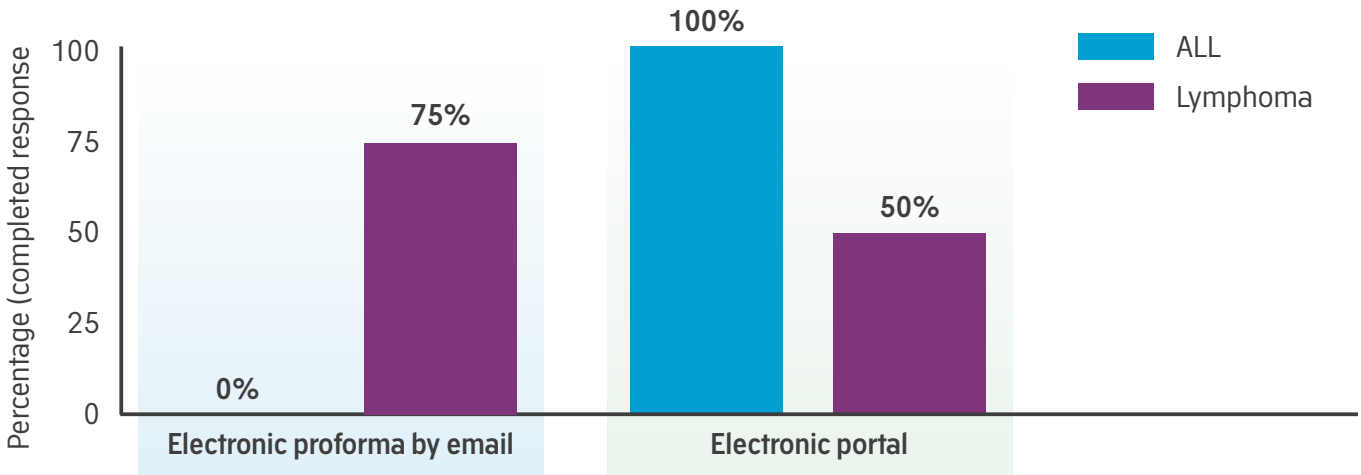
6% Paper proforma
18% Email to MDT coordinator
35% Electronic proforma by email
41% Electronic portal

Graph 3: Modes of referral to regional MDTs for both the SW and NW responses by percentage of the total responses

8% Paper proforma
17% Email to MDT coordinator
42% Electronic proforma by email
33% Electronic portal

CAR-T centres were asked which mechanism they use to refer to their local / regional MDT (Graph 4). The majority, across all disease groups and MDTs, use an electronic proforma sent via email or an electronic portal.

Graph 4: Mode of referral by national CAR-T centres to MDT, by disease group



Note some centres reply via 2 methods

With regards to patient referrals into the CAR-T pathway, it was found that:

- Referral and treatment centres communicate initially via phone call / email and follow up with a formal letter at referral. Letters are sent between centres to update on treatment.
- It would be particularly useful to have a shared patient record across referral and treatment centres, including clinic letters, and that safe storage of communications between referring and treating clinicians should be facilitated (but this would require an NHS wide change).
- Proformas to ensure all necessary information is given at the time of referral were thought to be helpful by the majority as a valuable way in which to standardise processes.
- However, both informal and formal routes of communication were valued to optimise efficient transfer of information and timely patient progression along the pathway.

Two CAR-T centres who responded from the perspective of myeloma were asked what process they would propose for referral of these patients for CAR-T, as an NHS funded therapy. They indicated differences in preference between a web portal, to share best practice and enable an audit and an email followed by a letter to CAR-T and disease group teams (in line with the myeloma autologous transplant pathway).

3.7 Clinical trials

Feedback from all centres noted that the same pathway and processes were used to access CAR-T via standard of care routes and trials. When asked about the constraints that can limit trial recruitment at their site, the following information was provided across all disease groups:

- Limited capacity across research nurses, clinical trials units, apheresis, inpatient, and ambulatory care
- Long set up times caused by limited capacity across the system
- Delays in regulatory approval
- Complexity of trials in co-ordinating multiple processes and teams
- Not all CART trials being open at the centre
- Meeting demand as the number of CAR-T indications grow

3.8 Meeting the needs of underrepresented patient populations

67% of respondents from CAR-T centres across the UK who treat Lymphoma and ALL thought there may be inequality in patient referrals amongst those suitable for CAR-T. Anecdotal feedback was that the following groups may be underrepresented in CAR-T treatment:

- Those in lower socio-economic groups
- Ethnic minorities
- Patients living in rural areas
- Those who live furthest away from treatment centres
- Older patients

We asked interviewees for feedback on which groups may be underserved and why, and were told that:

- Some patients are unwilling to travel long distances to receive CAR-T, though centre expansion may help here
- There is a reduced ability for patients from low socio-economic groups to access care, with travel and accommodation costs a factor here
- Centre expansion and the broadening of licensing to include additional lymphomas will help to facilitate access

3.9 Patient centred communication and feedback

Surveys were sent to six CAR-T advocacy groups across the UK and a patient representative to assess patient experience, with a 57% response rate. Themes included patient information resources already available, gaps in information and support available, and barriers to access:

1. **Patient information leaflets and resources currently available include:**
   - Links to manufacturer specific websites and booklets
   - Leaflets and resources available on several national websites, including a range of patient groups, NICE and NHS England
   - CAR-T specific leaflets provided by NHS trusts
2. **Gaps in information, resources and support available include:**
   - Case studies on UK CAR-T patient stories
   - Fertility data in relation to CAR-T
   - Information on other specialised treatments
   - Peer support and buddy groups
   - Travel and accommodation support
3. **Barriers to patient access include:**
   - Lack of availability of support for families of those undertaking CAR-T
   - Travel and accommodation costs
   - Absence of long-term data on treatment outcomes, leading to patient anxiety

This feedback underlines the need for accessible patient information packs to be disseminated to patients considering CAR-T as a treatment option. It aligned to that provided by referral and treatment centres, who highlighted the following feedback from patients as a deterrent to accepting CAR-T:

- Transport and accommodation costs
- Distance from treatment site and availability of family support
- The need to make child-care arrangements
- Language barriers

Examples of good practice in helping to mitigate these concerns are already in place in some CAR-T centres. One CAR-T centre we spoke to noted they provide patient information packs that include:

- General CAR-T planning information, including in relation to nutrition and advanced care planning
- A clinic letter with a summary of consent documents, in a patient appropriate language
- Further information on the advanced care planning session available, including around what to expect on neurotoxicity and ICU admission
- Multimedia patient information with signposting to a network of peer support available

3.10 The future landscape for CAR-T treatment centres

Treatment centres were asked about their plans to increase capacity for CAR-T therapy. Whilst answers varied according to the disease group treated, **75% of CAR-T treatment centres said they planned to expand capacity at their site,** with apheresis, ambulatory care, inpatient capacity and workforce highlighted as priority areas.

One centre treating lymphoma anticipated a reduced demand for Stem Cell Therapy would release internal capacity to provide more CAR-T therapy. The introduction of new therapies with similar side effects to CAR-T-cells (Bispecific T-cell Engagers) is also giving referral centres more experience, which may allow patients to be transferred back to their initial referring centre at an earlier time point after CAR-T. However, it was noted there would need to be significant training and education of medical and nursing teams to enable this.

To meet likely increased demand and maintain quality as demand increases, CAR-T treatment centres recommended:

- An increase in ambulatory care (some already operate a mixed model), particularly as less toxic products become available, to reduce the length of inpatient stays and in turn deliver improvements to patient experience. 100% of survey respondents said they either currently delivering CAR-T in an ambulatory setting or will consider doing so in the future, though it was noted more investment is required to deliver this. One respondent noted that they sat on a national group planning its introduction
- Bridging therapy should be delivered at more referral centres
- Longer term follow-up care should be provided in the community
- New CAR-T treatment centres deliver strong business cases, which include the requirement to have specific specialist staffing and intensive care capacity
- The introduction of a ring-fenced fund, for eligible CAR-T patients, to support with their travel and accommodation costs. It was suggested this could be funded by industry and distributed via a national charity, a model in place in some other countries

In order to deliver these recommendations, review and guidance around the infrastructure and capacity required to deliver CAR-T is needed to ensure sites are ready to deliver CAR-T in a timely fashion.

Discussion

Analysis of survey & interview responses

CAR-T therapy is now established as a standard-of-care treatment for certain haematological malignancies. The NHS was one of the earliest health services to adopt CAR-T therapy with an initial roll out of 7 sites. This has continued to grow over the last five years and a third wave of centre expansion is currently ongoing. This has coincided with an increase in CAR-T indications, with further extension expected over the next few years in other blood cancers (e.g. myeloma) and non haematological malignancies.

Referral pathways for existing and future indications are key for timely treatment and to ensure all eligible patients have access to CAR-T. Whilst significant progress has been made in increasing patient referrals to date, our study has identified several limitations in the process of CAR-T referral and treatment across the patient pathway in the UK. Four themes have been identified that capture the barriers in the pathway:

- **Streamlining patient identification and referral**
- **Addressing inequalities in access to CAR-T**
- **Overcoming barriers in capacity and infrastructure**
- **Delivering reforms aimed workforce, training, and communication**

Theme 1:
Streamlining patient identification and referral

The survey and interviews revealed that the majority of centres identified issues that can cause delays along the patient referral and treatment pathway. Interview feedback highlighted that delays were seen even before the start of the pathway, with patients not always referred at the optimal time. This can impact the effectiveness of treatment, increasing the need for bridging therapy, or in some cases meaning patents become ineligible for CAR-T. There was consistency in the findings from our survey that, whilst access to timely CAR-T was generally achievable within current systems in spite of pressures on the system, there was a lack of spare capacity should eligible patient numbers increase as anticipated.

It is also important CAR-T treatment centres receive all necessary information regarding the patient for the initial referral, including imaging, organ function & histopathology reports. In addition, further investigations may be required as part of this, such as re-biopsies or scans, which need to be performed in a timely fashion and data transferred rapidly.

As highlighted in the results section, electronic proforma and portal are being used now for referral at some centres, and it was suggested that a standardised checklist / electronic form and portal could be used for all referrals to any CAR-T centre to streamline the process, while ensuring all necessary data is included.

Graph 1 indicates up to 50% of centres do not have regional disease specific MDT meetings for the discussion of patient treatment. Whilst there are other meetings which have been used to discuss CAR-T patients, such as those relating to planning of stem cell transplant, they do not usually contain radiology or histology representation. There was near universal support that disease-specific regional MDTs should be a focus for the system in improving the referral pathway, both in terms of improving communication and education of referring centres and in improving governance of decision making – in particular if additional non-CAR-T therapies are approved, which may be more appropriate for the patient. This needs to be balanced with feedback on how additional meetings would fit into job plans and include consideration of support required to ensure effective and efficient running of meetings.

Whilst there are a number of CAR-T trials recruiting in the UK, it appears some potentially eligible patients are not being referred for trial consideration. Reported reasons included a lack of awareness from clinicians on referral routes, available trials, patient suitability and long-term management. It was felt that a UK-specific online resource listing all cellular therapy trials, recruiting sites and latest eligibility criteria would be beneficial to address this and help improve access and patient recruitment. Regional MDTs would also help to raise clinical awareness and ensure appropriate onward referral for clinical trials.

Theme 2: Addressing inequalities in access to CAR-T

The results of the surveys suggested that not all eligible patients may be receiving CAR-T therapy. Potential barriers to access include:

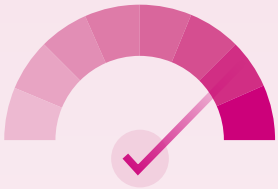
- Those managed by smaller hospitals or in rural areas, where there are long distances to the nearest CAR-T treatment centre
- Financial concerns
- Lack of availability of information in other languages than English
- Eligibility factors e.g. infection and patient fitness

Impact of such factors would be anticipated to have more impact in patients from areas of deprivation and ethnic minorities, the elderly, or patients with HIV related blood cancers.

Referral sites identified that they would like more information on available trials and current indications, whilst CAR-T treatment centres noted they provide regional training events to increase knowledge on these issues.

It is important to note that many of these issues are based on the opinions of those we engaged with therefore projects designed to gain more objective data are important. The issue of geographical distance will also be addressed in part through the addition of more CAR-T treatment centres. Earlier transfer back to local hospitals from CAR-T treatment centres could also help to address inequalities, however this would require a significant focus on training, communication, and support for local hospitals.

Theme 3:
Overcoming barriers in capacity and infrastructure



The current CAR-T delivery process is complex as it is used to treat aggressive diseases that tend to progress quickly, with time to treatment vital for the treatment effectiveness. However, many centres struggle to deliver treatment from initial referral in required timelines due to capacity challenges across the system. A lack of capacity in apheresis, clinical trial teams, inpatient beds, stem cell laboratory and manufacturing facilities were all identified as barriers in the treatment pathway. Meanwhile, whilst the ongoing expansion in the numbers of CAR-T treatment centres will improve the overall capacity of the system, this will not necessarily match the required increase over the next few years to accommodate expected increases in approved indications.

Looking forwards, we heard consideration of different models of delivery is required, for example either centralising capacity for apheresis collection and storage or introducing a networked approach, to allow for the best use of facilities and to maximise existing capacity where constraints are particularly acute. Delivering improvements will be dependent on CAR-T treatment centres' available space, capital, and workforce, as well as national oversight and distance between and timings of transfer between referring and treating centres. However most respondents expected to be able to begin to overcome some of these challenges, noting they planned to expand capacity at their site – with apheresis, ambulatory care, inpatient beds and staffing levels all raised as areas of focus.

In exploring the role of the NCCP in the referral pathway, its future divided opinion amongst survey respondents and interviewees – with various arguments for and against discussed. Some felt that it resulted in delays for more straightforward cases and would not necessarily be practical for possible future indications with higher numbers of patient demand. However, the ability to discuss complex cases and share knowledge on areas such as clinical trial activity was highly valued. Possible options to replace the function of the NCCP in future, including BlueTeq, may undergo a critical appraisal to determine the future eligibility of the decision-making model.

In relation to trials, the same barriers to treatment were also seen – though set up times and regulatory barriers have led to further delays. Some sites set to deliver CAR-T as standard of care may not have the experience or expertise in running such trials to accelerate adoption. To overcome these challenges, it would be useful if treatment pathways, including standardised referral proformas and MDTs, for standard of care products were mirrored in the trial setting.

Theme 4:
Delivering reforms aimed workforce, training, and communication

Education and training

Coordination of care processes between referring and CAR-T treatment centres is essential for successful treatment. Whilst regional MDTs provide an important forum for discussion, as patients are likely to receive more of their care in referring centres over time, communication regarding specific patients and support when late toxicity occurs will need responsive and secure mechanisms to be introduced.

Alongside investments in physical infrastructure, investment in workforce will also be required to manage increased activity. Specific guidance on some role requirements would also be beneficial, including for CAR-T coordinators and CAR-T trial nursing and clinical staff. Expanding education and training of workforce groups involved in the delivery of CAR-T will be particularly important if CAR-T therapy is used in non-haematological malignancy, where the base level of knowledge relating to the treatment will be lower. Whilst CAR-T treatment centres do provide training, we heard from referring centres that more support is required. Putting in place the relevant staff and associated resource to run the service, both currently and as it expands, goes hand in hand with the education and training to ensure a unified yet flexible approach.

Patient support

Communication and support for patients entering CAR-T therapy is very important in delivering good patient experience and satisfaction across the entire pathway, including long term follow up. Whilst existing resources are available to support this, it is important they are available consistently across all sites, including new CAR-T treatment and referring centres.

In light of regional variation in available patient support, national information sharing on good practice delivered to all centres would help to improve clarity and accessibility of patient information. Where possible, this should include the development and roll out of nationally available patient experience videos and the establishment of regional patient support networks. This would help to address concerns we heard from patient advocacy groups around access points for patients and their support, which improved provision of information could help to address. Where new indications become available, a gap analysis of existing information would be required to assess the consistency of information available.

Conclusion and recommendations for change

Summary of findings

The four discussion themes identified above highlighted key areas of change that would enhance the current and future CAR-T referral pathway to ensure maximum accessibility for eligible patients. Based on our engagement with referral centres, CAR-T treatment centres, and patient advocacy groups, we have developed a series of key recommendations across each of the themes.

This work sits alongside a recent report[14] looking at addressing variations in patient referrals and improving patient experience. Many of our findings are aligned, with key areas for change focused on establishing formalised guidance (principally around MDT processes), delivering workforce requirements and introducing flexible education and training, which is reflected in the below proposed recommendations.

Recommendations for change

A list of justified recommendations to improve the patient referral pathway, based on the data collected, are detailed below:

Theme 1: Streamlining patient identification and referral

1. **Formalised referral processes should be established from secondary care to CAR-T treatment centres, to support streamlined patient referrals across the UK, with mechanisms to ensure referrals are received at the earliest time to minimise delay.**

   As part of this:

   - A standard electronic referral system (with e-forms and/or checklist) and portal should be introduced, to ensure easy access for standard-of-care and trial pathway CAR-T, and to encourage earlier referral
   - Clear guidance should be developed and disseminated on CAR-T to support referring sites, for example detailing the imaging, organ function and histopathology report requirements and the expected timeframes to feed into CAR-T centre led MDTs
   - Standardisation is needed in the implementation of Haemato-oncology MDTs roles and requirements. This should be evaluated against current NICE guidance and where they are not already in place, the introduction of regional disease specific MDTs. It may be beneficial for NHS England to review variations in how MDTs are carried out
   - There should be support and encouragement of ongoing informal support/links within this formalised structure/guidance e.g., by having up to date contact telephone numbers and shared inboxes at CAR-T treatment centres.

2. **Mechanisms should be established to ensure referrals are received at the earliest time point to minimise delay in the patient pathway.**

   Expectations for timelines of different components of the pathway should be included within the service specification and incorporated into commissioning requirements for CAR-T treatment centres and referring centres. Where applicable, Service Level Agreements between different organisations in the pathway should contain expected timelines so that patients move through the treatment pathway at an appropriate rate to disease and service from including:

   - Referral to patient eligibility review
   - Apheresis to infusion
   - Infusion to discharge

Theme 2: Addressing inequalities in access to CAR-T

3. **Work should be carried out to identify causes of variation in access to CAR-T, with targeted measures then implemented to support access for this demographic.**

This should include:

- A gap analysis of existing patient information
- Strengthening of patient support information/packs at a national level, to ensure they are clear and accessible to all
- Dissemination of existing national patient information available to non-CAR-T and CAR-T treatment centres
- Access to nationally available patient experience video/s should be explored across all current indications (with a provision for new indications). Hosting and signposting should be defined and communicated through relevant channels, for example via ATTCs/NHS England
- Establishing regional patient support networks
- Introducing a ring-fenced fund, for eligible patients, to support with their travel and accommodation costs, where distance to CAR-T centre is an issue

Theme 3:
Overcoming barriers in capacity and infrastructure

4. **A review of the capacity and infrastructure across the system required to deliver CAR-T should be carried out, both now and in anticipation of future demands, to ensure the system is ready for anticipated increases in CAR-T patient numbers and approved indications.**

   This should include:

   - Enhancing coordination of care between referring and treating consultants, in line with formalised guidance on the referral process guidance called for above
   - Establishing guidance on staffing requirements, and associated investment needed, to deliver a CAR-T service as part of a new suite of guidance. This should include the role and requirement of a CAR-T coordinator, and quality, research and data management staffing
   - Guidance on infrastructure and capacity management should be developed, alongside relevant horizon scanning, to meet requirements for apheresis, stem cell laboratories, and the provision of inpatient/ambulatory care provisions in both the standard of care and trial setting

Theme 4:
Delivering reforms aimed workforce, training, and communication

5. **Reforms aimed at delivering improvements in training and communication within the CAR-T workforce should be implemented.**

   This should include:

   - As part of existing staffing guidance, a recommendation that consultant haematologists and other key staff allocate time and resource to running regional training with referral sites to address variation in local understanding of the CAR-T referral process
   - The development of a dedicated CAR-T education programme for stakeholders at all points of the CAR-T referral and treatment pathway
   - Encouragement of knowledge sharing, including examples of best practice - both formal and informal – as part of formalised CAR-T education guidance. This should include the setup of a UK specific website of active CAR-T trials with eligibility criteria and open sites, with collaboration and communication a key factor in driving earlier CAR-T patient referrals
   - The introduction of a UK based resource highlighting advanced therapy trials with eligibility criteria, open centres and routes for referral

References

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6 NICE Guidance (Tecartus for treating relapsed or refractory mantle cell lymphoma): https://www.nice.org.uk/guidance/ta677

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CAR-T referral centres in North West England

CAR-T referral centres in South West England

CAR-T treatment centres across England

Appendices

Appendix 1: Abbreviations

ABPI	Association of British Pharmaceutical Industry
ALL	Acute Lymphoblastic Leukaemia
ATTC	Advanced Therapy Treatment Centre
ATMP	Advanced Therapy Medicinal Product
BMT	Bone Marrow Transplant
CAR-T	Chimeric antigen receptor T-cell
CDF	Cancer Drug Fund
CGT Catapult	Cell and Gene Therapy Catapult
CRS	Cytokine Release Syndrome
DLBCL	Diffuse Large B-cell Lymphoma
ICANS	Immune effector cell-associated neurotoxicity syndrome
IEC	Immune Effector Cell
MCL	Mantle Cell Lymphoma
MDT	Multi Disciplinary Team
MHRA	Medicines and Health Care products Regulatory Agency
MM	Multiple Myeloma
NCCP	National CAR-T Clinical Panel
NHL	Non-Hodgkin Lymphoma
NHSBT	NHS Blood and Transplant
NICE	The National Institute for Health and Care Excellence
NHSE	NHS England
R/R	Relapsed or Refractory
SoC	Standard of Care
TYA	Teenage and Young Adult

Appendix 2:
Overview of MDTs involved in CAR-T patient referral pathway

Secondary care referral centre Multi-Disciplinary Team (MDT)

Membership of the MDT usually includes a Haematologist, Radiologist, Pharmacist, Specialist nurse, Oncologist.

Some sites also include a Pathologist and/or Haemato-pathologist.

Discussion focuses on potential: eligibility for CAR-T treatment; trials; Standard of Care (SoC) treatment; appropriate CAR-T centre.

CAR-T treatment centre MDTs

The following reflects CAR-T MDTs who discuss lymphoma treatment. Membership includes a Haemato-oncologist, Radiologist, Specialist nurse (patient advocate), Research Department representative, Medical / Clinical Oncologist.

Some sites also include a: Histopathologist; Pharmacist; Research nurse; Ambulatory care nurse; Stem Cell Lab representative; Prehabilitation lead; Haematology Malignancy Diagnostic Service representative; CAR-T and Palliative care Consultants.

Discussion on individual patients may take place at both eligibility and bridging therapy/scheduling MDTs. There is a focus on: organ assessments, especially where there is an impairment, the treatment plan; appropriate trial/s; potential treatment scheduling; response to bridging therapy.

National Clinical CAR-T Panel (NCCP) – lymphoma

The panel is usually attended by the Chair, a patient advocate, a CAR-T consultant, Haemato-oncologist, Non-CAR-T physicians, and a representative from NHS England.

Discussion focuses on eligibility to receive CAR-T. If eligible, the referring CAR-T centre will identify the product; if ineligible, reasons are provided, for example, further treatment required before eligibility can be re-considered, or patient no longer well enough to receive CAR-T.

They also discuss the management of complex cases, sharing of specialist knowledge between sites, and opportunities for new research and publications.

Appendix 3: Process maps

Process map key

Start / end point

Process step

Decision point

Start point

Site where referral begins

Referral route from secondary care site without stem cell therapy / CAR-T treatment centre

Referral route from secondary care site with autologous treatment centre

Referral route from secondary care site with allogeneic treatment centre

Referral route from secondary care site with CAR-T treatment centre

Referring site MDT process

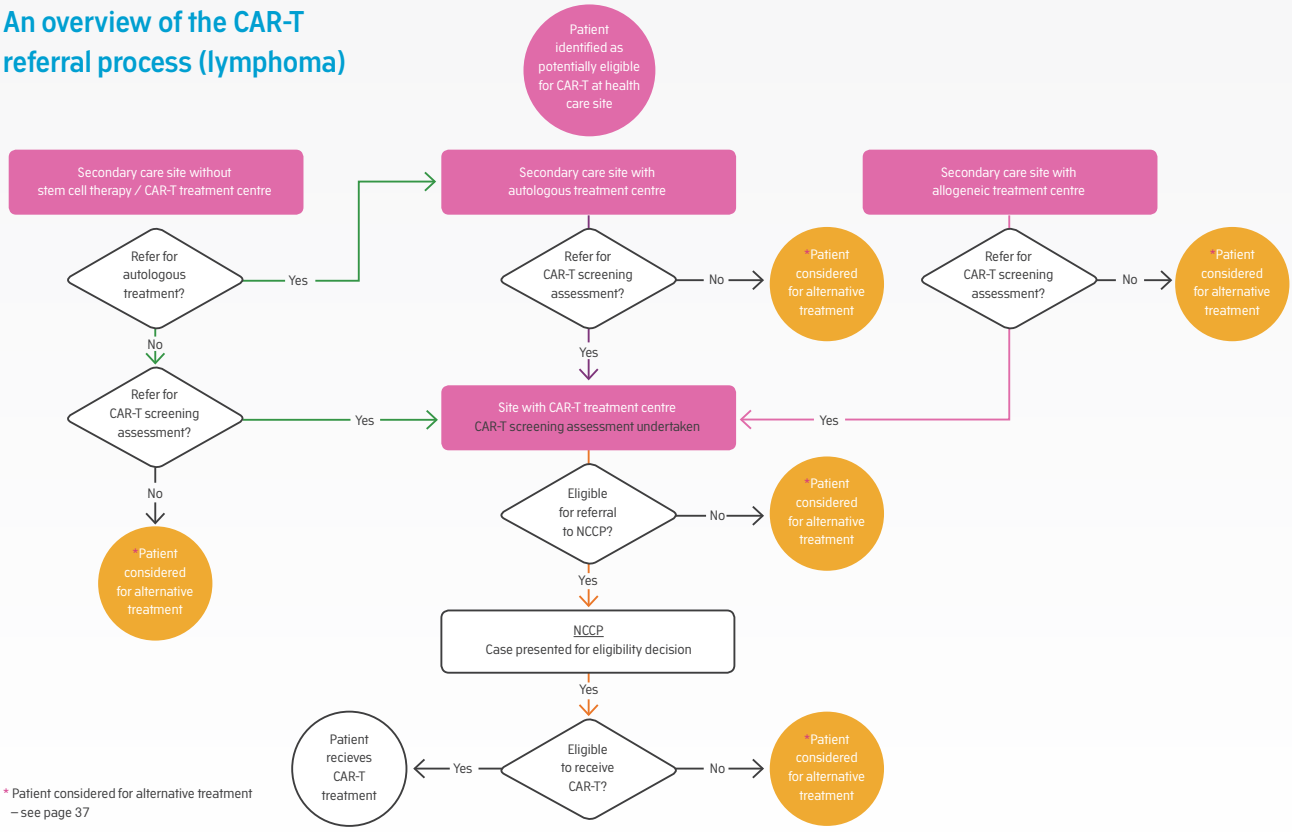
CAR-T centre MDT process

NCCP process

Referral route

Direction of work flow

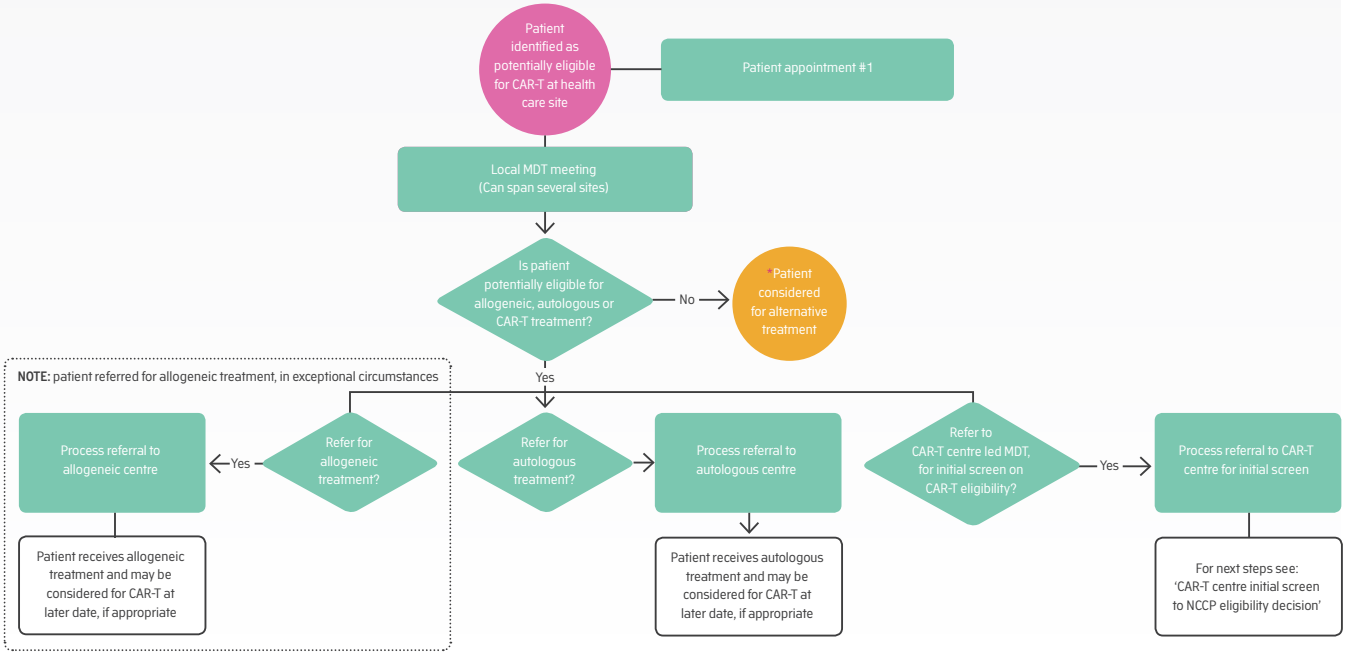
An overview of the CAR-T referral process (lymphoma)



* Patient considered for alternative treatment – see page 37

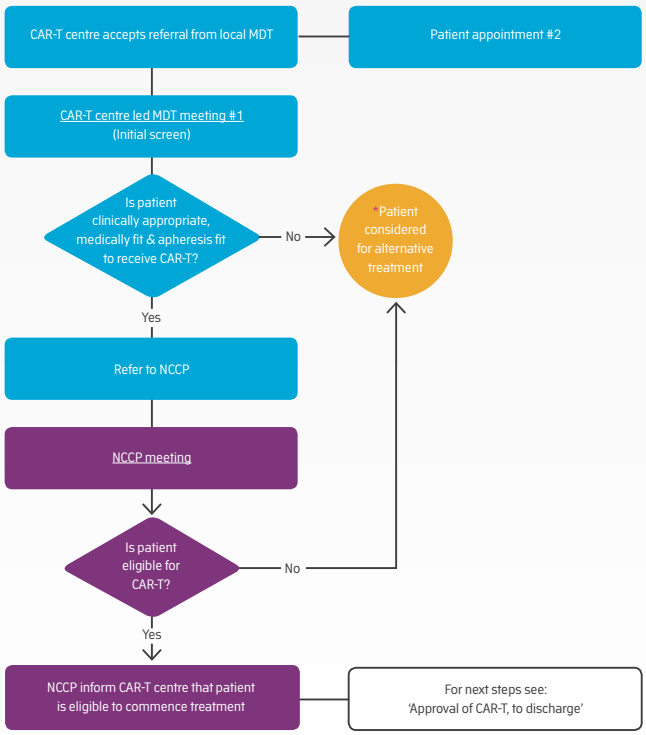
Patient identification, to initial eligibility screen at CAR-T centre (lymphoma)

This process map covers first identification of a potentially eligible patient in a health care setting (appointment 1). The MDT, which can cover one or more local sites, assesses potential eligibility and decides whether to i) refer the patient for autologous or in exceptional circumstances allogeneic treatment, prior to initial screen for eligibility at a CAR-T led MDT, or ii) refer direct to a CAR-T centre led MDT for eligibility screening.



CAR-T centre initial screen, to NCCP eligibility decision (lymphoma)

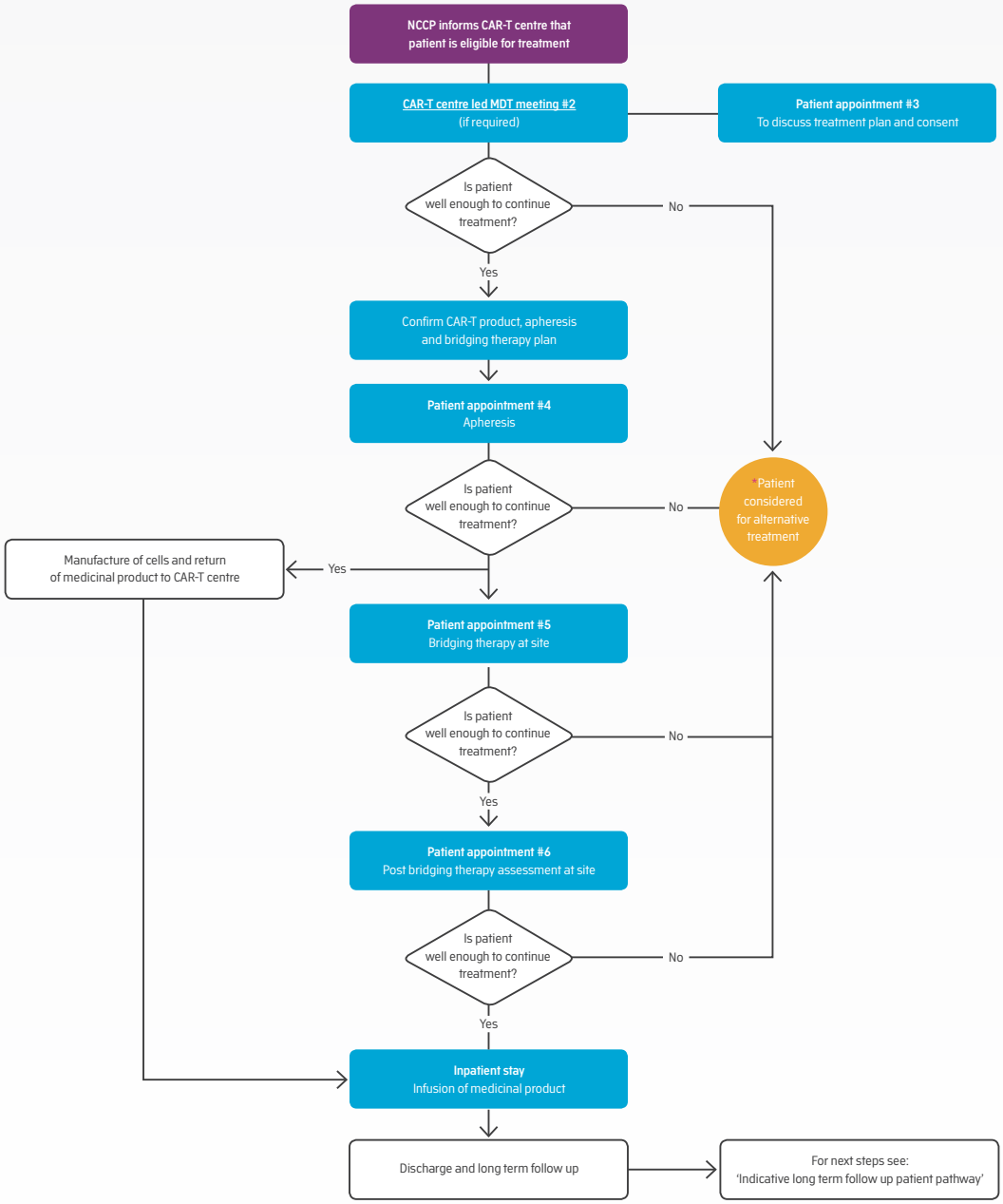
The CAR-T centre accepts a referral and completes the initial eligibility screen to determine whether the patient is suitable for CAR-T. If the patient meets the criteria (appointment 2) a referral is made to the NCCP who determine if and where CAR-T will be delivered with feedback to the CAR-T centre on its decisions. If the patient is ineligible, the reasons are communicated to the referring CAR-T centre who discuss alternative treatment options with the patient.



Approval of CAR-T treatment, to patient discharge (lymphoma)

Following a positive NCCP eligibility decision, the CAR-T centre led MDT discusses if the patient continues to be well enough to receive treatment. The following steps then occur:

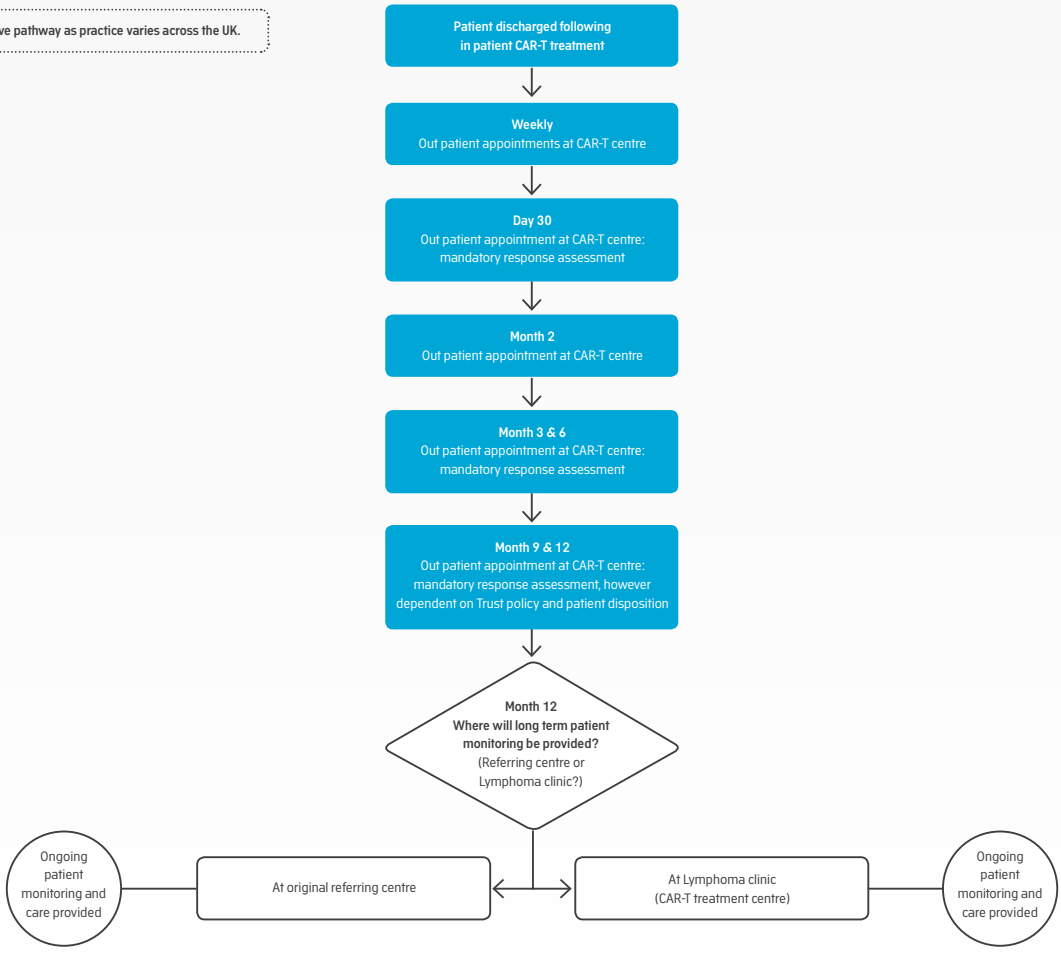
- Patient appointment 3 is made, to discuss a CAR-T treatment plan and consent. The CAR-T product is confirmed, and plans are then made for apheresis and bridging therapy.
- Apheresis is then undertaken (appointment 4) and cells are sent for manufacture.
- Bridging therapy is undertaken at the CAR-T centre/referring site (appointment 5) where appropriate.
- A post bridging therapy assessment takes place (appointment 6). Whilst the medicinal product is being manufactured, an inpatient stay (of at least 14 days) is scheduled, for the patient to receive a CAR-T infusion and monitoring for toxicities.



Indicative long term follow-up patient pathway (lymphoma)

Following discharge, follow up outpatient appointments take place weekly for the first month. At day 30 (post infusion), there is a mandatory response assessment. At month 2 progress is assessed and the mandatory response assessment is repeated at the end of months 3 and 6. Some sites repeat mandatory assessments at months 9 and 12. At month 12 there is a decision on where longer-term monitoring will take place (original referring site, or centre where CAR-T treatment was received).

This is an indicative pathway as practice varies across the UK.



Alternative treatment options

Alternative treatment options may be considered during the CAR-T referral pathway as indicated by the following symbol:

*Patient considered for alternative treatment

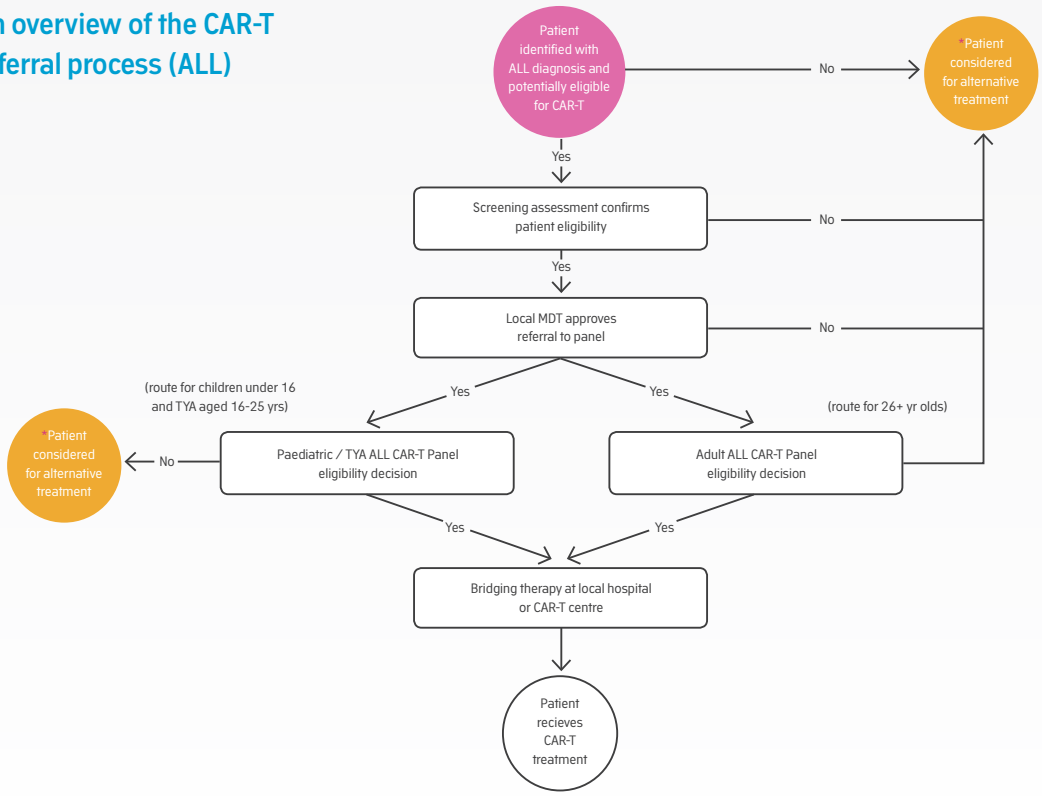
Alternative treatment options

These options may include:

- Further standard of care treatment, with the option of being considered for CAR-T, if the patient is well enough and beomes eligible at a later date
- Further standard of care treatment offered, as the disease has progressed to a stage where the patient is not likely to become well enough to be considered for CAR-T
- Consideration for recruitment to a clinical trial
- Best supportive care

Appendix 4: Process maps

An overview of the CAR-T referral process (ALL)



Appendix 5: Outline business case

Management Leads:

Departmental Impact:

Introduction

Summary

Reasons

The reasons for making a change (Based on the results/discussion of white paper)

Business Options

Analysis and reasoned recommendations for doing the below:

Do Something – The implementation of all the recommendations set out above

Do the Minimum – The implementation of some of the recommendations set out above

Do Nothing – Do none of the recommendations set out above

List all options/key milestones in line with sections 1-3 above

Justify the recommended option/s

State approvals needed (Boards etc.)

Expected Benefits / Dis-Benefits

What are the pros and cons of implementing the recommendations?

Benefits (SWOT Analysis) – type, baseline and measure (financial/quantitative/qualitative – link into data collection and peripheral impacts, followed by predicted improvements with dates)

Key considerations

Activity impact – patient type, specialities, research, education

Workforce impact

Equality and Diversity Impact

Informatics

Data Protection Impact Assessment

Estate and Facility Impact

Other themes to consider: Health Benefit/User experience/Corporate impact/Supporting innovation in the development of services/facilitating research

Timescale

Planned implementation date/s

Other relevant dates

Cost

Summary finance – by category (staff/capital/equipment) and Year – What and when

Staffing (Salaries/On-costs/overheads)

Source of funding

Provision for other resources

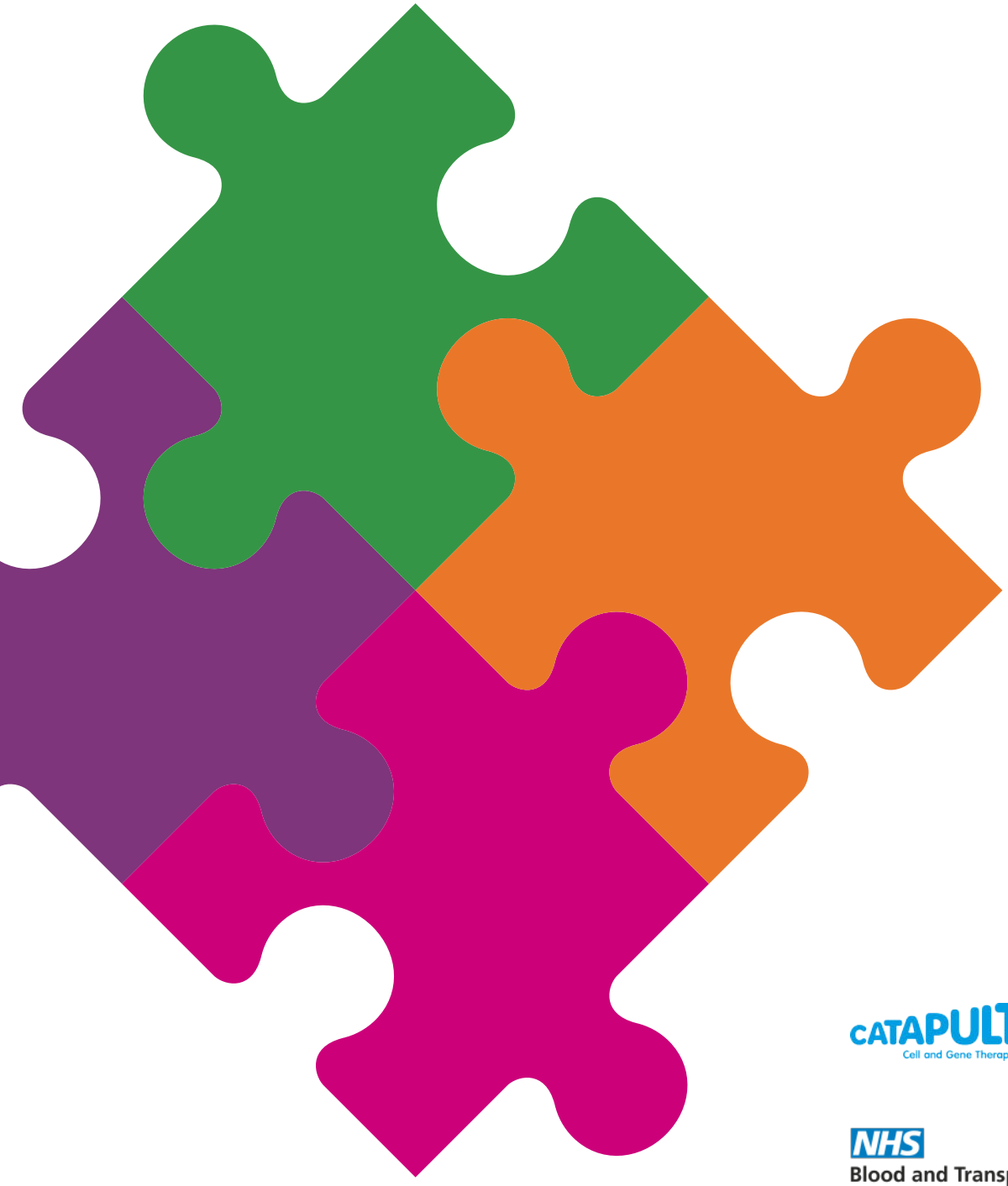
Investment Appraisal

Analysis of benefits of investment and how it meets all/some of the corporate objectives:

1. To demonstrate excellent and equitable clinical outcomes and patient safety, patient experience and clinical effectiveness for those patients living with and beyond cancer.
2. To be an international leader in research and innovation which leads to direct patient benefits at all stages of the cancer journey.
3. To be an international leader in professional and public education for cancer care.
4. To integrate our clinical, research and educational activities as an internationally recognised and leading comprehensive cancer centre.
5. To provide leadership within the local network of cancer care.
6. To maintain excellent operational, quality, and financial performance.
7. To be an excellent place to work and attract the best staff.
8. To play our part in the local healthcare economy and community.

Risks

Score before and after implementation and mitigations



Cell and Gene Therapy Catapult, The Advanced Therapy Treatment Centre Network, NHS Blood and Transplant, The Christie NHS Foundation Trust, Autolus Limited, Gilead Sciences Ltd, Janssen-Cilag Limited.

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