

White Paper

Healthcare system readiness for the adoption of advanced therapies: learnings from the introduction of CAR T cell therapies in the UK

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Executive Summary

The adoption of CAR T therapies in the UK NHS is a success story, especially seen in relation to the experience in many other countries. The UK NHS showed itself to be agile, and responsive to addressing the unique challenges these therapies present, which facilitated access to patients earlier than in many other countries. (including delivery centre selection, development of service specifications, collaboration with manufacturers throughout the preparation phase for adoption, establishment of national multidisciplinary CAR T team to ensure equity of access and prioritization of resources (where needed)).

As we look into the future and the several likely ATMP launches it holds, it is worthwhile to reflect on the experience so far, using the experience of the adoption of the CAR T therapies to inform learnings about factors that contribute to and determine healthcare system readiness, and the ability of more hospitals to adopt these therapies. These learnings can be taken onboard by key market access stakeholders with an emphasis at local level (i.e. hospitals looking to accommodate the increasing number of ATMPs and potential target patients).

We have identified the following key topics that are relevant to and influence the hospital-level readiness for adopting CAR T therapies in the NHS. Broadly speaking there are four groups of topics, and we elaborate on the challenges associated with each topic and their subcategories in this report.

1) Pre-requisites for treating centres adopting CAR Ts

- a. Centre accreditation:
- b. Staffing training
- c. Hospital infrastructure capacity

2) Treatment and patient pathway at the hospital level

- a. Diagnosis and patient selection
- b. Pharmacy team ordering and contracting for the product
- c. T-cell extraction (leukapheresis) and preparation for shipping
- d. Bridging therapy (for patients who deteriorate)
- e. Conditioning therapy
- f. Receipt of CAR T product from manufacturer
- g. Storage until infusion
- h. Issue of product from storage and preparation for infusion
- i. Administration/ infusion
- j. Post-treatment management in hospital and community (first four weeks post infusion)
- k. Post-discharge management (medium and long term)

3) Information management infrastructure (digital) requirements

- a. Systems to track product and patient between leukapheresis and infusion (*vein-to-vein*)
- b. Systems to record and track patient outcomes for the purposes of:
 - i. Ensuring the safety and well-being of the patient
 - ii. Complying with the regulatory requirements (i.e. EMA PASS), and the requirements of the Cancer Drugs Fund (CFD), as levied by NICE and NHS England, and the national MDT

4) Hospital reimbursement requirements

- a. The costs of the CAR T product and the associated patient care are considerable; availability of appropriate tariff payments for CAR Ts is crucial to ensure a financially sustainable access to these treatments
- a. To assign hospital activities to reimbursement tariffs, accurate clinical coding is required in order to capture all costs
- b. In a separate process to clinical coding, hospitals in England must collect and submit cost data to the NHS National Cost Collection, this needs to be accurate to determine future tariff prices of CAR T delivery
- c. Funding for capital items such as beds and buildings, as well as staff training, must come from hospital efficiencies, or applied for separately to service delivery funding

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Introduction

For many ATMPs, being approved for use in the NHS is not enough to enable timely adoption. Chimeric Antigen Receptor (CAR) T-cell therapies (e.g. Kymriah[®] and Yescarta[®]) rely on highly complex requirements in terms of the care pathway, clinical infrastructure, and skill of the clinical staff to be delivered successfully to patients. Institutional readiness is therefore a crucial component to enable timely adoption for advanced therapies after a reimbursement recommendation has been made, as well as for optimising patient outcomes. Furthermore, the costs incurred by hospitals for treating and managing these patients (e.g., costs of apheresis, storage and handling, infusion, managing toxicities, ICU stay etc.) are high and therefore there is need for timely funding arrangements to be in place so that hospitals can appropriately be reimbursed for the delivery of such therapies.

There are many initiatives underway to generate learnings from the early phase of adopting ATMPs in the NHS, and the implications in terms of institutional readiness, so that these can be taken onboard by other hospitals looking to adopt ATMPs in the future, including:

- Multiple initiatives on institutional readiness driven by the ATTC Network e.g.
 - ATTC knowledge hub (e-learning and webinars for upskilling staff)
 - NA-ATTC resource/ assessment tool for institutional readiness, based on learnings from clinical adoption of ATiMPs (through surveys of NHS/Industry) (3)
 - Paper titled *The Development of a CAR T Therapy Service at Leeds Teaching Hospitals Trust* (NA-ATTC /Leeds) – describing the challenges of setting up the service, lessons learnt and recommendations
 - MW-ATTC: primary research within the NHS by Nia Evans (Consultant Pharmacist ATMP & Haematology at Cardiff and Vale University Health Board) on lessons learnt from CAR Ts.
 - NA-ATTC/Autolus to develop a CAR T 'guide for patients and carers' detailing 'what to expect' at each stage of the journey (based on real patient experiences)
 - Initiatives on supply chain /logistics /procurement /labelling (but not CAR T specific)
- Initiatives by MHRA and EBMT's GoCART aim to harmonise site accreditation requirements, and collection of patient data post-treatment
- Initiatives of the pan-UK Pharmacy Working Group (4)
- Accelerated Access Collaborative (AAC) work streams (WS)

- WS#2: NHS England horizon scanning
- WS#4: Standardisation
- WS#5: On data infrastructure for managed access
- Industry-led initiatives generating learnings from the launch of CAR Ts (e.g. Kite/Gilead think piece on informing the future of ATMP provision, and call for the development of a national cell and gene therapy strategy for England)

Since Kymriah and Yescarta were commissioned for use in the NHS about two years ago, several successes have emerged from the experience so far. Manufacturers highlight the agility of the NHS in quickly identifying centres of excellence to provide the therapies, the rapid upskilling of staff in these centres, as well as the swift development of service specifications. Where issues did emerge, the NHS was able to act decisively to implement changes, and the close collaboration between the NHS and industry is highlighted as a key to the successful adoption. The early and sustained dialogue between these key stakeholders ensured rapid patient access, and that issues arising were dealt with timely and effectively.

In addition, as more NHS patients have been treated, the process of gathering patient outcomes data and economic data on the cost of caring for patient undergoing CAR Ts got underway. These processes are highly important from a broader NHS perspective, as they inform the assessment of long-term treatment safety and effectiveness of the therapies (for both regulatory and reimbursement purposes), as well as generating an evidence base of cost data to inform the creation of appropriate hospital payments for patients treated with CAR Ts in the future. Given the novelty of the marketed therapies and the limited number of patients they target at the moment, it can be a challenge to ensure that outcomes and cost data are collected and managed appropriately, and that these data management processes are fit for scaling as new therapies are adopted.

This white paper builds on the existing efforts and initiatives relevant to CAR T adoption to generate learnings for NHS hospitals seeking to provide cell and gene therapies.

Objectives

The objective of this white paper is to capture learnings across the Advanced Therapy Treatment Centres (ATTC) network and beyond from the recent launch of CAR Ts. These learnings will provide a resource to improve hospital-level readiness for adoption of advanced therapies, using the CAR T therapies as an exemplar.

Materials and methods

Secondary and primary research was performed to detail requirements across the different steps in the treatment pathway (in terms of infrastructure, training, processes, inter-stakeholder communication):

- The main point of focus is local-level readiness
- A secondary focal point is the touch points with national level, e.g. the development of appropriate information systems for collecting data on patient outcomes and for reimbursement of providers

In addition, we leveraged the expertise of different ATTC working groups, providing input from NHS and industry stakeholders. As these working groups already cover many of the topics relevant to the pre-requisites for treating hospitals and detail the patient and therapy journey, we focused the primary research effort (stakeholder interviews) on topics relating to the payment (reimbursement) of hospitals.

Key topics relevant to CAR T adoption

In the below, we outline some of the key hospital-level factors that determine the capacity for patient access and adoption of CAR T therapies in the UK NHS. We have divided this into four main categories:

1. Pre-requisites for prospective advanced therapy centres of excellence
2. Treatment and patient pathway at the hospital-level
3. Information management infrastructure requirements
4. Hospital reimbursement requirements

Pre-requisites for treating centres

Centre accreditation

Prospective providers of ATMPs are required to obtain accreditation from the Foundation for the Accreditation of Cellular Therapy (FACT)-JACIE (7th edition), and from the manufacturers of the relevant therapies (5-7). The accreditation process involves e.g. writing standard operating procedures, developing pathways and guidelines, which is very labour intensive, and can take “thousands of hours” (1). It is also work intensive for JACIE, who have a backlog of centres to accredit due to pandemic causing delays.

In addition, hospitals need to have a Human Tissue Authorisation License in order to enable procurement of the starting material for the CAR T therapies, as well as being able to export/import cell materials (e.g. where the manufacturing site is not in the UK, as is the case for e.g. Kymriah[®]) (7).

There are initiatives in place, like the EBMT’s GoCART initiative, that aim to harmonise accreditation requirements to simplify this process (8).

Staff training and establishing multidisciplinary teams (MDTs)

Having an adequate number of appropriately trained staff is key to enabling patient access and optimising outcomes from treatment with CAR Ts. With staff resources typically being stretched in the NHS, it can be a challenge to release staff from normal day-to-day duties to attend the required training (9). The Advanced Therapy Treatment Centres’ (ATTC) website provides a host of materials (e.g. webinars, e-learning, standard operating procedures [SOPs], etc.) that can facilitate this through their Knowledge and Resources sections (10, 11).

Establishing multidisciplinary teams (MDTs) at the trust-level is another key criterion for CAR T providers. The core team of local-level MDTs should consist of (12):

- Haemato-oncologists (either haematologists or some medical oncologists): at least two who specialise in each tumour type being discussed at that meeting (e.g. leukaemia or lymphoma). At least one from each hospital site contributing to the MDT.
- Haematopathologist: at least one haematopathologist from the specialist integrated haematological malignancy diagnostic services (SIHMDS) should be present; to provide the diagnostic information.
- Nurses: at least one clinical nurse specialist, also ward sisters from hospitals which provide high-intensity chemotherapy.

- Palliative care specialist: at least one palliative care specialist (doctor or nurse) who liaises with specialists from other sites. If, because of staff shortages, a palliative care specialist cannot regularly attend MDT meetings, the MDT should be able to demonstrate that it reviews patients regularly with such a specialist.
- Support staff: staff to organise team meetings and provide secretarial support.

Teams established to manage patients with lymphoma should include the following additional core members, who should be fully and regularly involved in MDT discussions (12):

- Clinical oncologist: at least one.
- Radiologist: at least one, who liaises with radiologists at other sites

The MDT should include the following extended team members. They do not have to be present at every MDT meeting (12):

- Clinical member of the transplant team to which patients could be referred
- Microbiologist (especially for patients with leukaemia)
- Pharmacist
- Vascular access specialist
- Registered dietitian
- Orthopaedic surgeon (myeloma MDT)
- Clinical oncologist (myeloma MDT and leukaemia MDT; provision of cranial radiotherapy for patients with acute lymphoblastic leukaemia (ALL) is an important role for a clinical oncologist)

The local, trust-level MDTs play a key part in the review of potential CAR T patient candidates, and once the assessment has been undertaken at the hospital level, the patient candidate profile is sent to the national MDT for confirmation (see the section on Diagnosis and patient selection below for more information).

Establishing MDTs took some centres longer, and needing to have neurology specialists on call was a barrier in one centre, while other centres highlighted challenges in convincing the hospital to make staff hours available. While these challenges were all manageable, they did contribute to delays in scaling up patient access, according to industry experience. Setting up the CAR T service and the availability of appropriate training were also highlighted among the key challenges in the white paper developed on learnings from the development of the CAR T Therapy Service at Leeds Teaching Hospitals Trust.

Hospital infrastructure capacity

Providing CAR T treatments also require appropriate infrastructure capacity, with two notable examples being cryopreservation and ICU capacity. While many hospitals already have liquid nitrogen tanks or freezing facilities suitable for the CAR T therapies (e.g. capable of meeting the -150 degrees Celsius specification (5)), additional capacity may be needed, as was the case e.g. in Manchester (the iMATCH ATTC), where a 50-fold increase in storage capability was implemented to increase capacity and future-proof the trust's ATMP delivery (communicated at Catapult Adoption Day 7 December 2021– not available online).

Additional beds are needed as there is currently no spare capacity in the NHS. The treatments are new options rather than replacing other options so there is no potential to displace existing resource use; new beds are required. Another key facility requirement is adequate (age-appropriate) ICU capacity for patients developing cytokine release syndrome (CRS) (5, 6).

Treatment and patient pathway at the hospital-level

Diagnosis and patient selection

A first and critical step in enabling patient access is the timely identification of potential CAR T candidates. This starts e.g. in general hospitals that refer patients to certified ATMP providers (5, 6), and requires local level physicians to be aware of the patient profile for which the CAR T therapy is an appropriate option. Evidence suggests that referral can be a 'lottery' depending on clinician knowledge of treatment availability. Audit of equitable access outlined in the draft CAR T specification may be helpful to quantify any disparity, but it would be useful to have methods in place to ensure equal opportunity at all stages of the referral process.

The patient is referred to a centre of excellence, where patients need to be screened and confirmed as potential candidates, in line with the manufacturer's licence with regard to age, fitness, disease and treatment stage. Subsequently, the treating hospital's MDT needs to convene to discuss and conclude on the patient candidate profile, and, if confirmed, obtain the patient's consent for undergoing the treatment (to ensure that the patient has been informed and understand the potential benefits, risks and complications of treatment). A relevant initiative in this regard is the effort underway by the NA-ATTC and Autolus to develop a CAR T 'guide for patients and carers', which details 'what to expect' at each stage of the journey (based on real patient experiences). The importance of the availability of translators is outlined in the draft specification, and it should be emphasised that language is only one type of barrier to access (e.g. other barriers may include mental capacity, geography, physical disability etc), and processes to address these barriers should exist from initial stages of patient contact such as elicitation of informed consent, to post-infusion care and follow-up to identify adverse events in a timely manner.

Once patient consent has been documented, the local MDT passes the candidate's case profile to the national level MDT, which meets once per week in order to ensure that patients referred meet the eligibility criteria, and to manage capacity planning and scheduling from a national perspective (5, 6). The national MDT has been highlighted by industry stakeholders as a success for enabling a consistent decision-making, avoiding a postcode lottery in terms of access to CAR Ts. However, stakeholders interviewed by industry also considered the value of the national MDT moving forwards: Some thought that they still had a useful role to play in coordinating data collection and aiding clinical prioritisation. Yet, it was also argued that now there is greater expertise within the centres, the Panels can adversely delay access.

Once the go-ahead has been granted from the national MDT, the treating hospital can prescribe the therapy and start the therapeutic process. A potential challenge is in cases where this process causes delays in initiating patient treatment, which can be detrimental to patients who are at a very advanced cancer stage.

Prescription and order of CAR T product

As part of the prescribing process, the CAR T product is added to the electronic SACT/Bluteq prescribing system, and included in the pharmacy ordering system (13). This facilitates contracting between the treating hospital and the manufacturer, and if this involves special commercial arrangements (e.g. discount or rebate agreements), this also needs to be reviewed by the pharmacy (14). Initial contract negotiations with manufacturers (before a standardised agreement is in place) can be lengthy and delay patient access. One example of this includes a two-year delay between commissioning and provision of one ATMP. Decentralisation of contracting may cause duplication of efforts, and there have been calls for centralisation of contracting to ensure equity of access (15).

T-cell extraction (leukapheresis) and preparation for shipping

Once the treatment has been prescribed, a viral serology test is required in order to export and ship human autologous-derived materials (16). Once this has been completed, leukapheresis can commence. The scheduling of leukapheresis must be coordinated with the pharmaceutical company as capacity for timely manufacture once the patient's cells reach the manufacturing site is crucial (16). Confirmation of an agreed manufacturing slot is therefore mandatory prior to setting a date for leukapheresis. The capacity of the leukapheresis clinic in terms of available slots is a potential bottleneck in this respect, as illustrated by the experience of the hospital trust in Newcastle where this was reportedly a challenge initially (1). Industry stakeholders indicate that building the apheresis capacity and the set-up of storage facilities took some centres longer than others (2).

The leukapheresis procedure usually takes 3.5–4.5 hours, and needs to follow product-specific leukapheresis protocols (these are confidential). The apheresis clinic will procure the starting material for the CAR T manufacture under their UK Human Tissue Authority (HTA) licence (13).

Once the patient's leukapheresis product has been obtained, appropriate labelling and linkage to the manufacturer's logistics/tracking system (e.g. TrakCel) is crucial. As is the ability to match the cell materials to the patient in question (to ensure the appropriate match of autologous product to the right patient once manufacturing has been completed) (16). In many cases it is necessary to cryopreserve and store the cell material before handover to the courier for shipping to the manufacturing site, and appropriate freezing capacity may be an issue.

The handover and custody of the cell material for transit purposes is another important aspect (17). As mentioned above, a HTA licence is required also to export the cell material and for importing the manufactured medicinal product, and in addition, the cross-border shipment of the collected cell product requires compliance with national regulations both in the country of origin and in the country of destination.

Bridging therapy (for patients who deteriorate)

Maintaining control of the patient's disease in the 3-4 week period between leukapheresis and administration of the CAR T product is imperative. Sometimes this requires administration of (bridging) anticancer drugs including chemotherapy. The goal of bridging therapy is to prevent clinically significant disease progression leading to impaired organ function or any other complications that might prevent the patient proceeding with lymphodepletion and receiving the CAR T cells. The aim is not to achieve disease remission, but to establish adequate disease control prior to the CAR T-cell infusion. The optimal bridging therapy for any individual will depend on disease- and patient-specific factors (16).

Conditioning therapy

Patients require chemotherapy conditioning to ensure lymphodepletion before treatment with CAR T products. A trained haematology pharmacist must screen the prescription and co-ordinate with the pharmacy aseptic unit, nurses and stem cell laboratory to ensure safe and accurate timing of chemotherapy (e.g. fludarabine and cyclophosphamide)/ lymphodepletion (18), which should be completed 2-14 days before infusion (this is typically done on an inpatient basis) (5, 6).

The timing of conditioning therapy has to be coordinated with the manufacturer/ courier so that the 2-14 day time window is met, so effective inter-stakeholder communication is key.

Receipt of CAR T product from manufacturer

Ensuring clarity around the exact point of courier delivery of the CAR T cell product at the hospital trust is important, as couriers sometimes have difficulty finding the appropriate delivery point if the trust comprises several hospitals. The organisation of the delivery reception area is also important, e.g. appropriate control of receipt and monitoring (17).

A potential challenge is the availability of a trained, named individual to receive the product at the hospital and sign for the receipt of the product. This is typically done by a member of the pharmacy delegated by the Chief Pharmacist to a member of pharmacy team or Stem Cell Processing Unit (SCPU) (with pharmacy oversight/agreement in place) and recorded in line with regulatory requirements (7). The individual will document the temperature of the product upon receipt, check the integrity of the product, labelling and temperature compliance during transit. Similarly, certificates of analysis or quality control detailing the dose (if applicable) should be reviewed by an appropriately trained member of staff, e.g. clinical pharmacist (14).

Ex-vivo (cell-based) gene therapies are generally not handled in pharmacy (usually in stem cell laboratories) but receipt, storage, preparation, and issue are pharmacy responsibilities and should be co-ordinated under pharmacy oversight (14).

Storage until infusion

Once the CAR T product has been appropriately received and recorded, it should be transferred to a liquid nitrogen tank or suitable freezer immediately. Continuous temperature monitoring and alarms are required, e.g. to comply with specific temperature requirements (i.e. -120°C or -150°C). The product may be stored at the hospital in the vapour phase of liquid nitrogen until the patient is ready to receive the infusion (13). Continuous temperature monitoring (and alarms) is advised, and a potential challenge is to ensure appropriate storage capacity, and adequate monitoring of temperature.

In addition, there are other potential challenges around the containers the products arrive in from manufacturers (e.g. vials or cassettes), and how products are wrapped or 'bagged' during storage. To avoid cross-contamination, hospitals commonly conform to double-bagging of materials stored in the vapour phase of liquid nitrogen, however, some of the ATMP products currently available come in different containers that may not fit with the hospitals' storage processes and infrastructure. As the volume of products increases, there is an increasing need for standardisation to ensure that appropriate measures can be employed to avoid cross-contamination during storage, and that the containers for various products can be accommodated by hospital storage facilities. There might be scope for industry to harmonise the containers used for storing the ATMPs, so that management at the hospital level can become more uniform.

Issue of product from storage and preparation for infusion

Once it is confirmed that the patient's lymphodepletion has been completed, if the patient is well and has no signs of infection and the infusion is scheduled, the product can be issued from storage and preparations for infusion can commence. If patient is not well or has signs of infection such as fever the infusion must be delayed. Before thawing/reconstitution, the patient and product identifiers need to be confirmed and matched (among other things, drug/dose/patient confirmation by two persons), and the certificates of quality need to be need to be verified (13, 19).

The CAR T product needs to be retrieved from the liquid nitrogen tank/freezer, and transported on dry ice/vapour phase to clinical or thawing area (if different from clinical area) by a trained stem cell lab staff member (13). Most clinical cryo-stores are in the basement of hospitals, which leads to a ~30 min transfer time between storage and the area where it is thawed (20).

The frozen CAR T product is then thawed/ reconstituted according to manufacturer instructions in clinical areas or preparation area by trained stem cell lab staff members, or trained nurses in many units. According to a Northern Alliance Advanced Therapies Treatment Centre (NAATTC) gap analysis, there are units that currently offer controlled thaw, but these are not widely used. Clinical sites often do not always record critical steps such as thawing/administration time. The NAATTC recommends that thaw should be standard with digital recording of thawing process (20).

The product should then be released by a pharmacist and will be in its ready-to-administer presentation (19). Between centres, there is variation in practice between pharmacy release and pharmacy oversight via SOPs without physical supervision; most centres are somewhere inbetween.

Administration/ infusion

At least four doses of tocilizumab (per patient) need to be confirmed available prior to infusion (5, 6). This needs to be coordinated with the pharmacy team. A final verification matching the patient identity and CAR T product is done (21).

Infusion is then facilitated by a trained member of nursing staff, and the product is aseptically connected to the port of a central venous catheter. The line to be used for the CAR T-cell infusion must be clearly designated; as with blood and stem cell products, no concurrent medication may be given during the CAR T-cell infusion. Infusion should begin as rapidly after spiking as possible, but no later than 30 minutes thereafter. The small volumes and cell numbers allow for rapid (less than 30 min) drip infusion of the cell suspension (16).

Following CAR T infusion, the second Blueteq entry should be confirmed as completed and documented on electronic SACT prescribing system (13).

Post-treatment management in hospital and community (first four weeks)

Patients are typically kept inpatient for circa 10 days, during which frequent daily monitoring is required. Access to several specialised diagnostic services is required to assess potential complications, incl. electroencephalogram (EEG), echocardiography along with either cardiac monitoring by telemetry, or continuous ECG monitoring and pulse oximetry (5, 6). A minimum of 4-hourly observations using Early Warning Scores (EWS) should be undertaken. Patients who develop grade 1 symptoms and signs should have monitoring escalated according to their EWS. Anti-infective prophylaxis is also given (7).

The first four weeks after infusion require particularly careful monitoring of the patient to manage AEs and toxicities, to the extent that the CAR T product licenses require patients to be within two hours travelling distance of a certified clinical facility for at least four weeks following infusion (some hospitals operate with 1 hour travelling distance). As patients may not recognise the onset of encephalopathy on their own, 24-hour availability of a carer is mandatory (5, 6).

The effective management of toxicities is critical to optimising patient outcomes. Neurotoxicity is defined as Immune effector cell-associated neurotoxicity (ICANS), and its severity should be scored using an appropriate tool, e.g. CARTOX. Median onset time to ICANS is 5 days (ranging from 1-17 days), and anti-IL6 / IL-6R (tocilizumab) therapy has been reported to reverse ICANS during the first, whereas corticosteroids are the preferred treatment for the second phase (5, 6).

Cytokine release syndrome (CRS) is one of the most common non-haematological adverse reactions to CAR T therapy, and careful management of this includes several key considerations (5, 6):

- Age-appropriate ICU (e.g. for paediatric patients), complying with either or both the draft service specification for adult critical care or Paediatric Critical Care service specification (5th edition PICS standards 2015), and with proven capacity
- Grade >1 (i.e. worse) CRCS patients should be on ICU with neurological assessment including use of regular standard EEGs (up to daily) or other treatment as indicated
- Co-location with neurosurgery is preferred but not a mandatory requirement; An evidenced referral pathway for neurosurgical input is required
- Experience in the management of multi-organ failure
- 24/7 access to a wide range of support specialists in intensive, renal, respiratory, cardiovascular and neurological medicine

- Access to ECG along with either cardiac monitoring by telemetry, or continuous ECG monitoring and pulse oximetry monitoring if patients develop CRS symptoms of grade 2 or above
- Access to steroids and four doses of tocilizumab (tocilizumab use is tracked through Blueteq)

In addition to managing AEs and toxicities, measuring and recording treatment response is another key factor.

Post-discharge management (medium and long-term)

Medium-term complications, i.e. between day 28 and day 100 after infusion include potential toxicities such as delayed tumor lysis syndrome, delayed hemophagocytic lymphohistiocytosis/ macrophage activation syndrome and CRS, B-cell aplasia, hypogammaglobulinemia, graft-versus-host disease (GvHD), and infections. In ALL, hypogammaglobulinaemia is a fairly common AE, which may require immunoglobulin replacement therapy (5). Neutropenia, thrombocytopenia and anemia are common but generally resolve slowly over several months. Growth factor support may be indicated in the early stages (16). A key challenge is the effective identification and management of emergencies in the community, and patients should carry a patient information card stating that they have received marketed CAR T cells along with instructions to be followed in the event of an emergency (16).

Patients will be discharged from the CAR T therapy-delivering hospital to an appropriate local follow-up to capture disease status and the late effects of CAR T-cell and prior treatments. It is the duty of the MDTs of the CAR T-cell-administering centres to ensure that this transition is done appropriately. The national MDT is responsible for the tracking patient outcomes. In cases of geographical transition, formal communication, including discharge correspondence and other clinical material such as imaging files, should be provided to new healthcare providers (16). A related consideration is around the potential for emergency admissions in the local setting, and thus the ability of local A&E staff to identify potential late-onset AEs for patients is important.

Long-term management and follow-up can potentially be incorporated into local arrangements for generic allogeneic HCT 'late effects' clinics (16). Regardless of the follow-up arrangement, it is crucial that it can capture and provide NHS England with access to the long term follow-up data required by safety registries and a clear outline for how they will ensure the accuracy and sustainability of this data collection. The marketing authorisation for the CAR T therapies require 15 years of data collection through the EMA's Post-Authorisation Safety Surveillance (PASS) (16), where data is submitted to the EBMT through the Cell Therapy MED-A forms (22).

The long-term follow-up clinics should systematically monitor the following outcomes (16):

- i. Patient/disease status – remission, minimal residual disease, relapse, management of relapse, death
- ii. Further treatments administered after CAR T-cell therapy, including allogeneic HCT and other immune effector cell therapy/ATMPs
- iii. Late effects – for stable patients in ongoing remission, 3-monthly monitoring for the first year, annually thereafter or as clinically appropriate
- iv. Infections
- v. Immunological status – cell markers, immunoglobulins, including CAR T-cell persistence
- vi. New cancers, including secondary myeloid diseases
- vii. New autoimmunity and autoimmune diseases
- viii. Endocrine, reproductive and bone health (including growth and development in children and young adult patients)
- ix. Neurological status (including recovery from immune effector cell-associated neurotoxicity syndrome [ICANS])
- x. Psychological status and quality of life
- xi. Cardiovascular status, including echocardiographic assessments and risk factors for cardiovascular disease, such as ‘metabolic syndrome’
- xii. Respiratory status
- xiii. Gastrointestinal and hepatic status

Information management infrastructure (digital) requirements

Information management and the associated (digital) infrastructure requirements are important for a multitude of reasons, and in the below we differentiate between two key categories of use:

- 1) Information management to operationalise the delivery of CAR Ts
- 2) Data collection and management post-treatment for the purposes of complying with regulatory and reimbursement requirements

Operationalising CAR T delivery

Due to the live nature of the materials and medicinal product, timing is of the essence for a successful product and patient pathway execution. Considering the multiple stakeholders involved in this pathway, e.g. treating hospital, courier service, and manufacturer, it is crucial that all stakeholders have clearly defined responsibilities, and appropriate information available to them in order to facilitate the successful delivery of the treatment.

Appropriate information management systems are key to this success, both for the purposes of product tracking between leukapheresis and infusion (*vein-to-vein*) and for recording patient outcomes after treatment. Information management and sharing in the vein-to-vein pathway serves several purposes:

- Product location tracking
- Verification of patient/product match (especially important for autologous products)
- Logistics, quality control (QC)/ quality assurance (QA), governance, and custody
 - Stem cell lab/storage/handling from and to bedside
 - (International) transport to and from manufacturing site
- Pharmacy purposes
 - Filling prescription
 - Issue/administration of drug product
 - Contracting/billing

Timely communications between treating hospitals and manufacturers is key. Another challenge is that different hospital trusts may operate with different information management systems and processes, which can create interoperability issues when dealing with external stakeholders, e.g. different manufacturers.

Data collection to comply with regulatory and reimbursement requirements

Patient outcome tracking after infusion is important first and foremost to ensure the safety and well-being of patients, but also in order to comply with the regulatory requirements (i.e. EMA's Post-Authorisation Safety Study [PASS]), and the requirements of the Cancer Drugs Fund (CDF), as levied by NICE and NHS England in their HTA and commissioning decision. Key challenges in this respect include ensuring data security and governance, enabling adequate visibility to relevant parties (and defining who the relevant parties are), as well as the potential for duplication of efforts (as data is recorded in different systems for different purposes). In the below, we explore some of the key features of the data collection infrastructures and practices relevant to ATMPs, and how these can be optimised as more therapies become available.

In England, Kymriah[®] and Yescarta^{®1} are reimbursed through the CDF, which is a cancer-specific funding source that enables access to drugs for which there is plausible potential that they would satisfy the criteria for routine commissioning, but where there is significant remaining clinical uncertainty. NICE recommended the two CAR Ts for use through the CDF on the condition of gathering more evidence to mitigate the uncertainty stemming from limitations in the clinical data available at launch. In order to be covered through the CDF, Novartis and Kite/Gilead have to provide confidential discounts and submit additional data for the purposes of a future price reassessment (after five years of commissioning via the CDF) (23-25). The primary data sources informing the price reassessment are the follow-up data from the ongoing trials (23-25). Additionally, real-world evidence (RWE) will be collected for both CAR T cell therapies through the Systemic Anti-Cancer Therapy (SACT) dataset and Bluteq (both standard requirements for treatments funded through the CDF), as well as through other Public Health England (PHE) datasets (23, 25). This combination of data sources allows NICE and NHS England to more firmly establish the long-term efficacy (through the trial follow-up data) as well as the (shorter-term) real-world effectiveness in the English setting.

As the SACT dataset is used to collect data on real-world use in England, it is worth looking at in more detail, to better understand its potential as an infrastructure to collect outcomes for reimbursement purposes on a greater scale as more ATMPs are adopted in the NHS. The SACT dataset collects data relevant to all systemic anti-cancer therapies provided in England, and aims to identify treatment patterns and outcomes for cancer patients on a national scale (26). It is mandatory for hospital trusts to submit data to SACT, and 141 hospital trusts upload data on a regular (monthly) basis (26, 27). Failure to comply with data submission can have financial consequences for the trusts, as payment for drugs funded through the CDF is contingent on compliance with SACT (28, 29).

¹ And now also Tecartus[®]

The SACT dataset comprises several data categories, including patient demographics and consultant details, clinical status, programme and regimen details, cycle information, drug details, and outcomes (29). According to the SACT data completeness report detailing completeness of the outcomes data field (from 2017-18), only 12% of trusts submitted data for the outcomes section (27). The most recent data completeness report (from 2018-19) does not include the results for the outcomes field in the dataset (30), so it is not possible to say with certainty how this may have changed. However, this has been identified as an issue, and in 2019, Public Health England in 2019 set out to change this by implementing a separate outcomes upload, which was rolled out from December 2020 (31). This initiative aims to overcome one of the hurdles to completing the outcomes section, i.e. that outcomes are not always reported at the time of the initial SACT data submission. Under the new arrangement, outcomes data can be submitted separately after the initial SACT submission, and matched to the original entry to provide a more complete patient record in SACT. Interestingly, the outcomes data submitted separately appears to be coming from an audit field in the electronic chemotherapy prescribing system (31), illustrating the fragmentation of recording and managing patient outcomes data in NHS systems.

Importantly, the data fields in the SACT submission are not standardised (e.g. using drop-down menus for data fields) (32), meaning that different submissions may report results differently, and thereby making a standardised analysis across submissions more challenging.

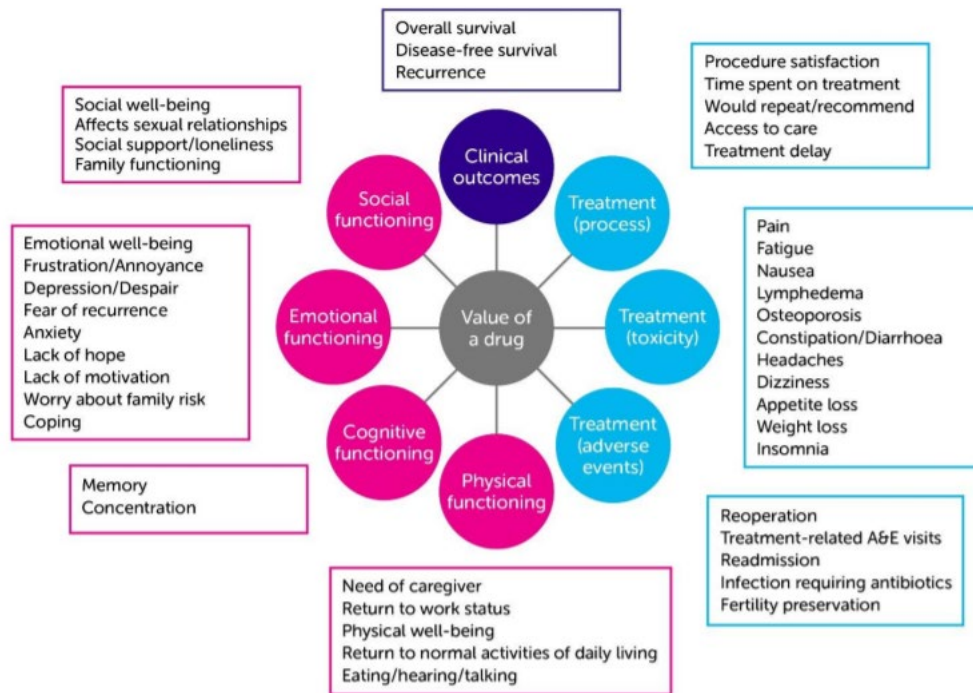
The European Society for Blood and Marrow Transplantation (EBMT) maintains registries encompassing data on all haematopoietic stem cell transplant (HSCT) procedures for all indications, as well as a Cellular Therapy Registry (CTR). EBMT's focus was originally on HSCT, however, established the CTR with the aim to collect data also on the administration and long-term follow-up of somatic cell therapy medicinal products and gene therapy medicinal products, including (but not limited to) CAR T-cell therapies, as well as data on the clinical characteristics and outcomes (33). In 2019, the EMA qualified the EBMT registry as a suitable platform for the collection of data for PASS (34). The registry is now used to collect outcomes for PASS purposes for Kymriah® and Yescarta® (35, 36).

Data collection for the CTR is done through a set of different forms, which include sections for diagnosis, cell material type, cell manipulation, infusion episode(s), and outcomes such as death, toxicities, best response after completed treatment (e.g. remission), complications, first relapse/progression, persistence of infused cells, and several disease area-specific sections (22). Data are to be collected (and submitted subsequently) at day zero, day 100 (after infusion), six months, 12 months, and annually thereafter (37, 38).

An important difference between the forms used for submission of data to the SACT dataset and the EBMT's CTR is that the CTR forms are standardised, with boxes to be ticked for e.g. different patient statuses like survival (or cause of death), response, toxicities experienced, secondary malignancies, relapse, persistence of infused cells, etc. This allows for an easier and more scalable analysis of patient outcomes through the EBMT than through the SACT dataset, which will be important as more therapies launch.

In addition, EBMT is involved in other initiatives relevant to ATMPs, like the GoCART strategic partnership with the European Hematology Association (EHA) (39). GoCART aims (among other things) to harmonise qualification criteria for treating centres, and importantly to “promote harmonisation of data collection, education, standards of care, regulatory approval and reimbursement processes in Europe” (8). If successful, this initiative can represent an important lowering of barriers to entry for hospitals seeking to provide ATMP treatments (as obtaining accreditation is a labour intensive hurdle to overcome).

Worth noting is that neither the SACT dataset or the EBMT CTR collects data on economic outcomes or humanistic outcomes such as quality of life, which are increasingly recognised as important factors in patient-centred care as well as in HTAs. In February 2019, Cancer Research UK (CRUK) published a report (with an analysis undertaken by the Office for Health Economics), which highlighted shortcomings around SACT's outcomes data, and recommended that “...a mapping exercise should be undertaken to ascertain the appropriate data sources, and identify “gaps” in the capacity to collect [outcomes] data...” (40). They further suggested that humanistic patient outcomes linked to social, emotional, physical and cognitive functioning should be captured and recognised as inherently important components of a new drug's value (see figure below). E.g. the ability to return to normal activities of daily living is crucial to patients, however, this is not currently routinely captured in NHS clinical practice, and CRUK's recommendation is for this to be recognised and included in the assessment of the value of new therapies:



In previous work (41), we undertook a gap analysis of the SACT dataset and the EBMT CTR with the view to understand what would be required to upgrade these to address post-launch RWE requirements of regulators and payers for cancer therapies in England. We found that SACT appears well-placed to facilitate OBR as it has a high number of trusts in England contribute. However, we also found that SACT, in isolation, is suboptimal as a framework for enabling comprehensive RWE collection, and that upgrades and integration with other data sources are required. Furthermore, SACT is only used in England, and is therefore not scalable to the other devolved nations of the UK (or beyond), where other data collection infrastructures apply. Importantly, SACT does not allow for a systematic tracking of clinical outcomes such as overall survival (OS), progression-free survival (PFS), response or remission, which means that additional data needs to be collected either through new data fields in SACT or from other sources (e.g. electronic health records). Whereas some of these additional data could potentially be collected through other NHS data sources, it increases complexity, especially when compared to EBMT, where all of these clinical outcomes are collected in one place. Furthermore, SACT in its current form is less well suited for long-term longitudinal data collection which can be an issue for certain cancers where patient survival is better (this is echoed also in CRUK’s 2019 report (40)) as well as for ATMPs with curative claims where longer term evidence collection is needed to substantiate therapy claims (especially solid tumors).

The cell therapy form currently used in the EBMT shows a greater potential to serve as a conduit for ATMP RWE collection, however, this only applies to key clinical outcomes. The suitability of the EBMT cell therapy form for tracking patient outcomes is illustrated by the EMA's endorsement of this as a potential vehicle for implementing the regulatory requirements for ATMPs to collect data post launch. The initiatives to involve industry and importantly also physicians (the development of the EBMT forms is driven by physicians) should act to increase buy-in also from these stakeholders. Importantly, it is also scalable across the devolved nations of the UK and across Europe, meaning that it has the potential to become a larger-scale source of real-world data, which would be particularly valuable in rare and ultra-rare indications, which many cell and gene therapies in development are targeting.

Neither SACT nor EBMT allow the capture of economic outcomes or patient reported outcomes or experience measures (PROMs/PREMs). In terms of economic outcomes, this can potentially be sourced from Hospital Episode Statistics (HES), (Electronic) Health Records (EHR), Secondary Uses Services (SUS), and other sources using patients' NHS ID numbers, however, this requires investment in systems integration, as well as overcoming governance issues (e.g. EHR data are under the governance of individual trusts). PROMs and PREMs such as ability to return to normal daily activities are increasingly regarded as important (40), however, there are currently no national databases to collect these data. Nor is there currently an agreed standard or consensus on what PROMs and PREMs are most relevant in cancer, meaning that efforts would need to be made to identify these as well as facilitating an infrastructure to capture the data. There are initiatives underway that aim to bridge these gaps, e.g. the PROMics study, led by the Centre for Patient Reported Outcomes Research (CPROR) at Birmingham University in conjunction with the Midlands & Wales Advanced Therapy Treatment Centre (MW-ATTC) and Dignio, a Norwegian remote health monitoring company. The PROMics study is developing an electronic capture system to assess quality of life and symptoms, both at the point of receiving therapy and on a longer-term basis following discharge from hospital for ATMP patients (42).

In terms of the costs required to upgrade SACT and EBMT to enable more comprehensive RWE collection for ATMP regulatory and reimbursement purposes, we have previously researched and reported on the different scenarios of upgrades and associated costs (41).

Large scale initiatives on the collection of outcomes data for regulatory and reimbursement purposes (such as the AAC WS5 and GoCART initiatives) have the potential to facilitate large scale favorable change in optimising digital infrastructure for RWE collection, as they can enable both a centralised aligned approach (rather than a segmented at local trust level approach) and also reduce multiplication of efforts.

Hospital reimbursement requirements

Types of hospital payment models

In England, most hospital services are paid for by commissioners using a price per unit of activity approach via the national tariff (43). Paying for hospital activities by defined tariffs was introduced as a way of replicating the efficiency of a competitive market in a monopolistic sector. The tariff price paid to hospitals is calculated from averages of collected cost data from all hospitals, or the expected costs of best clinical practice. Hospitals must be efficient in order to perform activities within the tariff price they are paid. This system is criticised by some stakeholders, such as the BMA (British Medical Association), who argue that it penalises struggling hospitals, creating conditions that lead to poor patient care (44). In Scotland and Wales, there is no national tariff, and hospitals are paid through pre-agreed block contracts which outline all the services they are expected to deliver, determined by the needs of the local population. Primary care in the UK is funded by another mechanism – capitation – whereby individual GP practices are paid a fee for each patient they have registered.

The NHS discussed moving away from the national tariff towards funding hospitals through block contracts in England in the NHS long term plan published in 2019(45). Block contracts have been introduced as an emergency interim measure in response to the coronavirus pandemic in 2020(46), but it is unclear how funding mechanisms will progress beyond 2020/2021.

Most hospital activities are funded at a local level by clinical commissioning groups (CCGs). Specialist services, such as CAR T delivery, that are only performed on a small number of patients and by centres with specialist expertise are directly commissioned by NHS England (NHSE) with local pricing. Within the Specialised Commissioning service, there are six National Programmes of Care (NPoC), with CAR T delivery currently falling under the Cancer NPoC.

It is not confirmed but expected that from the second half of 2021 the local prices for CAR T delivery will change and funding will be fixed regardless of patient volumes, and negotiated annually. This will mean that funding, in year, for the delivery of the existing infusions (not the infusion cost itself though) will be fixed regardless of patient volumes. As a result, should there be an unexpected and significant increase in patient volumes then either funding would need to be re-negotiated in-year or patients would have to wait until the following financial year to be treated. Should additional therapies/indications be commissioned they would be subject to additional funding rather than being required to be delivered out of the existing fixed funding (unless they replaced existing therapies). It is assumed that the following year would be subject to an additional update so if patient volumes change, the fixed value would be updated the following year to reflect this.

Calculation of provider funding

In Scotland and Wales funding is based on expected NHS spending and is a fixed amount for the whole service (including overheads) rather than variable funding dependent on the number of patients treated. As a result, calculating the amount of funding to be given to the provider on a per patient basis does not need to be calculated.

In England the funding per patient for routine (i.e. reasonable volume with relatively predictable costs) services is known as the National Tariff and is calculated by taking into account the previous year's National Tariff, any changes in how activity is reported and any changes in how the relative costs of care have changed.

The majority of the National Tariff is set through Health Resource Groups (HRGs) for inpatient care (47). They are developed by the National Casemix Office over a number of years using patient-level costing data, and are first introduced into reference costs, then can be included in the tariff. They are clinically meaningful groups that represent patient episodes with similar costs, based on diagnosis or intervention (such as stroke or knee replacement), with a complexity factor (complications and comorbidity; CC) that allocates higher funds to more complex patient episodes (Figure 1). HRG4+ is the most recent and currently used collection, used since 2014, and updated annually in line with an uplift for inflation, and a reduction for an assumed increase in efficiency. For 2020 the inflation uplift was 2.9%, and the efficiency factor was -1.1%, so tariffs increased by net 1.8% on the previous year(48).

Figure 1: Screenshot of national tariff workbook showing HRG codes and proposed tariffs for 2019/2020 (latest publicly available at time of writing)

HRG code	HRG name	Combined day case / ordinary elective spell (£)	Ordinary elective long stay trim point (days)
PM40A	Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more, with CC Score 3+	8,731	20
PM40B	Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more, with CC Score 1-2	3,405	10
PM40C	Paediatric Acute Lymphoblastic Leukaemia with length of stay 1 day or more, with CC Score 0	3,026	7
PM41Z	Paediatric Other Haematological Malignancies with length of stay 1 day or more	8,199	24
SA31A	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC Score 15+	11,607	77
SA31B	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC Score 10-14	6,525	49
SA31C	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC Score 6-9	2,307	18
SA31D	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC Score 4-5	1,185	8
SA31E	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC Score 2-3	808	5
SA31F	Malignant Lymphoma, including Hodgkin's and Non-Hodgkin's, with CC Score 0-1	508	5

The creation of HRGs requires robust and high quality data. Whether enough data has been collected to define an HRG depends on the variability of patient costs within the group. There are different statistical methods to quantify the variability. One measure is the RIV, which is a measure of how much variability in costs is explained by the HRG. If the RIV was 100%, this would mean all patient episodes within the HRG have the same cost. The average RIV for all HRGs (HRG4+) is 33% (49), so this shows that there is significant variation in costs within one HRG, so multiple hospitals would be underfunded for patient episodes.

Prescribed Specialised Services tariffs are calculated based on a model published by the University of York in 2015, which identified the areas where extra funding is required (50). These services are funded through a top-up to the HRG4+ tariff for the equivalent non-complex case-mix when patients fall into many different HRGs, or have separate tariffs that are re-defined to separate complex care patients from the non-complex cases.

CAR T funding is not via the National Tariff, and instead is subject to local negotiation between providers and NHS England. There is no standardised approach to these negotiations. Prices paid to providers are derived from:

- 1) Expected costs being calculated by providers involved in CAR T trials
- 2) Other providers validating these costs
- 3) NHS England reviewing overall impact and taking into account funding available.

Once prices were agreed in 2019/20 there is an annual review (which was skipped in 2020/21 due to the pandemic). There is no standard approach to how this review is carried out and normally each provider will agree how they are to update/amend agreed funding levels per patient with the commissioner.

As NHSE has offered the same funding per patient, split Adult and Child, to all providers (plus each provider published Market Forces Factor to reflect local cost differences due to location), it is likely that updating this would be a co-ordinated project across all providers rather than individual NHSE/provider negotiations.

The NHS Standard Contract (Service Conditions 36.9) sets the contractual position that, where the funding per patient is not agreed between the provider and commissioner, the next year's funding is the existing funding per patient with National Tariff inflation added on and National Tariff efficiency deducted off. For 2020/21 funding levels were kept constant due to the temporary contracting arrangements introduced during the pandemic.

Sources of funding of CAR T

In Wales, every health board funds the Welsh Health Specialised Services Committee and they in turn then fund specialised services. It is understood a similar approach occurs in Scotland.

In England, as the CAR T drug is on the high-cost drugs list, it is excluded from the National Tariff, and funded by the Cancer Drugs Fund/ Innovative Medicines Fund, via pass-through costs directly to hospitals. NHSE Specialised funds CAR T pre infusion care, infusion delivery and 100 days post infusion care predominantly via funding per patient (as confirmed in the British Journal of Clinical Pharmacology this is £92,000(51) (plus the provider's market forces factor)) with then additional funding for critical care bed days, chemotherapy drugs and any other high cost drugs. Children's CAR T individual outpatient attendances are also funded in addition at the relevant National Tariff + market forces factor. Commissioning responsibility for patient care beyond 100 days lies with the CCGs. According to the 2021 NHSE CAR T draft service specification:

“In 2019/20 and 2020/21, interim treatment tariffs are in place to cover estimated service cost. As experience with CAR T improves, the approach to reimbursement for service costs will be reviewed and aligned with the financial regime from 1st April 2021 onwards.”

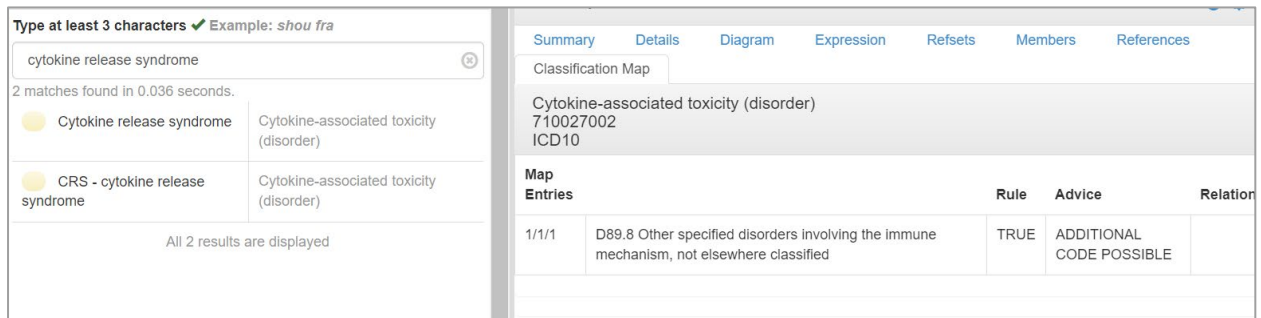
At the time of writing, the delivery payment approach for 2022 onwards has not been put forward for consultation. The payments for acute hospital activities are not ring fenced and should a provider be over-spending generally, all areas might be required to contribute to financial recovery regardless of whether they are the cause of the overspend or not.

Clinical coding

Hospitals are reimbursed for activities defined by clinical codes. Clinical coders translate the actions described in the patient's medical notes into OPCS-4 codes, which are submitted with the patient's diagnosis codes (ICD-10). HRGs are allocated based on the OPCS-4 and ICD-10 codes submitted. For example, a patient might have a diagnosis code of C835 Lymphoblastic (diffuse) lymphoma and, if appropriate a procedure code of X728 Other specified delivery of chemotherapy for neoplasm.

A patient record contains as many codes as deemed appropriate and there are nearly 10,000 procedure codes and 16,000 diagnosis codes that clinical coders have available to them to apply to patient notes. All the codes available can be found on SNOMED CT, which is a searchable database maintained by NHS Digital (52). The codes may not be specific, for example, if a patient experiences cytokine release syndrome, the related code is for “Other specified disorders involving the immune mechanism” (Figure 2).

Figure 2: Screenshot of SNOMED CT browser showing OPCS-4 code for cytokine release syndrome



When the codes are submitted, hospital activities are flagged as specialised services using Identification Rules (IR)(53), which link to a highly specialised service line code, to identify which commissioner is responsible for funding.

There are no OPCS codes that specifically identify patients as pre-infusion, infusion, post-infusion for CAR T therapy. As a result, patients are currently manually identified by the CAR T service to finance/contracting so their activity can be manually split out and reported to NHSE Specialised (via service line NCBPS02C CAR T-CELL THERAPY SERVICE). Finance/contracting can also use pharmacy information to identify when CAR T products are used and ensure that no patients have been missed as part of this manual process.

Currently, the lack of codes is not causing any problems as patient volumes are low. However, as patient volumes grow the manual methods of identifying activities may not be sustainable, causing avoidable overheads to delivering the service. It can take years from request for additional codes to them being mandated for use and incorporated into the software that identifies activity as being allocated to NHS England Specialised budget.

Costs of CAR T service delivery

There is no available accurate costing study literature for CAR T delivery in the UK. A study on the experience of using CAR T in the US, leveraged patient outcome and costing data to estimate the total cost of CAR T treatment compared with HSCT at the patient-level (54). The infusion-related hospital procedure costs are significantly higher for CAR T administration, but with the addition of non-CAR T drug costs, the total treatment cost for CAR T is 40% of the cost for HSCT (Table 1). Due to the limited comparability in healthcare provision and difference in drug costs between the US and the UK, it cannot be inferred from this study the extent of the difference in costs between administering the two treatment modalities for the NHS, but it is suggestive that the price paid for CAR T service delivery is sufficient to cover the hospital procedure costs.

Table 1: Total average costs of infusion-related hospital procedures and medicines per patient for treating ALL with CAR T and HSCT

	CAR T	HSCT
Hospital procedures	\$50,676	\$17,241
Medicines (excluding CAR T)	\$5,542	\$135,196
Total	\$56,217	\$152,437
The CAR T infusion period covers the time from 8 weeks before to 6 weeks after the CAR T infusion date; the HSCT period covers the time period from 15 weeks before to 8 weeks after the date of the procedure.		

Currently services are funded at cost in Wales and Scotland or at a fixed price (split Adult/Child and taking into account where a provider is located). This approach is currently working but as volumes grow and more indications are covered this might need to change to take into account complexity of care etc. The cost of treating individual patients can vary considerably as some may not experience toxicity, require no critical care and have a relatively short stay at hospital, whilst others can require significantly more resources. Patients must stay near the hospital for a month following discharge with a 24 hour carer. In cases where no accommodation is available, or there is no suitable carer for the patient such as a guardian, the patient must remain as an inpatient at the expense of the provider.

This should not currently be causing a financial burden for providers, as the additional bed days, with complexity impact on critical care is already separately identified, reported and funded in addition to the overall infusion funding, but this method and costs may not be sustainable as patient volumes increase.

Submission of data to the national cost collection

In a separate process to the clinical coding, hospitals must submit patient level costs – Patient Level Integrated Costing; PLICS – to the NHS National Cost Collection. The submitted costs are analysed by NHS Improvement and contribute to the creation of the National Tariff. The National Cost Collection (previously Reference Costs Collection) only occurs in England and there is no equivalent level of detail collected in Wales and Scotland.

Whilst CAR T service delivery is predominantly funded as a single item (plus Critical Care and Chemo/High Cost Drugs plus infusion) it is costed on the basis of the individual units of activity. For example, each time a patient attends outpatients, the cost of the outpatient attendance (including all staff cost, attributable consumables, overheads etc.) will be included in the National Cost Collection as a cost per attendance and will be included with other activity that has the same “Treatment Function Code” (a national list of 3 digit number such as 370 Medical Oncology, 303 Clinical Haematology, 650 Physiotherapy). Currently Cell and Gene Therapy Catapult is a trading name of Cell Therapy Catapult Limited, registered in England and Wales under company number 07964711, with registered office at 12th Floor Tower Wing, Guy’s Hospital, Great Maze Pond, London SE1 9RT. VAT number 154 4214 33. +44(0)20 3728 9500 www.ct.catapult.org.uk

this guidance requires the cost of the CAR T product specifically to be excluded from the reported cost per attendance/admission. The cost allocation process, which covers the allocation of CAR T product delivery to the associated attendance/admission, Costing Method 28 Blood Services, is in the process of being updated at time of writing to better address the costing of CAR T services.

As there is no clinical coding specifically for CAR T therapy there is no way of identifying, nationally, which costs are CAR T therapy costs in the national cost collection and instead they are included within all the other patient level costs. Local providers can access costs for individual patients, so could sum up total costs to estimate the cost of the CAR T delivery (after subtracting irrelevant costs). It is important that hospitals keep track of available funding and attributable costs to ensure that the funding is directed towards CAR T services as closely as possible, as the funding is not ring-fenced.

Hospitals have had difficulty in collecting accurate cost data, as it can involve complex algorithms to translate patient notes. One service provider did not submit an annual cost collection for 2019/2020 as there was a technical issue with their patient records system and accurate activity codes were not captured. This could have a significant impact on the quality of cost data available for CAR T delivery, due to the service provider's significant market share of all CAR T delivery so far.

Infrastructure and overheads funding

Service delivery funding is separate to infrastructure funding for capital items such as equipment, buildings, beds, and thawing tanks. In England, NHSE Specialised fund the service delivery, but Integrated Care Systems are given a capital "resource" (i.e. permission to spend on capital items) allocation to distribute across providers based on need. Hospitals can also apply to the Department of Health for funding, as a loan or Public Dividend Capital. Similarly, in Wales, the Welsh Health Specialised Services Committee funds the service delivery but the local Welsh Health Board funds the capital items.

Due to the separate funding processes, there is a risk of disparity between service delivery volume and the infrastructure required to support it. Currently, this has not impacted service delivery, but as further therapies are commissioned, this risk is increased. Method of delivery may become less infrastructure-intensive in the future, as care may transition to a medical ward-based ambulatory (with outreach) or outpatient approach.

Providers must fund considerable overheads in the short term before the service starts to be delivered (e.g. accreditation, setting up of processes etc.), potentially at risk. As activity levels increase the cost per patient of CAR T delivery starts to drop as fixed overheads get shared across more patients.

Recommendations

1. NHS England Specialised Services request NHS Digital to create 3 new OPCS codes being pre-infusion, infusion and post-infusion CAR T care.

This will not change how activity is reported but these codes could be used to automatically identify CAR T related care and streamline the costing and charging of this activity.

2. Clinical leads come together to discuss how CAR T is being delivered to identify if there are improvements that can be shared.

The dependence on critical care is reducing over time with a shift to ambulatory and even outpatient delivery, which could suggest there is a benefit of the various leads sharing how they are developing their services.

3. Given the significant set up costs prior to a CAR T service starting to generate income it is important that services make use of the Patient Level Information and Costs data (submitted at least annually to NHS Improvement) to ensure CAR T funds are fully utilised on the CAR T service.

4. Plans for infrastructure expenditure, taking into account horizon scanning, are joined up with service delivery plans to ensure that any infrastructure requirements do not constrain service delivery.

Discussion

The adoption of Kymriah and Yescarta into the NHS provides a number of learnings to take forward as more ATMPs mature and approach the market. Importantly, the NHS showed itself as a highly agile organisation, capable of quickly adapting to the various requirements associated with the new advanced gene therapies, and thus enabling timely patient access to transformational therapies. This is a success to build on and an entrepreneurial mindset to keep up. Horizon scanning efforts and the close collaboration with manufacturers should continue to be tied in with planning for patient pathway redesign (as needed) and service capacity.

As more ATMPs launch, there will undoubtedly be pressure on the treatment centres' capacity to accommodate all eligible patients, and effectively managing this capacity will be an important part of the road ahead. This could include increasing the number of ATMP accredited centres, increasing the amount of hospital estate available to these treatment centres, redesigning hospital sites to bring the different clinical specialties physically closer together, and facilitating outpatient administration of ATMPs (where the safety and toxicity profile of products allow this). Also, any opportunities to create service preparedness efficiencies through standardisation of processes where possible and appropriate should be seized upon. E.g. facilitating national level contracting for the ATMPs would reduce the risk of duplication of efforts associated with each hospital contracting individually, which is the case currently.

A further feature of the current process, which may not be scalable or possible to take forward with greatly increased ATMP volumes, is that of the local level *and* national level MDTs. Currently, referred patients need to be confirmed both at the treating hospital's level and by the national MDT, which can create delays in initiating patient treatments. For many patients, such delays may mean the difference between life and death, and this is something that should be taken great care to eliminate. While the current number of patients treated with ATMPs may be manageable for a single body to review in detail, this will not be the case as more therapies become available, and targeting larger target patient populations. Part of the remit of the national MDT is to manage current ATMP treatment capacity across the nation, and to ensure equity in access to these treatments. They contribute to excellent sharing of knowledge and ideas, standardization of practice, how to deal with rare side effects, also the out of specification panel has expertise that would not be possible inhouse. The MDT should not cause delay to treatment as the meetings occur weekly, and apheresis can be booked provisionally in expectation of a positive decision. As more centres become accredited and capacity increases, the need for national capacity management might diminish, and treatment decisions may be made by the individual hospital MDTs.

There is scope for harmonisation also in the collection of RWE in the form of patient outcomes data for regulatory and reimbursement purposes. Currently, the EBMT registry is used for the former and the SACT for the latter, which means that already thinly stretched NHS resources are used to enter the same information into separate systems. This may be necessary and feasible in the current “*boutique*” chapter of the ATMP story, where there are relatively few patients treated in a relatively small number of centres. However, as the number of products and patients increase significantly, as is expected over the next five to 10 years, such duplication of efforts can hardly be sustained, and more centralised solutions should be sought.

Adequate and timely funding of treatment centres to deliver the service is necessary to prevent this becoming a barrier to adoption as patient numbers increase. Treatment centres in England are currently funded by a single payment per patient treated. In Wales and Scotland, service provision is included in annual contracts between commissioner and treatment centres with fixed budgets; it is likely that England will shift to this approach. There is significant uncertainty associated with the true costs of the overall delivery of CAR T, as there are no specific clinical codes to identify a clinical activity as part of CAR T service delivery. As well as the activities performed to deliver the therapies, funding for infrastructure and overheads must be adequately funded and joined up with service delivery and horizon scanning to prevent a deficit in treatment centre facilities and capacity.

A striking feature of the ATMP story in the NHS so far is the close collaboration between manufacturers and NHS stakeholders from an early stage. This collaborative spirit should be nurtured and carried forward, and will undoubtedly contribute to lowering the barriers to patients accessing novel and potentially transformative therapies in the future.

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