Implementing CAR T cell therapy in the NHS

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Purpose

This presentation will:

- Summarise the CAR T landscape in England;
- Highlight lessons learnt from the NHS experience to date; and
- Propose next steps for CAR T within the wider context of advanced therapeutic medicinal products.

NICE and NHS England have limited experience to date with a range of ATMPs

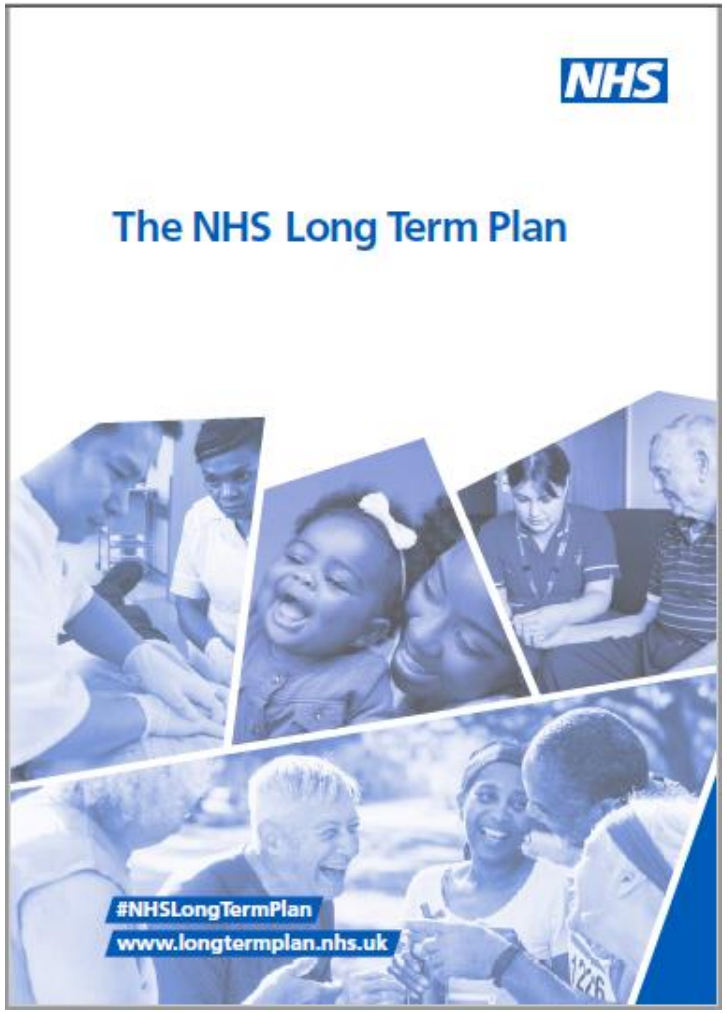
Drug	Company	Commissioner	Indication	Implementation
Holoclar (ex vivo expanded autologous human corneal epithelial cells containing stem cells)	Chiesi	NHS England	Limbal stem-cell deficiency - moderate-to-severe, unilateral or bilateral, due to physical or chemical ocular burns in adults	• NICE recommendation: August 2017 • Technology Appraisal 467
Autologous chondrocyte implantation (ACI)	OsCell John Charnley Laboratory	NHS England	Symptomatic articular cartilage defects of the knee	• NICE recommendation: October 2017 • Technology Appraisal 477
Autologous chondrocyte implantation (ACI) using chondrosphere (Spherox)	Co.Don	NHS England	Symptomatic articular cartilage defects of the knee	• NICE recommendation: March 2018 • Technology Appraisal 508
Tisagenlecleucel (immune-cellular CAR T-cell therapy)	Novartis	NHS England	Acute lymphoblastic leukaemia (ALL), chemotherapy-resistant or refractory B-cell ALL in patients up to age 25	• NICE Recommendation: Nov 2018 • Technology Appraisal: 554 • Patients started accessing treatment from December 2018 • Available through the Cancer Drugs Fund
Axicabtagene ciloleucel (immune-cellular CAR T-cell therapy)	Kite-Gilead	NHS England	Diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B cell lymphoma, and relapsed/ refractory aggressive B-cell non-Hodgkin lymphoma	• NICE recommendation: January 2019 • Technology Appraisal 559 • Patients access treatment from January 2019 • Available through the Cancer Drugs Fund
Tisagenlecleucel (immune-cellular CAR T-cell therapy)	Novartis	NHS England	Diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B cell lymphoma	• NICE recommendation: March 2019 • Technology Appraisal TA567

Nb: NICE have also rejected a number of ATMPs (e.g. Darvadstrocel for treating complex perianal fistulas in Crohn's disease (TA 556) and Cenegermin for treating neurotrophic keratitis (TA532)).

Implementing CAR-T therapy has a number of key and integrated issues

Service provision	The collection, storage, manufacturing and infusion of CAR T, and post-infusion care of patients is highly regulated requiring multiple processes of safety and quality assessment, accreditation and contracting akin to that required for bone marrow or stem cell transplantation.
Production	The production process was different for the CAR T products developed by Novartis and Kite-Gilead and it is highly dependent on supply chain logistics across UK, Europe and the USA. Whilst the care pathway is similar to an allogenic transplant, the treatment is a medicine requires the oversight of hospital chief pharmacists, the use of specialist pharmacy equipment and other medicines not routinely commissioned.
Toxicity of treatment	The toxicity profile of CAR T therapy requires patient proximity (1-2 hours for 30 days following treatment) and intensive care and neurology support as core requirements of the multidisciplinary team approach, not generally required for cancer care involving medicines.
Timing of treatment	The nature of acute lymphoblastic leukaemia and diffuse large B-cell lymphoma and CAR T side effects means that the treatment 'window' for patients is highly time sensitive, requiring careful patient selection. Annual patient eligible populations are estimated to be c.30 for paediatrics/adolescents and c.200 for adults
Data collection	As a genetically modified treatment, 15-year patient follow up data is required. Despite the promising phase II data on which assessment was undertaken, access has been recommended via the Cancer Drugs Fund (CDF) as NICE concluded that further data is required to robustly assure the clinical and cost effectiveness.
Pricing and reimbursement	CAR T cell therapy has a relatively high budget impact (list price per patient is just under £300,000) and market access has been secured through robust negotiations - often requiring senior involvement and innovative commercial flexibilities (e.g. outcome based pricing) to reach an agreement. New reimbursement mechanisms have had to be designed.
Managing supply in a globally competitive market	There is the need to manage the supply chain to ensure that companies guarantee sufficient and timely supply of the treatment for NHS patients.

The NHS Long Term Plan has set the scene for the next ten years



People will get more control over their own health and more personalised care when they need it

Advances in precision medicine also mean treatment itself will become increasingly tailored to individuals, and patients will be offered more personalised therapeutic options….

… this autumn the NHS became the first national health system in Europe to give the go ahead to a breakthrough cancer treatment based on modifying a patient's own CAR-T cells.

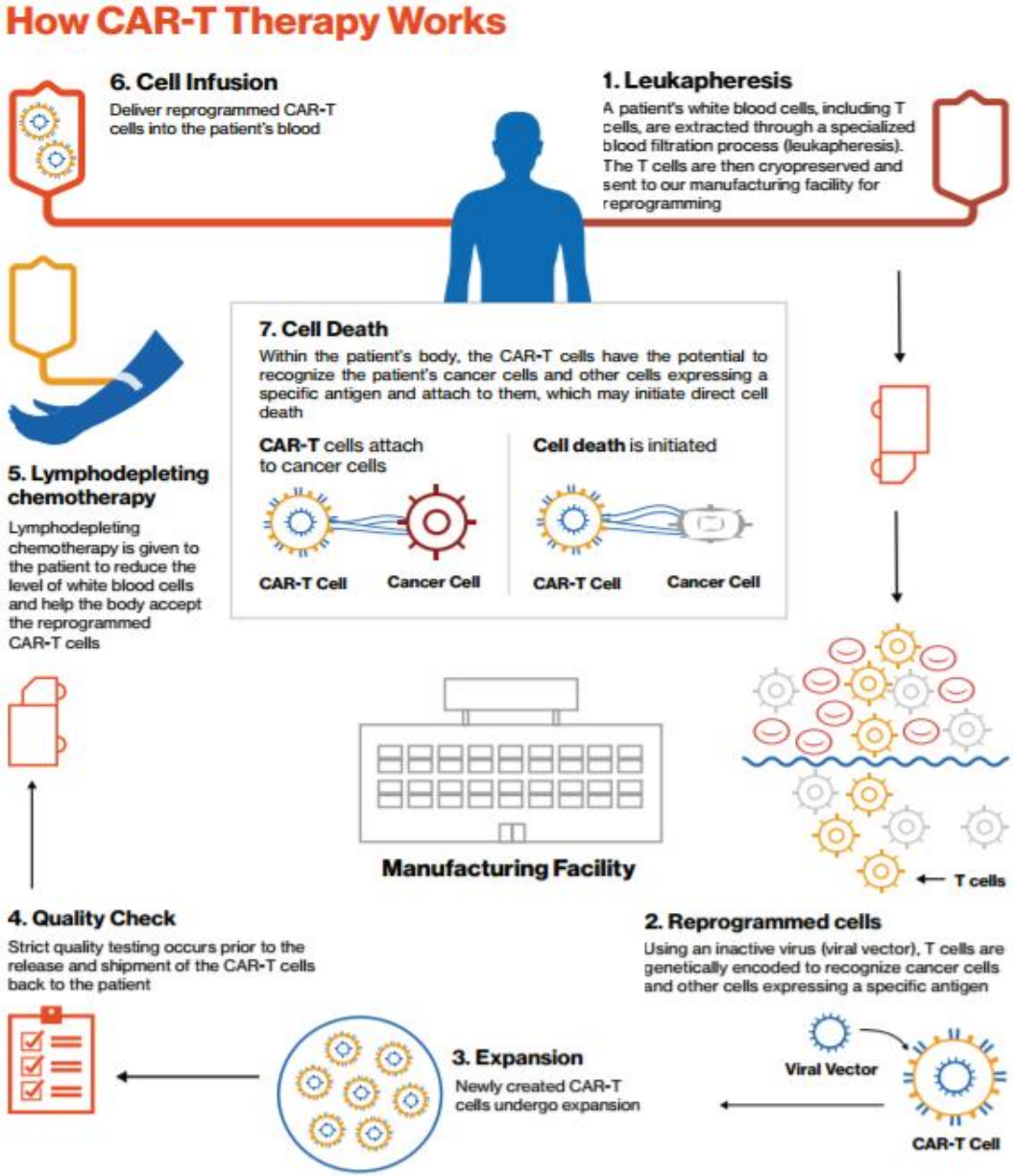
Children and young people with cancer

From 2019, we will begin to offer all children with cancer whole genome sequencing to enable more comprehensive and precise diagnosis, and access to more personalised treatments …

… children and young people in England will also be amongst the very first in Europe to benefit from a new generation of CAR-T cancer therapies.

CAR-T Cell Therapy is a disruptive innovative immunotherapy technology

- CAR-T is a disruptive innovative technology with the potential to become a leading anti-cancer cell therapy.
- It is a type of immunotherapy which involved collecting and using the patients' own immune cells to treat their condition.
- CAR-T is produced by removing white blood cells from the affected patient by a process called leukapheresis .
- The white cells, specifically T cells, are then cooled and shipped to the manufacturing plant where they are genetically modified and reprogrammed to express "chimeric antigen receptors" which target the patient's cancer.
- The CAR-T is then transported back to the hospital. The patient is pre-treated (conditioned) with chemotherapy which depletes the T cells in the bloodstream prior to receiving the CAR-T.
- CAR-T is then administered and **may be curative** in some instances.



Patients are accessing CAR T cell therapies before a routine commissioning decision due to the Cancer Drugs Fund

- NICE makes one of three decision on whether a drug should be available for patients through the NHS. The decisions are:

I. Yes – the drug should be routinely commissioned

II. No – the drug should not be routinely available

III. Maybe – the drug can be made via the Cancer Drugs Fund so that NICE can determine how effective it is.

Patients are accessing CAR T cell therapies before a routine commissioning decision due to the Cancer Drugs Fund

- NICE recommended CAR T cell therapies via the Cancer Drugs Fund to enable to collection of data on clinical and cost effectiveness for a pre-determined time period. There are two key benefits to this approach:

Patient access

Patients can access the most promising and innovative treatment. Without the CDF, NICE would not be able to recommend CAR T cell therapy for routine commissioning on the current evidence.

Building the evidence

Over the time period that CAR T cell therapies are in the CDF, data is collected to gather more evidence on clinical and cost effectiveness of the treatment.

NHS patients have started the treatment process for CAR T cell therapy - a potentially curative complex and distributive innovation

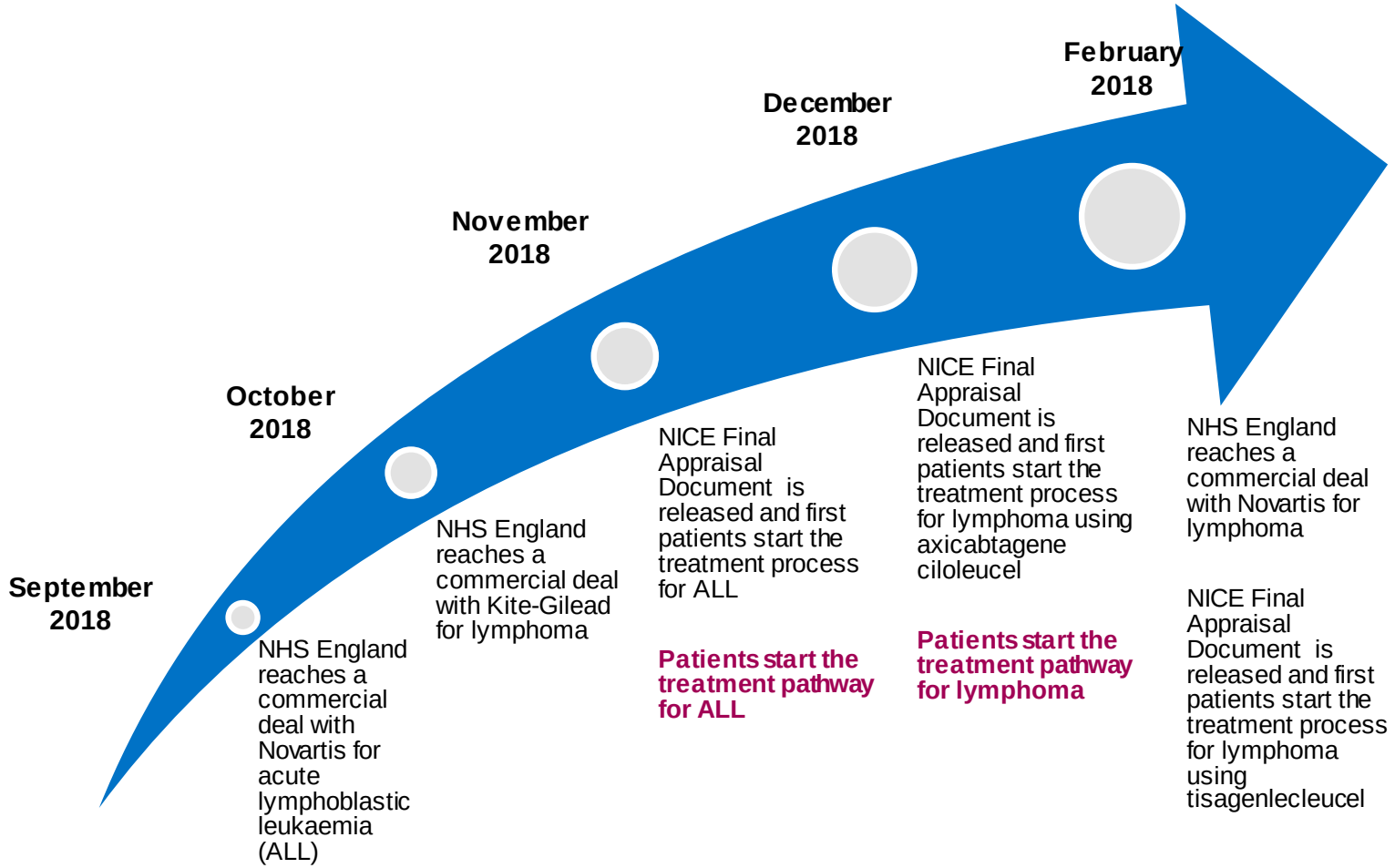
- For a CAR-T cell therapy to become an approved medicine in the UK it needs to become approved by NICE. There are lots of different types of CAR-T cell therapies in development; however currently there are three that are approved by NICE. The table below provides more detail on the approved indications.

	Tisagenlecleucel		Axicabtagene ciloleucel
Product name / Company	Kymriah®/ Novartis	Kymriah®/ Novartis	Yescarta®/ Gilead
Condition	Lymphoblastic leukaemia (ALL)	Diffuse large B-cell lymphoma (DLBCL)	Diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma
Age	Patients up to the age of 25 years (day before their 26th birthday)	Adults	Adults
Expected number of patients	c.15 – 30 patients per year	c.200 patients per year	c.200 patients per year
Number of providers	9 providers including 3 paediatric providers	7 providers	7 providers

- **Note that tisagenlecleucel and axicabtagene ciloleucel for lymphoma treat the same 200 patients – the two products are in competition**

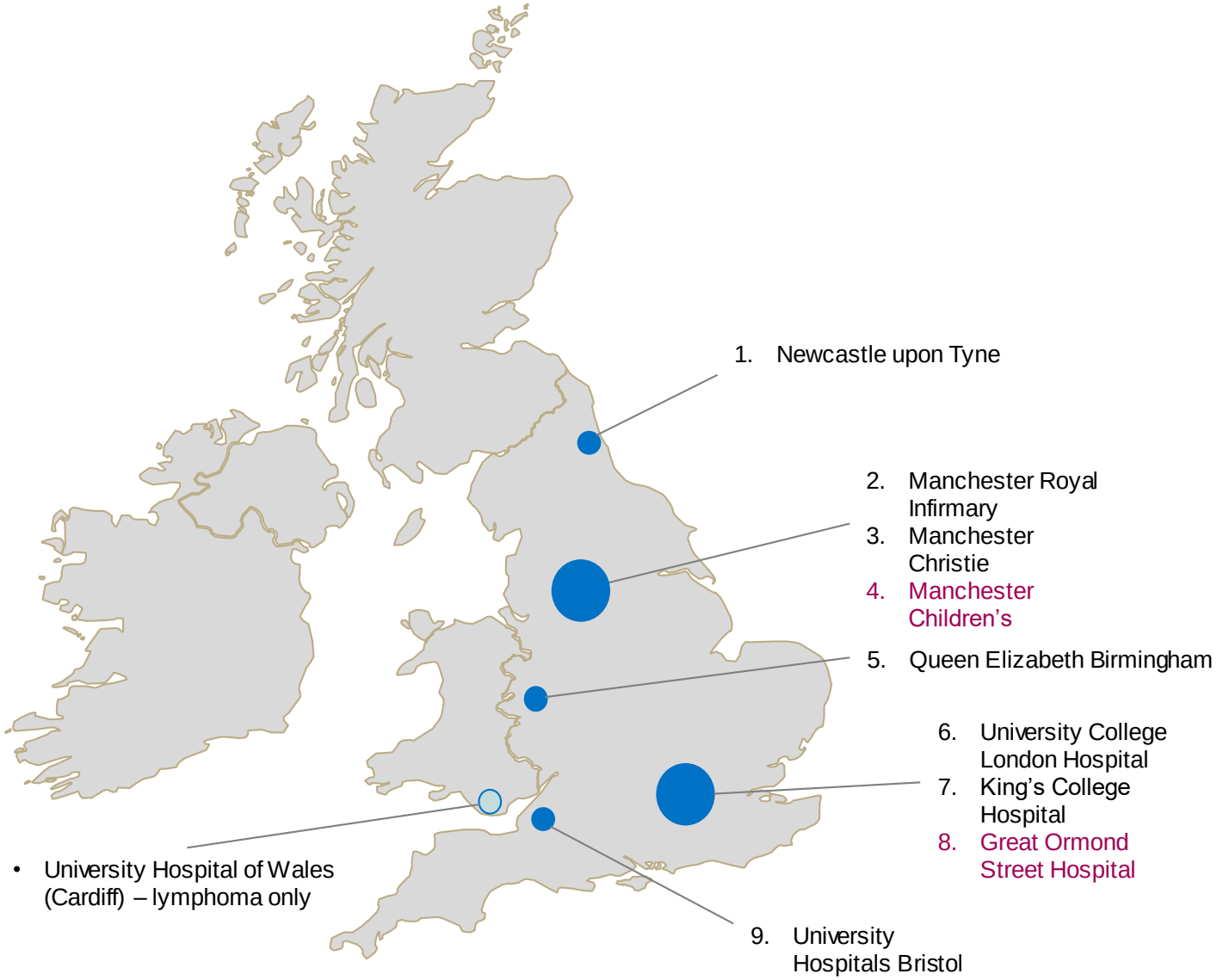
Successive commercial deals enabled patient access to three indications of CAR T cell therapy

NHS England's commercial deal with Novartis for the ALL indication was the first in Europe, and came less than 10 days after the treatment was granted its European marketing authorisation. The timeline below summarises the commercial deals for CAR T cell therapy and the subsequent NICE Final Appraisal Document release.



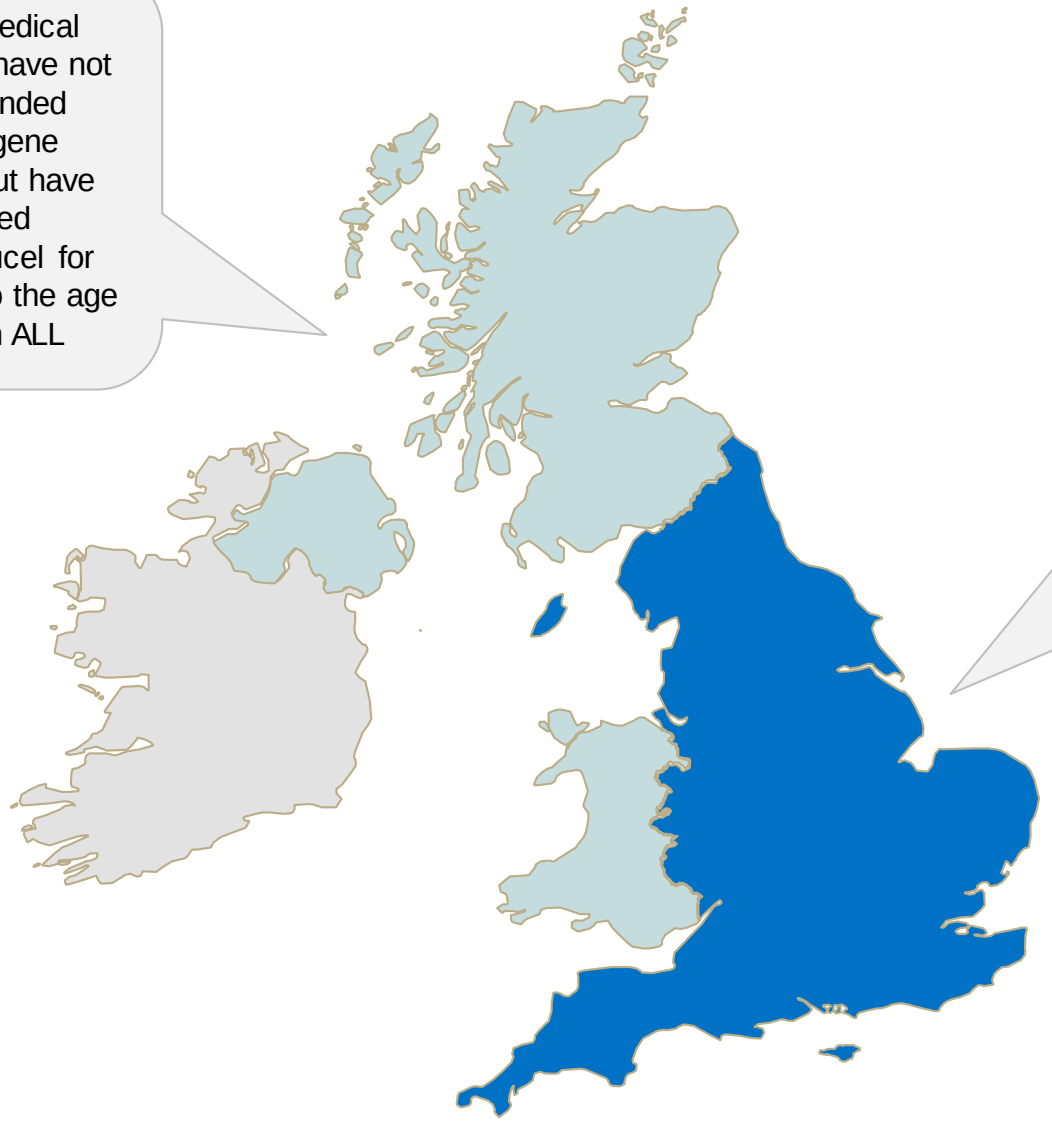
CAR T cell therapy for acute lymphoblastic leukaemia and lymphoma is available in 9 centres across the country (Wave 1)

- Hospitals in purple only provide CAR T for paediatric ALL, the remaining providers offer CAR T for ALL and Lymphoma
- To ensure there is enough capacity in the system to treat c. 200 patients for lymphoma and c.20 patients for ALL, NHS England has called for applications for wave 2 centres.
- We expect more centres to be commissioned in 2019 Wave 2 Announced April19
- In future transition to rolling programme of centre onboarding to meet demand



NHS England hospitals will also be providing access for patients in the devolved administrations

Scottish Medical Consortium have not recommended axicabtagene ciloleucel but have approved tisagenleleucel for patients up to the age of 25 with ALL

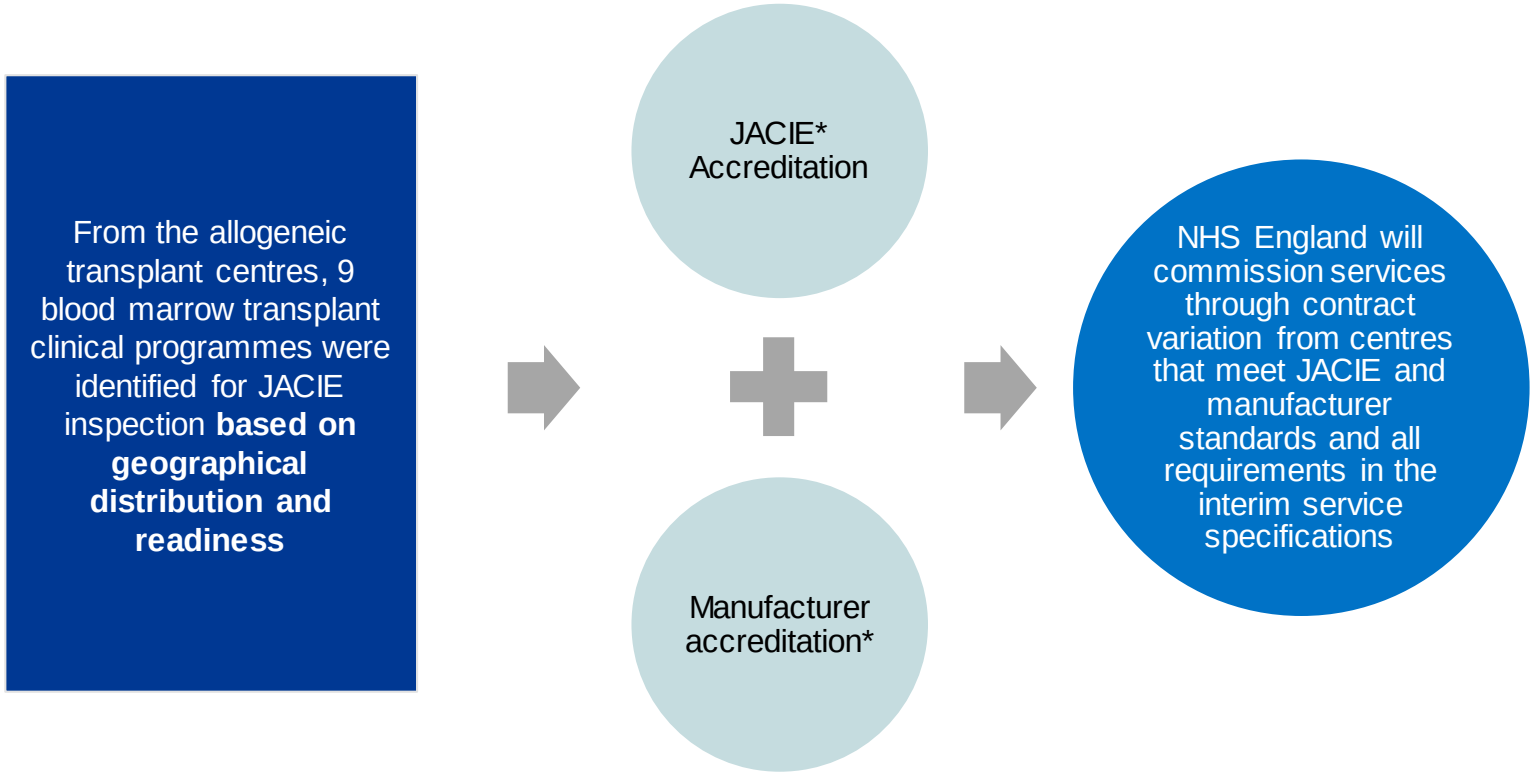


Currently, all the hospitals that can provide CAR-T cell therapy are located in England.

Cardiff will be able to provide CAR T for lymphoma later in 2019

NHS England worked with the companies and JACIE to get hospitals ready for providing this highly complex treatment

To enable NHS services to meet the quality and safety requirements of the drug manufacturers and services requirements we followed a two-step process. This process ensured that right infrastructure in place to support clinical safety and regulatory compliance. The process we followed is summarised below.



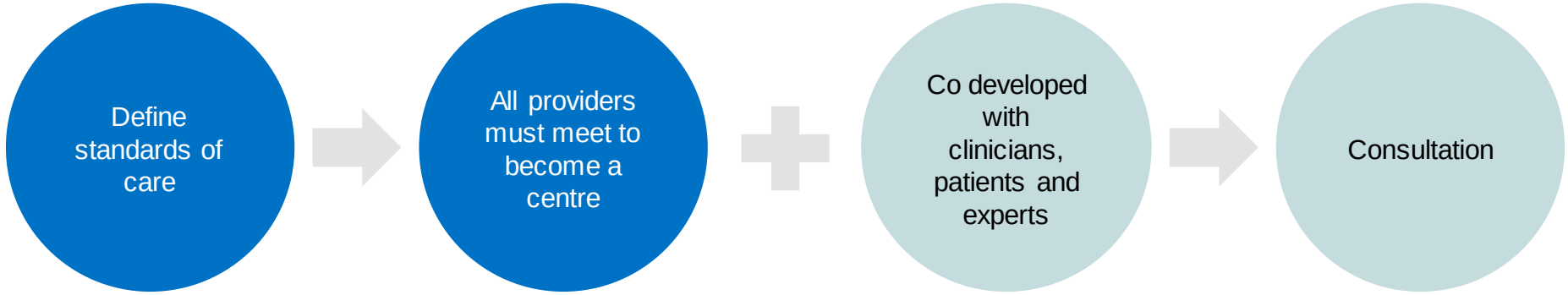
*Joint Accreditation Committee ISCT-Europe & EBMT (JACIE) accreditation against the general cellular therapy standards has long been a pre-requisite for providers to be commissioned to deliver stem cell transplantation in England. Whilst not all European commissioners insist on such accreditation, the role of JACIE is well recognised and respected as a kite-mark type quality system for stem cell transplantation.

*Providers must compete a separate onboarding process for Novartis and Kite-Gilead

Interim service specifications were developed to ensure providers met safety and quality standards for CAR T

- Separate interim service specifications were developed for tisagenlecleucel and axicabtagene ciloleucel indication due to differences in manufacture, logistics and company regulatory assurance. Service specifications are developed by NHS England.

- Interim service specifications are published on the NHS England webpage.



National CAR T Clinical Panels were developed to ensure patient eligibility and manage supply and demand

- As the NHS may not be able to provide access for all eligible patients in the short term, as providers and manufacturers' ramp up capacity, we have established a National CAR T Clinical Panel (NCCP) to help prioritise eligible patients. There is be a panel for acute lymphoblastic leukaemia and another one for lymphoma.

- The panels are clinically led with representation from clinicians from commissioned CAR-T centres and from patient and public representatives.

- The role of the panel is to:

    1. Provide expert advice on CAR T cell therapies
    2. Provide assurance of patient clinical eligibility
    3. Prioritise patients for treatment to match capacity and the distribution of patients
    4. Monitor outcomes for all eligible patients at various treatment stages

- Capacity has not been an issue for acute lymphoblastic leukaemia; however for lymphoma difficult decisions about prioritisinghave been made due to limited capacity in the system.

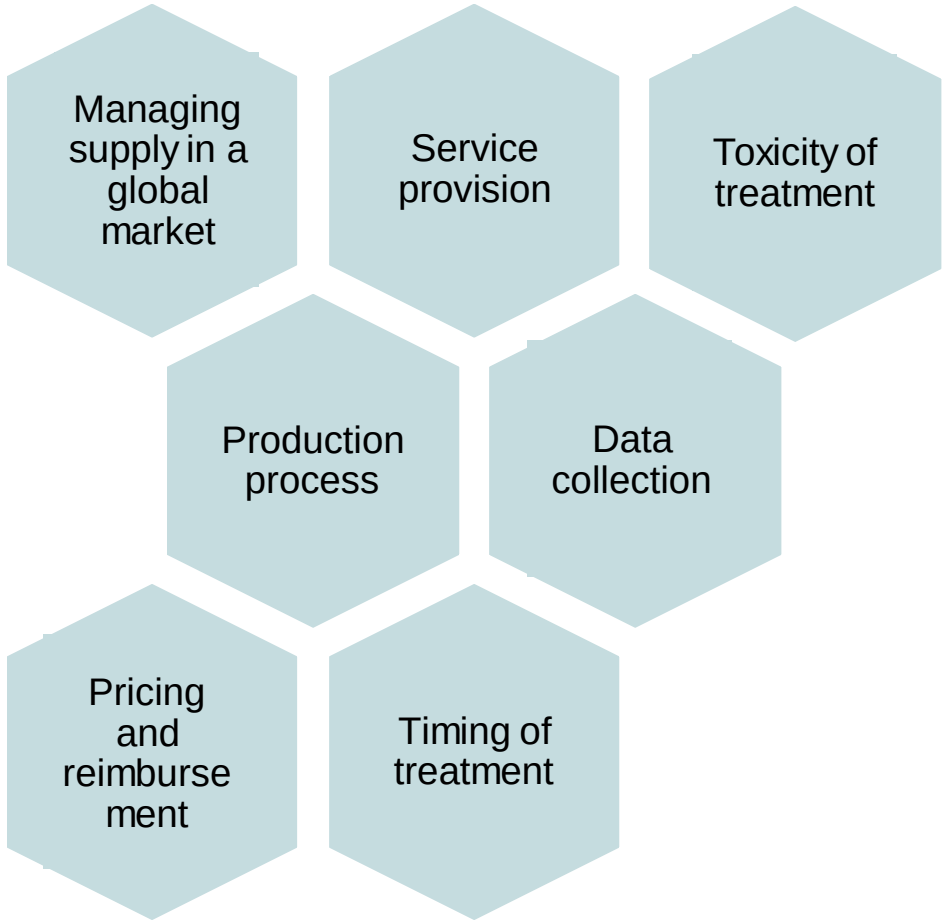
- We anticipate that the capacity restraints will lessen as more providers complete the onboarding process.

Five key lessons from implementing CAR T cell therapy

1	**Developing standards**	A different approach to service specifications may need to be developed in the long term – this could be encouraged by industry reducing or aligning the different manufacturing, logistics and company regulatory assurances processes.
2	**Working in partnership**	Partnering with international organisations like JACIE can be beneficial in accrediting providers across the country. A new way of working has also been developed with industry by both NHS providers and NHS England. We will need to continue working in partnership with a range of partners to offer ATMPs for NHS patients.
3	**Role of evaluative commissioning**	Patients are able to access CAR T for ALL and lymphoma while the evidence on clinical and cost effectiveness is further developed due to the existence of the cancer drugs fund. This means that patient can access the treatment before a routine commissioning decision is made.
4	**Managing demand and capacity**	The National CAR T Clinical Panels for acute lymphoblastic leukaemia and lymphoma are necessary for ensuring patients meet the eligibility requirements and for prioritising patients should demand outstrip capacity. The panels may not be necessary should there be enough capacity in the system.
5	**Toxicity profile**	Toxicity profile of CAR T means that the requirements to provide this service were higher than for other cancer services (i.e. co-location of neuroscience). Some centres found it challenging to meet this standard. If the toxicity profile were to decrease for future iterations of CAR T or different ATMPs then more centres could offer ATMPs. However there may be a continued role for NHS England in managing the provider landscape and to ensure expertise is concentrated.

The key lessons from implementing CAR T cell therapies will need to be applied to our approach to AMTPs

- Advanced therapeutic medicinal products (ATMPs) are disruptive innovative technologies because at both individual and 'whole class' level they bring the potential for fundamental change that may require the need for the health service to work differently. CAR T cell therapy is one example of AMTPs.
- It is thought that there are over 850 trials of gene and cell therapies currently underway worldwide covering a wide range of clinical indications - although over 50% are for cancer indications and10% for cardiovascular disorders.
- Not all the treatments in development will receive market authorisation licenced and will not be launched commercially
- 7 considerations will need to be applied to future high cost and disruptive innovations like ATMPs – learning should be gathered from the experience to date to understand the implications on the wider health and care system.



Lessons learnt: Staff Training in the NHS

- NHS England was keen to understand the cost of implementing CAR T cell therapy and the impact on referral centres.
- Anecdotical evidence suggested that it is not sustainable for providers to redesign processes and train dozens of staff for each advanced therapy medicinal product.
- In addition there is a need to work with companies to align their procedures for future products coming through to reduce administrative burden for providers
- All wave one providers were asked to fill out a questionnaire to understand the workforce and infrastructure cost of implementing CAR T cell therapy.

Note that this information is based on submissions from the Christie, MRI, Newcastle, Birmingham, King's and Bristol. All wave one centres were given the opportunity to respond to the questionnaire

To ensure a sustainable model, additional staff were trained at providers through ‘train the trainer’

- We know that more staff were trained indirectly by providers to ensure whole departments had the right skills to deliver CAR T:

- Some providers have chosen to appoint additional staff to lead the service.
  - One provider appointed a clinical lead to lead CAR T cell therapy for the Trust.
  - At another a business plan was put in place for extra staffing including apheresis and stem cell laboratory staff.
  - Another provider has appointed an CAR-T co-ordinator admin post

- Providers were able to manage the training requirements by prioritising training within existing job plans and organising intensive days of training to minimise the time staff spent in training. In some instances, staff worked extra hours to be able to complete the required training.

- All providers noted the challenge in releasing staff for the required training time.

The Future: Advanced therapy medicinal product (ATMP) issues for consideration

There are three key areas to consider for ATMPs.

NHS England position will work to develop the way forward with all key stakeholders.

Managing ATMPs that are **currently available** for NHS patients, including CAR T

Identifying AMTPs that **may be available in the short to medium** term, including NHSE action

Determining the NHS **strategic direction of travel** for all ATMPs

NHS Experience to Date

For further information on NHS Experience with CAR T please contact: england.nccp@nhs.net

Thank You for Listening