REPORT

Access and Provision of CAR-T Therapies in Ireland for Cancer Care

The Current & Future Landscape, Opportunities and Challenges: Legal, Ethical and Broader Policy Considerations.

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The final report and the project recommendations reflect the authors' own opinions alone. Any omissions or errors in any aspect are the authors' own.

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As noted, this report and the recommendations contained herein reflect the authors' view alone, and are not representative of the views of any other organisations, funders etc.

CIVIL SOCIETY PARTNER: DR FRANCES DRUMMOND, BREAKTHROUGH CANCER RESEARCH

Dr Frances Drummond

Dr Frances Drummond is the Research Manager at Breakthrough Cancer Research. Having qualified with a PhD in Biochemistry from University College Cork, Frances shifted her focus to patient focused research for her post-doctoral career. She has fifteen years of experience in cancer research in the National Cancer Registry of Ireland and University College Cork. Frances has published more than 50 peer-reviewed papers and reports. She is a Board member of the Health Research Charities of Ireland and a pre-accredited counsellor and psychotherapist.

Breakthrough Cancer Research

Breakthrough Cancer Research is an Irish medical research charity focused on cancer. Breakthrough works to significantly impact the number of children and adults who can survive this disease. It invests in world-class research in Ireland and beyond to impact the quality of life for people with cancer and save lives. Breakthrough are particularly focused on improving outcomes for those cancers, which are poorly served by current treatment options.

Breakthrough funds cancer research that responds to current clinical challenges and offers a clear and demonstrable path to positive clinical outcomes. Research programmes funded by Breakthrough must focus on translating lab discoveries into new treatment opportunities. To this end, Breakthrough work closely with clinicians in practice all over Ireland and internationally so that their research is targeted at finding new options for poor prognosis and currently incurable cancers.

EXECUTIVE SUMMARY

This research was conducted as part of the Irish Research Council funded, 'Patients' Access to Advanced Cancer Therapies: Ethics and Equity of Access' (PAACT) project. It aims to examine and map the current framework in Ireland for the provision of Chimeric Antigen Receptor T-cell therapy (hereafter 'CAR-T therapy') and to examine sustainable pathways to develop and provide access to such therapies in future. CAR-T therapy is a type of immunotherapy which aims to use cells from a patient's own immune system as part of the therapy. In simple terms, as part of the treatment, immune cells called T-cells are removed from the patient's body, then outside the body these cells are modified so that they can target and kill cancer cells effectively. The modified T-cells are then reinfused or put back into the patient's body to treat the cancer. When this therapy is successful, in some cases it has led to cancer going into remission – where such patients were previously terminally ill with no other viable potential treatment options. There are side effects associated with CAR-T therapies, including some which can prove fatal. However, clinical teams have developed strategies to try to minimise these risks, and to optimise management of such side effects. Nonetheless, ethical issues can arise in such contexts.

CAR-T therapies were approved by the European Medicines Agency (EMA) for use in Europe in 2018. The provision of CAR-T therapies commenced in Ireland in 2021 for adult patients and in 2022 for paediatric patients in certain clinical contexts. Before this, patients based in Ireland (for whom such therapies were clinically indicated) needed to travel abroad to obtain CAR-T therapies. Currently several different CAR-T therapies have regulatory approval in Europe and are approved to treat certain types of haematological (blood) cancers such as lymphoma, leukaemia and myeloma, in specific contexts. Research in the field suggests they may have potential to treat other types of cancers, and other conditions in future. Accordingly, the numbers of patients who may benefit from such therapies may increase over time.

However, there are remaining challenges for patients in accessing CAR-T therapies in Ireland. There are also challenges to providing CAR-T therapies within national

public health systems, including the high costs of such therapies currently, and other legal, ethical, regulatory, resourcing, and infrastructural issues around increasing the development and provision of CAR-T therapies at a national level.

This report examines the literature in the field and aims to provide an overview of the current landscape for the provision of CAR-T therapies for patients based in the Republic of Ireland (hereafter Ireland), it also outlines some of the main potential challenges for patients in accessing such therapies, and at a health systems level in providing CAR-T therapies. It concludes by offering ten main recommendations which aim to promote a deeper multi-disciplinary conversation around the provision of CAR-T therapies in Ireland to address the main legal, ethical and broader policy challenges in this area, and to create further sustainable pathways to increase the development and provision of CAR-T therapies in Ireland in future.

1 INTRODUCTION

Cancer is currently one of the leading causes of serious illness and death in Ireland.[1] It accounts for an estimated 30% of all deaths in Ireland annually (approximately 9,751 deaths in Ireland each year during 2018-2020).[2] There are approximately 43,470 new cases of cancer diagnosed annually in Ireland, and there is a culminative risk of 1 in every 2 people in Ireland developing cancer during their lifetime.[3] Furthermore, predictions from the National Cancer Registry Ireland (NCRI) are that if current trends continue, the number of cases of cancer in Ireland is expected to almost double by 2045.[4]

Due in large part to advances in cancer screening, monitoring and the development of improved therapies, cancer survival rates are significantly improving. Survival rates

[1]Unless otherwise stated, the use of the term 'Ireland' in this report refers to the Republic of Ireland; See: Irish Cancer Society, 'Cancer Statistics' https://www.cancer.ie/cancer-information-and-support/cancer-information/about-cancer/cancer-statistics accessed 16 October 2023; For a more detailed breakdown of statistics in relation to cancer rates and deaths in Ireland see: National Cancer Registry Ireland, 'Cancer in Ireland 1994-2020: Annual Statistical Report of the National Cancer Registry' (2022) NCRI, Cork, Ireland, 15-17 https://www.ncri.ie/sites/ncri/files/pubs/NCRI_AnnualStatisticalReport_2022.pdf accessed 16 October 2023; Central Statistics Office Statistical Publication, 'Vital Statistics Yearly Summary 2020' (28 May 2021) https://www.cso.ie/en/releasesandpublications/ep/p-vsys/vitalstatisticsyearlysummary2020/ accessed 30 August 2023; see also: 'Dying and Death in Ireland: What Do We Routinely Measure, How Can We Improve?' Trinity College Dublin (2021) https://hospicefoundation.ie/wp-content/uploads/2021/11/Dying-and-Death-in-Ireland-what-do-we-routinely-measure-how-can-we-improve-2021.pdf accessed 16 October 2023.

[2] National Cancer Registry Ireland, 'Cancer in Ireland 1994-2020: Annual Statistical Report of the National Cancer Registry' (2022) NCRI, Cork, Ireland, foreword, 1 https://www.ncri.ie/sites/ncri/files/pubs/NCRI_AnnualStatisticalReport_2022.pdf accessed 16 October 2023; See also: Irish Cancer Society, 'Cancer Statistics' https://www.cancer.ie/cancer-information-and-support/cancer-information/about-cancer/cancer-statistics accessed 30 August 2023.

[3] National Cancer Registry Ireland, 'Cancer in Ireland 1994-2020: Annual Statistical Report of the National Cancer Registry' (2022) NCRI, Cork, Ireland, 10 https://www.ncri.ie/sites/ncri/files/pubs/NCRI_AnnualStatisticalReport_2022.pdf accessed 16 August 2023.

[4] National Cancer Registry Ireland, 'Cancer Incidence Projections for Ireland 2020-2045' (2019) NCRI, Cork, Ireland, 1 https://www.ncri.ie/sites/ncri/files/pubs/CancerIncidenceProjections_NCRI_fullreport_09042019_final.pdf accessed 16 October 2023 which predicts by 2045 "numbers of cancers (excluding NMSC) would be expected to increase by more than double in men and to almost double in women by 2045 – to 43,000 cases in total, a doubling of numbers overall."

vary depending on cancer types, however, the Irish National Cancer Registry's report (2022) highlights major improvements in survival rates for most forms of cancer.[5] At the end of 2020, the National Cancer Registry recorded that approximately 207,000 people living in Ireland were cancer patients or former cancer patients – which equates to 1 in every 24 people.[6] Nonetheless, survival rates from cancer at different sites on the human body is not equal.[7]

Cancer treatment is most commonly in the form of surgery to remove the cancer, radiotherapy (the use of radiation to kill cancer cells), chemotherapy (the use of drugs to kill cancer cells), and most recently targeted therapy and immunotherapies.[8] Targeted therapy in general terms 'is a type of cancer treatment that targets proteins that control how cancer cells grow, divide, and spread.'[9] Immunotherapies aim to use or harness the body's own immune system to help attack and destroy the cancer cells.[10]

CAR-T therapy is one type of cellular immunotherapy,[11] which aims to use cells from a patient's own immune system as part of the treatment. In simple terms, CAR-T

[5] National Cancer Registry Ireland, 'Cancer in Ireland 1994-2020: Annual Statistical Report of the National Cancer Registry' (2022) NCRI, Cork, Ireland, 15-17 https://www.ncri.ie/sites/ncri/files/pubs/NCRI_AnnualStatisticalReport_2022.pdf accessed 30 August 2023.

[6] National Cancer Registry Ireland, 'Cancer in Ireland 1994-2020: Annual Statistical Report of the National Cancer Registry' (2022) NCRI, Cork, Ireland, 6 https://www.ncri.ie/sites/ncri/files/pubs/NCRI_AnnualStatisticalReport_2022.pdf accessed 30 August 2023.

[7] National Cancer Registry Ireland, 'Cancer in Ireland 1994-2020: Annual Statistical Report of the National Cancer Registry' (2022) NCRI, Cork, Ireland, 20-23 https://www.ncri.ie/sites/ncri/files/pubs/NCRI_AnnualStatisticalReport_2022.pdf accessed 30 August 2023.

[8] Irish Cancer Society, 'Cancer Treatments and Side-Effects' https://www.cancer.ie/cancer-information-and-support/cancer-information/cancer-treatments-and-side-effects accessed 30 August 2023.

[9] National Cancer Institute (US), 'What is targeted therapy' available at https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies#what-is-targeted-therapy accessed 31 August 2023.

[10] Vanessa Innao, Andrea Gaetano Allegra, Caterina Musolino, et al., 'New Frontiers about the Role of Human Microbiota in Immunotherapy: The Immune Checkpoint Inhibitors and CAR T-Cell Therapy Era' (2020) 21 (8902) International Journal of Molecular Sciences https://doi.org/10.3390/ijms21238902 accessed 30 August 2023.

[11] Also called cellular adoptive immunotherapy which is defined by the US National Cancer Institute as "A type of immunotherapy in which T cells (a type of immune cell) are given to a patient to help the body fight diseases, such as cancer", see: National Cancer Institute 'adoptive cell therapy' https://www.cancer.gov/publications/dictionaries/cancer-terms/def/adoptive-cell-therapy accessed 30 August 2023.

therapy involves immune cells called T-cells which are collected from the patient's body, outside the body these cells are modified so that they can target and kill cancer cells more effectively. The modified T-cells are then reinfused into the patient's body to treat the cancer. CAR-T therapies fall within the regulatory category of Advanced Therapy Medicinal Products (ATMPs) which are 'medicines for human use that are based on genes, tissues or cells.'[12]

Currently several types of CAR-T therapies have regulatory approval in Europe and are approved to treat certain types of haematological (blood) cancers such as lymphoma, leukaemia and myeloma.

As will be discussed below, CAR-T therapies currently offer significant potential for cancer treatment for certain indications and, where successful, such therapies have led to complete remission of cancer for some patients who in many cases were previously terminally ill with no other viable treatment options remaining. Accordingly, such immunotherapies have been described as potentially revolutionary for cancer care.[13] Having said this, CAR-T therapies can give rise to side effects, including cytokine release syndrome which can be fatal in some instances. However, strategies have recently been developed which can help reduce the instance and severity of such side effects.[14] Nonetheless, the risks of these side effects occurring also pose ethical issues which must be considered.

Moreover, despite the promise of CAR-T therapies, there are challenges to providing such therapies within national public health systems. A key barrier to providing CAR-T therapies currently is the high costs of these therapies - the list prices for

[12] ATMPs include gene therapy medicines, somatic-cell therapy medicines, and tissue-engineered medicines. For a discussion see: European Medicines Agency, Advanced Therapy Medicinal Product: Overview' https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview#:~:text=Advanced%20therapy%20medicinal%20products%20(ATMPs,on%20genes%2C%20tissues%20or%20cells accessed 30 August 2023.

[13] Alex D Waldman, Jill M Fritz, and Michael J Lenardo, 'A guide to cancer immunotherapy: from T cell basic science to clinical practice' (2020) 20 Nature Reviews Immunology 651-688.

[14] 'CAR-T Therapy: Combatting Cytokine Release Syndrome' News Medical Life Sciences (21 May 2021) https://www.news-medical.net/whitepaper/20210521/CAR-T-Therapy-Combating-Cytokine-Release-Syndrome.aspx accessed 31 August 2023; Francis Ayuk Ayuketang and Ulrich Jäger, 'Management of Cytokine Release Syndrome (CRS) and HLH' in Nicolaus Kröger et al, *The EBMT/EHA CAR-T Cell Handbook* (Springer 2022).

commercially produced CAR-T therapies in Europe are often in excess of approximately €300,000 per patient per infusion.[15] This figure does not include other necessary indirect costs, such as the costs associated with patient hospital stays etc.[16] Other challenges in providing CAR-T therapies include: logistical and manufacturing challenges; challenges around ensuring sufficient relevant personnel are available to provide such therapies including, multi-disciplinary clinical teams; and regulatory challenges. Alongside this, especially for emerging personalised CAR-T therapies, broader ethical and safety considerations may arise which must be carefully considered and balanced.

This report examines the current landscape for the provision of and access to CAR-T therapies for adult and paediatric patients living in Ireland. In doing so, for context, it first briefly outlines the potential benefits and future opportunities CAR-T therapies may offer for cancer care. It then provides an overview of the key current challenges for patients in accessing such therapies in Ireland and of the current (and likely future) challenges for health systems in providing such therapies in Ireland, focusing on the legal, ethical, and other broader policy challenges. Based on this research, it then offers ten policy recommendations which are aimed at seeking to reduce, and where possible over time, address these challenges.[17]

The report is structured as follows: Part two provides a general overview of CAR-T therapy - what it is, how it works, how the treatment process operates, and the main potential benefits and risks for patients who undergo CAR-T therapies. Part three provides a brief overview of the timeline for the first CAR-T therapies obtaining regulatory approval in the US and EU, and an overview of the currently approved CAR-T therapies in both regions. Part four outlines the current landscape for adult and child

[15] See discussion in: Renaud Heine, et al., 'Health Economic Aspects of Chimeric Antigen Receptor T-cell Therapies for Hematological Cancers: Present and Future' (2021) 5(2) Hemasphere e524. For a discussion of this in the US context, see: Rebecca Borgert, 'Improving outcomes and mitigating costs associated with CAR T-cell therapy' (2021) 27(13 Suppl) Am J Manag Care S253-61.
[16] See also discussion in: European Cancer Patient Coalition, 'CAR-T Therapy: White Paper' (2022), https://ecpc.org/wp-content/uploads/2022/11/White-Paper-CAR-T-therapy.pdf accessed 30 August 2023.
[17] Many of the general issues raised may have relevance for other ATMPs, although it should be noted that specific issues raised by other types of ATMPs are outside of the scope of this report.

patients living in Ireland to access CAR-T therapies in Ireland. Part five outlines the avenues for such patients to obtain access to CAR-T therapies (where it was clinically indicated for them) abroad prior to these therapies being provided in Ireland. Part six reflects on the current landscape for patients living in Ireland to access CAR-T therapies in Ireland. It considers key potential legal, ethical, and broader policy challenges around accessing CAR-T therapies for patients, and around providing CAR-T therapies from a health systems perspective. In doing so, it sets set out ten recommendations seeking to address these challenges. Part seven concludes by arguing CAR-T therapies offer significant potential for cancer care, however, a broader national policy and strategy is needed to consider and address challenges around providing such therapies currently, and to design sustainable pathways to develop and provide such therapies (and other ATMPs) in Ireland for those who may need them in future. This section also summarises the key report recommendations.

2 CAR-T THERAPIES: AN OVERVIEW

CAR-T therapy is a type of immunotherapy also called an adoptive cell therapy (as it involves the transfer of cells into a patient's body).[18] The human immune system contains cells called *lymphocytes* which are a type of white blood cell that ordinarily fight infection.[19] One type of lymphocyte is a T-cell. Ordinarily, such cells kill harmful pathogens in the body, including cancer cells.[20] However, sometimes cancer cells cannot be detected by the immune system and CAR-T therapy works by modifying the patient's own T-cells so that they can find and kill such cancer cells more effectively. CAR-T therapy is currently provided as a personalised cancer treatment (or *autologous* therapy) as it involves using some of each individual patient's own T-cells, modifying these cells outside the body, and then using these modified cells as part of the therapy.

2.1 A BRIEF OVERVIEW OF THE CAR-T THERAPY PROCESS

In general terms, the clinical process for CAR-T therapies in Ireland currently operates as follows:[21] First, a sample of the patient's lymphocytes is collected from the patient's

[18] Cancer Research Institute, 'How Cellular Immunotherapies Are Changing the Outlook for Cancer Patients' reviewed by Philip D Greenberg, https://www.cancerresearch.org/en-us/immunotherapy/treatment-types/adoptive-cell-therapy accessed 3 August 2023.

[19] Cleveland Clinic, 'T Cells' https://my.clevelandclinic.org/health/body/24630-t-cells#:~:text=T%20lymphocytes)%3F-,T%2Dcells%20are%20a%20type%20of%20white%20blood%20cell%20called,harmful%20cells%2C%20like%20cancer%20cells accessed 30 August 2023.

[20] Cleveland Clinic, 'T Cells' https://my.clevelandclinic.org/health/body/24630-t-cells#:~:text=T%20lymphocytes)%3F-,T%2Dcells%20are%20a%20type%20of%20white%20blood%20cell%20called,harmful%20cells%2C%20like%20cancer%20cells accessed 30 August 2023.

[21] For general information on the CAR-T therapy process, see: 'CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers' National Cancer Institute (updated 10 March 2022) https://www.cancer.gov/about-cancer/treatment/research/car-t-cells#:~:text=CAR%20T%2Dcell%20therapy%3A%20A%20%22living%20drug%22&text=They%20are%20made%20by%20collecting,the%20surface%20of%20cancer%20cells accessed 30 August 2023; 'CAR T-cell therapy' Cancer Research UK (last reviewed 20 May 2021) https://www.cancerresearchuk.org/about-cancer/treatment/immunotherapy/types/CAR-T-cell-therapy accessed 30 August 2023; Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes

blood in the hospital setting in Ireland via a process called *apheresis*. Apheresis involves separating blood into its individual elements to collect or remove the required element(s), in this case the lymphocytes, while the patient is connected to the separation device.[22] The removed lymphocytes are then frozen (cryopreserved) and transported from the hospital where they were obtained to the manufacturer (abroad in the cases of CAR-T therapies provided in Ireland currently, discussed below) for them to be processed. Initially, T-cells are isolated from the collected lymphocytes. Following this, a protein called a chimeric antigen receptor (CAR) is inserted into the T-cells and expressed on the T-cell's surface so that the modified T-cells (so-called CAR-T cells) will target or focus on the antigen which is found on the surface of specific cancer cells.[23] The modified CAR-T cells are then expanded and multiplied. The modified CAR-T cells are then packaged, cryopreserved and transported back to the hospital in Ireland where they are infused into the patient as part of the CAR-T therapy. The aim of this infusion is that these modified CAR-T cells, once infused into the patient's body, will be capable of more effectively targeting the specific cancer cells inside the patient's body. [24] Where CAR-T therapy is successful, the aims is that cancer will be eradicated from the patient's body.

Currently, for patients who obtain CAR-T therapies in Ireland, the processing of the cells takes place outside Ireland. This can add additional complexity, time, and cost to the process because it means such cells must be packaged, cryopreserved, stored

following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-371 https://doi.org/10.1038/s41571-023-00754-1 accessed 31 August 2023; Craig A Portell, 'How Does CAR T-Cell Therapy Work in Treating Cancer?' (17 June 2021) https://www.cancer.net/blog/2021-06/how-does-car-t-cell-therapy-work-treating-cancer#:~:text=Activated%20CAR%20T%20cells%20multiply,the%20cancer%20cell%20to%20die. accessed 30 August 2023.

[22] Cancer Research UK, 'CAR T-cell therapy' (last reviewed 20 May 2021) https://www.cancerresearchuk.org/about-cancer/treatment/immunotherapy/types/CAR-T-cell-therapy accessed 30 August 2023; See discussion of apheresis in: Muna Qayed et al., 'Leukapheresis guidance and best practices for optimal chimeric antigen receptor T-cell manufacturing' (2022) 24 Cytotherapy 869–878.

[23] For an overview, see: 'CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers' National Cancer Institute https://www.cancer.gov/about-cancer/treatment/research/car-t-cells#:~:text=CAR%20T%2Dcell%20therapy%3A%20A%20%22living%20drug%22&text=They%20are%20made%20by%20collecting,the%20surface%20of%20cancer%20cells accessed 30 August 2023.

[24] See also: Cancer Research UK, 'CAR T-cell therapy' (last reviewed 20 May 2021) https://www.cancerresearchuk.org/about-cancer/treatment/immunotherapy/types/CAR-T-cell-therapy accessed 30 August 2023.

and transported outside the country. They must then be processed abroad, packaged, cryopreserved and then returned to the treating hospital in Ireland for thawing and re-infusion in the patient's body. The entire process under this type of centralised manufacturing model from the initial collection of the lymphocytes from the patient's body to the re-infusion of the modified T cells back into a patient's body takes up to four weeks approximately.[25] During this time, the patient may need to receive additional cancer treatment (bridging treatment) to try to keep their cancer condition at bay, while they wait to receive the CAR-T therapy infusion.[26]

2.2 The Potential Benefits of CAR-T Therapies for Patients

CAR-T therapies offer significant potential benefits for certain patients, particularly because these therapies have the potential to lead to complete remission of certain types of cancers. The benefits of CAR-T therapy are illustrated by the case of Emily Whitehead. Emily was diagnosed with acute lymphoblastic leukaemia (ALL) when she was five years old in May 2010.[27] She was treated with chemotherapy which proved promising initially. In 2011, her condition relapsed, and chemotherapy was unsuccessful.[28] By 2012, after unsuccessful chemotherapy, her condition worsened. Emily became terminally ill, and her medical team had exhausted all existing approved treatment options.[29] However, her family found an early-stage clinical trial for CAR-T therapy for paediatric patients with ALL at the Children's Hospital of Philadelphia which Emily was deemed clinically suitable for, and was enrolled on.[30] During the therapy

[25] Tao Ran, Stefan B Eichmüller, Patrick Schmidt, et al., 'Cost of Decentralized CAR T-Cell Production in an Academic Nonprofit Setting' (2020) 147(12) International Journal of Cancer 3438–3445, https://doi.org/10.1002/ijc.33156 accessed 30 August 2023.
[26] Shakthi T. Bhaskar et al., 'Role of bridging therapy during chimeric antigen receptor T cell therapy' (2021) 19(3) E J Haem 39-45.
[27] Emily Whitehead Foundation, 'Our Journey' https://emilywhiteheadfoundation.org/our-journey/ accessed 30 August 2023.
[28] Alliance for Cancer Gene Therapy, 'Meet Emily Whitehead' https://acgtfoundation.org/for-patients/patient-stories/emily-whitehead/ accessed 30 August 2023.
[29] Cancer Research Institute, 'Patients: Emily Whitehead' https://www.cancerresearch.org/stories/patients/emily-whitehead accessed 30 August 2023.
[30] Children's Hospital Philadelphia, 'Emily Whitehead, First Pediatric Patient to Receive CAR T-Cell Therapy, Celebrates Cure 10 Years Later' (11 May 2022) https://www.chop.edu/news/emily-whitehead-first-pediatric-patient-receive-car-t-cell-therapy-celebrates-cure-10-years accessed 30 August 2023.

Emily experienced significant adverse side effects.[31] However, the therapy was ultimately successful.[32] Emily subsequently went into full remission from cancer, and has been in remission for over ten years.[33] Emily Whitehead and her family's experience is illustrative of the benefits that CAR-T therapy can offer for some patients – and although the therapy is not without risks, given its potential to lead to remission against cancer, it is seen as revolutionary by many.

To date, the available evidence suggests that current CAR-T therapies are most effective against haematological (blood) cancers including leukaemia, lymphoma, and multiple myeloma.[34] CAR-T therapies have currently more limited effectiveness in treating solid tumour cancers.[35] However, there is an expectation that CAR-T therapies use will 'grow exponentially and will include other diseases in coming years.'[36] A brief general overview of the current outcomes and suggested success rates of these therapies for certain patients is now provided. This overview is provided to give context around the potential benefits of CAR-T therapies for patients and it focuses on some of the recent literature examining the outcomes of CAR-T therapies.

[31] Alliance for Cancer Gene Therapy, 'Meet Emily Whitehead' available at https://acgtfoundation.org/for-patients/patient-stories/emily-whitehead/ accessed 30 August 2023.
[32] Children's Hospital Philadelphia, 'Emily Whitehead, First Pediatric Patient to Receive CAR T-Cell Therapy, Celebrates Cure 10 Years Later' (11 May 2022) https://www.chop.edu/news/emily-whitehead-first-pediatric-patient-receive-car-t-cell-therapy-celebrates-cure-10-years accessed 30 August 2023.
[33] Children's Hospital Philadelphia, 'Emily Whitehead, First Pediatric Patient to Receive CAR T-Cell Therapy, Celebrates Cure 10 Years Later' (11 May 2022) https://www.chop.edu/news/emily-whitehead-first-pediatric-patient-receive-car-t-cell-therapy-celebrates-cure-10-years accessed 30 August 2023.
[34] Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-371.
[35] Franziska Hauth et al., 'Radiotherapy to Enhance Chimeric Antigen Receptor T-Cell Therapeutic Efficacy in Solid Tumors: A Narrative Review' (2021) 7(7) JAMA Oncology 1051-1059 http://doi.org/10.1001/jamaoncol.2021.0168 accessed 30 August 2023.
[36] 'First patient in Ireland receives ground-breaking cell therapy for blood cancer at St James's Hospital' (St James's Hospital, 13 December 2021) https://www.stjames.ie/aboutus/news/2021/firstpatientinirelandreceivesground-breakingcelltherapyforbloodcanceratstjamesshospital.html accessed 30 August 2023;
See also: Daniel J Baker et al., 'CAR T therapy beyond cancer: the evolution of a living drug' (2023) 619 Nature 707–715; Haig Aghajanian, Joel G Rurik, and Jonathan A Epstein, 'CAR-based therapies: opportunities for immuno-medicine beyond cancer' (2022) 4 Nature Metabolism 163–169. For example, recent studies have shown that CAR-T therapy has potential in bringing about remission in refractory Systemic Lupus Erythematosus (SLE) which is discussed further below: Andreas Mackensen et al., 'Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus' (2022) 28(10) Nature Medicine 2124–2132.

Importantly, however, this overview does not aim to offer a comprehensive account of the scientific developments in the field, which is beyond the scope of this report.

CAR-T therapies for treatment of certain haematological (blood) cancers

In terms of the potential benefits CAR-T therapies can have for patients, in 2023, Cappell and Kochenderfer published a review of outcomes following CAR-T therapy, which provides one of the most recent reviews of the data in the field at the time of writing. [37] This review offered several findings in relation to the current outcomes/success rates of CAR-T therapies, in various contexts. For example, it reported that in ten studies where outcome data was available for over 2 years, the overall response rates (ORR) in patients with Relapsed/Refractory (R/R) B Cell Lymphoma or Chronic Lymphocytic Leukaemia who received CAR-T therapy ranged from 44-91%, and for such patients complete remission (CR) rates ranged from 28-68%.[38] Persistence or recurrence of B-cell lymphoma after CAR-T therapy does occur in such contexts.[39] Nonetheless, based on available data, this review stated that:

[37] Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-371.

[38] Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-371, 360; The authors cite the following ten studies in this context: Katherine M Cappell et al., 'Long-term follow-up of anti-CD19 chimeric antigen receptor T-cell therapy' (2020) 38 Journal of Clinical Oncology 3805–3815; Frederick L Locke et al., 'Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma' (2022) 386 New England Journal of Medicine 640–654; Elise A Chong et al., 'Five-year outcomes for refractory B-cell lymphomas with CAR T-cell therapy' (2021) 384 New England Journal of Medicine 673–674; Caron Jacobson et al., 'Long-term (≥4 year and ≥5 year) overall survival (OS) by 12- and 24-month event-free survival (EFS): an updated analysis of ZUMA-1, the pivotal study of axicabtagene ciloleucel (axi-cel) in patients (pts) with refractory large B-cell lymphoma (LBCL)' (2021) 139 (Suppl. 1) Blood 1764; Stephen J Schuster et al., 'Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study' (2021) 22 The Lancet Oncology 1403–1415; Alexandre V Hirayama et al., 'High rate of durable complete remission in follicular lymphoma after CD19 CAR-T cell immunotherapy' (2019) 134 Blood 636–640; Michael Wang et al., 'Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study' (2023) 41 Journal of Clinical Oncology 555–567; Noelle V Frey et al., 'Long-term outcomes from a randomized dose optimization study of chimeric antigen receptor modified T cells in relapsed chronic lymphocytic leukemia' (2020) 38 Journal of Clinical Oncology 2862–2871; Jeremy S Abramson et al., 'Two-year follow-up of transcend NHL 001, a multicenter phase 1 study of lisocabtagene maraleucel (liso-cel) in relapsed or refractory (R/R) large B-cell lymphomas (LBCL)' (2021) 138 (Suppl. 1) Blood 2840; Tanya Siddiqi et al., 'Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL' (2022) 139 Blood 1794–1806.

[39] Ana Alarcon Tomas et al., 'Outcomes of first therapy after CD19-CAR-T treatment failure in large B-cell lymphoma' (2023) 37(1) Leukemia 154-163.

'these results demonstrate that some patients with R/R B cell lymphoma who receive CD19-targeted CAR T cell therapy are probably cured of their disease without a need for further intervention.'[40]

In relation to the efficacy of CAR-T therapy in patients with B cell acute lymphoblastic leukaemia (B-ALL), Cappell and Kochenderfer reviewed twelve studies (which had patient outcome data ranging from 1 year - 4.8 years of follow up). Such data suggested initial complete remission rates of 62-86%.[41] However, Cappell and Kochenderfer highlighted that the duration of remission varied between studies, and a significant and variable proportion of patients had received additional treatment via a consolidative allogenic haematopoietic stem cell transplantation (HSCT)[42] while in remission which they concluded 'obscures the interpretation of the ability of CAR T cells alone to elicit a curative response.'[43]

Tisagenlecleucel (brand name Kymriah) is currently approved for paediatric patients with B-ALL in certain contexts. Campbell and Kochenderfer stated that 'the long-term follow-up of such patients… who received Tisagenlecleucel in the ELIANA study indicates a complete remission rate of 82% and a median EFS ['Event Free Survival'] duration of 24 months.'[44] Such studies highlight the potential benefits CAR-T therapies can have for certain patients in such populations, especially as noted, when we

[40] Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-371, 361 https://doi.org/10.1038/s41571-023-00754-1 accessed 31 August 2023.
[41] See discussion in: Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-371, 361 https://doi.org/10.1038/s41571-023-00754-1 accessed 31 August 2023.
[42] This is also more commonly referred to as a bone marrow transplant, for a general overview of this, see Childhood Cancer and Leukemia Group, 'Stem Cell Transplant' available at https://www.cclg.org.uk/csoir/stem-cell-transplant accessed 31st August 2023
[43] Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-371, 361 https://doi.org/10.1038/s41571-023-00754-1 accessed 31 August 2023.
[44] Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-371 which cites the following: Theodore W Laetsch et al., 'Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA trial' (2023) 41 Journal of Clinical Oncology 1664-1669.

consider that for many of these patients, other traditional treatment options were not successful.

For patients with Relapsed/Refractory Multiple Myeloma (RRMM) who received BCMA- (B Cell Mature Antigen) targeted CAR-T cells, Campbell and Kochenderfer highlight that there is less data available on the outcomes due to the later development of these therapies.[45] However, in their review they stated that 'patients with RRMM can have prolonged maintenance free remissions after CAR-T BCMA-target cell therapy, albeit with a continued risk of disease progression over time.'[46]

Overall, Cappell and Kochenderfer conclude that current data suggest that 'CD19-targeted CAR-T cells can induce prolonged remissions in patients with B cell malignancies, often with minimal long-term toxicities, and are probably curative for a subset of patients.'[47]

Solid Tumours

There are currently challenges in seeking to use CAR-T therapies for the treatment of solid tumours.[48] Dagar et al, indicate that one of the hurdles in seeking to treat solid tumours with CAR-T therapy is *target antigen heterogeneity* i.e., unlike in blood cancers, in which tumour cells express tumour-specific antigens that can be targeted by the specific CAR-T therapy, solid tumours rarely express one tumour-specific

[45] Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-37 which cites the following evidence here: Syed Abbas Ali et al., 'T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma' (2016) 129 Blood 1688–1700; Jennifer N Brudno et al., 'T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma' (2018) 22 Journal of Clinical Oncology 2267-2280.
[46] Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-371, 365.
[47] Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-371.
[48] These are discussed in: Gunjan Dagar et al., 'Harnessing the potential of CAR-T cell therapy: progress, challenges, and future directions in hematological and solid tumor treatments' (2023) 21 Journal of Translational Medicine 449.

antigen.[49] However, there are studies ongoing with some promising results, and Dagar et al, highlight CAR-T therapy as having future 'potential in solid tumours.' [50]

Other Disease Indications

CAR-T therapies may also have potential for use for other disease indications. For example, recent studies consider this in the context of systemic lupus erythematosus (SLE). SLE is more commonly known as Lupus and can be a life threatening autoimmune disease.[51] There have been significant advances in the treatment of Lupus, however, despite these, some patients do not respond to such therapies and they can be at risk of organ failure and in some cases death.[52] According to Makensen et al., there is currently no clear strategy to achieve treatment free remission of Lupus for patients.[53] In 2023, Makensen et al., reported that for five seriously ill and treatment-resistant patients with Lupus, who received CAR-T therapy, improvement of clinical symptoms was observed. They highlighted that all five patients experienced remission of SLE according to clinical parameters, three months post CAR-T therapy.[54] Furthermore, CAR-T therapy was well tolerated for all patients, and these patients experienced either no or mild cytokine-release syndrome.[55] Makensen et al. note that these data suggest that CAR-T therapy is 'feasible, tolerable and highly effective in SLE' in certain contexts,[56] however they indicate that longer follow-up studies with larger cohorts of patients are required 'to confirm sustained absence of

[49] Gunjan Dagar et al., 'Harnessing the potential of CAR-T cell therapy: progress, challenges, and future directions in hematological and solid tumor treatments' (2023) 21 Journal of Translational Medicine 449.
[50] Gunjan Dagar et al., 'Harnessing the potential of CAR-T cell therapy: progress, challenges, and future directions in hematological and solid tumor treatments' (2023) 21 Journal of Translational Medicine 449.
[51] Andreas Mackensen et al., 'Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus' (2022) 28(10) Nature Medicine 2124–2132 at 2124.
[52] Agner R Parra Sánchez, Alexandre E Voskuyl, and Ronald R van Vollenhoven, 'Treat-to-target in systemic lupus erythematosus: advancing towards its implementation' (2022) 18 Nature Reviews Rheumatology 146–157, as cited in Andreas Mackensen, Fabian Müller, Dimitrios Mougiakakos, et al., 'Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus' (2022) 28(10) Nature Medicine 2124–2132.
[53] Andreas Mackensen et al., 'Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus' (2022) 28(10) Nature Medicine 2124–2132, 2124.
[54] Andreas Mackensen et al., 'Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus' (2022) 28(10) Nature Medicine 2124–2132, 2125.
[55] Andreas Mackensen et al., 'Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus' (2022) 28(10) Nature Medicine 2124–2132, 2128.
[56] Andreas Mackensen et al., 'Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus' (2022) 28(10) Nature Medicine 2124–2132, 2124.

autoimmunity and resolution of inflammation in patients with SLE who have received CAR T cell therapy.'[57]

Long Term Outcomes

CAR-T cell therapy is still a relatively new treatment. As will be discussed in section three, the first CAR-T therapy obtained regulatory approval from the European Medicines Agency in Europe in 2018, and from the United States (US) Food and Drug Administration (FDA) in 2017. Thus, there is limited data on the long-term outcomes. To date, the success rates and patient outcomes are promising, however, more will be known on the long-term outcomes as time progresses, but many are optimistic about the future potential of CAR-T therapies for cancer care.

2.3 Potential Side Effects of CAR-T Therapies

However, despite potential benefits, CAR-T therapies are associated with several side effects. When first used as a treatment, one of the most common serious side effect of CAR-T therapy was the acute systemic inflammatory syndrome known as cytokine release syndrome (CRS), which can be fatal.[58] CRS can present as a 'flu-like syndrome with fever, fatigue, headache, arthralgia, myalgia, and malaise' and may also involve gastrointestinal symptoms.[59] In more severe cases, CRS presents with unstable blood pressure and organ dysfunction.[60] However, as more patients have been treated with CAR-T therapies, there is now a greater understanding of how to

[57] Andreas Mackensen et al., 'Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus' (2022) 28(10) Nature Medicine 2124–2132, 2132.
[58] Emma C Tallantyre et al., 'Neurological updates: neurological complications of CAR-T therapy' (2021) 268 Journal of Neurology 1544–1554; 'CAR-T Therapy: Combatting Cytokine Release Syndrome' News Medical Life Sciences (21 May 2021) https://www.news-medical.net/whitepaper/20210521/CAR-T-Therapy-Combating-Cytokine-Release-Syndrome.aspx accessed 31 August 2023.
[59] Alexander Shimabukuro-Vornhagen Philipp Gödel, Marion Subklewe, et al., 'Cytokine release syndrome' (2018) 6(1) Journal for Immunotherapy of Cancer 56.
[60] Lucrecia Yáñez, Miriam Sánchez-Escamilla, and Miguel-Angel Perales, 'CAR T Cell Toxicity: Current Management and Future Directions' (2019) 3(2) Hemasphere.e186 https://doi.org/10.1097/HS9.0000000000000186 accessed 31 August 2023.

best manage risks in this context, thereby reducing its effects.[61] Moreover, early recognition of symptoms and toxicities and early intervention have also improved survival.[62]

Other potential side effects of CAR-T therapy include risks of neurological issues, such as tremors, seizures and motor weakness which may result in intensive care being needed, however, such effects are rarely fatal.[63] Previously, in 2020, Gust et al. stated that: 'While neurotoxicity is apparently fully reversible in most cases, fatal cerebral edema and other life-threatening complications such as seizures and coma continue to occur both in clinical trials and with commercial CAR T cell products.'[64] Other side-effects of CAR-T can include low blood count and infections (as low white blood cell count weakens immunity);[65] and low blood pressure.[66]

Research is still developing in terms of the potential longer-term toxicities (or side effects) of CAR-T therapy. The most commonly observed longer term side effects, include: 'B cell depletion (aplasia), hypogammaglobulinaemia, cytopenias and infections.'[67] Nonetheless, as noted, clinical teams continue to develop strategies to minimise the risks and optimise management of such side effects.

[61] 'CAR-T Therapy: Combatting Cytokine Release Syndrome' News Medical Life Sciences (21 May 2021) https://www.news-medical.net/whitepaper/20210521/CAR-T-Therapy-Combating-Cytokine-Release-Syndrome.aspx accessed 31 August 2023; Francis Ayuk Ayuketang and Ulrich Jäger, 'Management of Cytokine Release Syndrome (CRS) and HLH' in Nicolaus Kröger et al, *The EBMT/EHA CAR-T Cell Handbook* (Springer 2022).

[62] Sattva Neelapu, 'Managing the toxicities of CAR-T cell therapy' (2019) 37(1) Hematological Oncology 48-52.

[63] Emma C Tallantyre et al., 'Neurological updates: neurological complications of CAR-T therapy' (2021) 268 Journal of Neurology 1544–1554.; see also Lorna Neill, Jeremy Rees, and Claire Roddie, 'Neurotoxicity—CAR T-cell therapy: what the neurologist needs to know' (2020) 20(4) Practical Neurology 285-293.

[64] Juliane Gust et al., 'Cytokines in CAR T Cell–Associated Neurotoxicity' (2020) 11 Frontiers in Immunology https://doi.org/10.3389/fimmu.2020.577027 accessed 31 August 2023.

[65] Ellie Leick, 'Optimal Management Needed for Blood Count Recovery Following CAR T-Cell Therapy' OncLive (27 March 2020) https://www.onclive.com/view/optimal-management-needed-for-blood-count-recovery-following-car-tcell-therapy accessed 31 August 2023.

[66] Leukemia & Lymphoma Society, 'Chimeric Antigen Receptor (CAR) T-Cell Therapy' https://www.lls.org/treatment/types-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy accessed 31 August 2023.

[67] Kathryn M Cappell and James N Kochenderfer, 'Long-term outcomes following CAR T cell therapy: what we know so far' (2023) 20 Nature Reviews Clinical Oncology 359-371.

Moreover, currently, adult and paediatric patients who obtain CAR-T therapy will generally have exhausted all other clinically indicated treatment options, CAR-T therapy may present their only potential avenue for therapy and survival. Thus, careful and (often) difficult ethical considerations can arise.[68]

2.4 Future Developments: Potential Allogenic CAR-T Therapies?

As indicated, CAR-T therapies are currently generally personalised to each patient (*autologous*, i.e., the patient is their own donor) and the personalised nature of these therapies can increase the costs, infrastructural needs, manufacturing complexity, expertise and the time needed to prepare therapies personalised for each patient. There is ongoing research looking at developing so-called 'off-the-shelf' CAR-T therapies (allogenic therapies, i.e., manufactured from donors and not based on cells taken from the patient's own body). This research is showing potential and allogenic CAR-T therapies could be a possibility for certain patients in future.[69] If the development of allogenic therapies were successful, this would likely reduce the costs involved, as therapies could be made in larger quantities and offered to a greater range of patients.[70] It would also likely reduce the production and infrastructural requirements needed to develop such therapies from each individual patient's cells

[68] See discussion in: Tisagenlecleucel for B-Cell Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma — Ethics and Implementation Report' (2019) 8 (3d) CADTH at 2.4 https://www.cadth.ca/sites/default/files/pdf/car-t/op0538-tisagenlecleucel-ethics-and-implementation-jan2019.pdf accessed 31 August 2023.

[69] Peter Sidaway, 'Allogeneic CAR T cells show promise' (2022) 19 Nature Reviews Clinical Oncology 748 https://doi.org/10.1038/s41571-022-00703-4 accessed 31 August 2023; for an example of recent studies, see in the multiple myeloma context: Sham Mailankody et al, 'Allogeneic BCMA-targeting CAR T cells in relapsed/refractory multiple myeloma: phase 1 UNIVERSAL trial interim results' (2023) 29 Nature Medicine 422–429; see also: Kenneth Caldwell, Stephen Gottschalk and Aimee C Talleur, 'Allogeneic CAR Cell Therapy—More Than a Pipe Dream' (2021) 11(6) Frontiers in Immunology https://doi.org/10.3389/fimmu.2020.618427 accessed 31 August 2023.

[70] See discussion in: Lorenzo Giorgioni et al, CAR-T State of the Art and Future Challenges, A Regulatory Perspective (2023) International Journal of Molecular Sciences 11803 at 3.4; Michael Jenkins and Suzanne Farid, 'Cost-effective bioprocess design for the manufacture of allogeneic CAR-T cell therapies using a decisional tool with multi-attribute decision-making analysis' (2018) 137 Biochemical Engineering Journal 192-204.

under current autologous routes.[71] Thus, depending on how the research develops, allogenic CAR-T therapies could potentially increase accessibility of the therapies for certain indications in future. It could also mean that therapies become available for more immediate use in patients, reducing the need for patients to wait for CAR-T therapy infusions due to the need for the cell production process under autologous processes.[72]

However, allogenic CAR-T therapies are still in development, and challenges remain, including the risk of patients developing graft-versus-host disease, which can be fatal.[73] Allogenic products can also be quickly 'eliminated by the host system, limiting their anti-tumour activity,' [74] and hence, in some cases limiting their potential effectiveness. [75] More recently, research teams have used CRISPR gene editing alongside allogenic CAR-T therapies to try to address such shortcomings.[76] There is also work developing around the potential to use allogenic CAR NK cell therapies, including encouraging results in pre-clinical studies looking at CAR-NKs ability to target multiple myeloma antigens.[77]

Recent developments include: in December 2022, Ebvallo (Tabelecleucel) was authorised by the EMA for use in Europe and is used in certain contexts 'to treat adults

[71] See generally: Cynthia A Challener, 'Moving from Autologous to Allogeneic Cell Therapies: Drivers and Hurdles' Pharma's Almanac (31 January 2023) https://www.pharmasalmanac.com/articles/moving-from-autologous-to-allogeneic-cell-therapies-drivers-and-hurdles accessed 31 August 2023; See also: Michael Anbar, 'The future of cell-based immunotherapy: autologous vs allogeneic treatment' Horizon Discovery (23 December 2020) https://horizondiscovery.com/en/blog/2020/the-future-of-cell-based-immunotherapy#:~:text=An%20allogeneic%20cell%20therapy%20that,for%20the%20benefit%20of%20patients. accessed 31 August 2023.
[72] See: S Depil et al., '"Off-the-shelf' allogeneic CAR T cells: development and challenges' (2019) Nature Reviews 185-199, 186.
[73] Graft-versus-host-disease is an immune response that is activated when the body (the host) recognises the graft (the allogeneic CAR-T in this context) as a foreign entity. On its potential effects in this context, see discussion in: S Depil et al., '"Off-the-shelf' allogeneic CAR T cells: development and challenges' (2019) Nature Reviews 185-199, 186.
[74] This is discussed in S Depil et al., '"Off-the-shelf' allogeneic CAR T cells: development and challenges' (2019) Nature Reviews 185-199.
[75] S Depil et al., '"Off-the-shelf' allogeneic CAR T cells: development and challenges' (2019) Nature Reviews 185-199, 186.
[76] Alexander Dimitri, Friederike Herbst and Joseph A Fraietta, 'Engineering the next-generation of CAR T-cells with CRISPR-Cas9 gene editing' (2022) 21(1) Molecular Cancer 78.
[77] This is discussed in: Catherine Duane, Michael O'Dwyer, Siobhan Glavey, 'Adoptive Immunotherapy and High-Risk Myeloma' (2023) 15 *Cancers* 2633.

and children from 2 years of age who, after receiving an organ- or a bone marrow-transplantation, develop a blood cancer called Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD).'[78] It is used 'in patients who have received at least one previous treatment, when the disease comes back (relapsed) or when the treatment does not work (refractory)'.[79] This is an allogenic CAR-T therapy targeting Epstein Barr infected cells.[80] In 2023, early trials for ALLO-715,[81] an allogenic CAR-T cell therapy for use in certain patients diagnosed with multiple myeloma, have shown promising results.[82]

[78] European Medicines Agency, 'Ebvallo', https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo accessed 31 August 2023.
[79] European Medicines Agency, 'Ebvallo' https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo accessed 31 August 2023.
[80] See European Medicines Agency, 'Ebvallo' https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo accessed 31 August 2023; Fraiser Kansteiner, 'Atara makes history with world-first nod for allogeneic T-cell therapy Ebvallo' FiercePharma (19 December 2022) https://www.fiercepharma.com/pharma/atara-makes-history-world-first-nod-allogeneic-t-cell-therapy-ebvallo accessed 31 August 2023; see also: Catherine Eckford 'World's first approval of an allogeneic T-cell immunotherapy' European Pharmaceutical Review (20 December 2022) https://www.europeanpharmaceuticalreview.com/news/177795/worlds-first-approval-of-an-allogeneic-t-cell-immunotherapy/ accessed 31 August 2023.
[81] See Memorial Sloan Kettering, 'Allogeneic CAR T Cell Therapy for Multiple Myeloma Shows Promise' (15 February 2023) https://www.mskcc.org/clinical-updates/allogeneic-car-cell-therapy-multiple-myeloma-shows-promise accessed 31 August 2023.
[82] Sham Mailankody al., 'Allogeneic BCMA-targeting CAR T cells in relapsed/refractory multiple myeloma: phase 1 UNIVERSAL trial interim results' (2023) Nature Medicine 422–429.

3 CAR-T THERAPIES: REGULATORY APPROVAL IN THE UNITED STATES AND EUROPE

CAR-T therapies have been in development for many years; 1993 saw the development of the first generation engineered T-cell with chimeric molecules in a laboratory.[83] The first time CAR-T cells were used under clinical application within the clinical trial context was in 2011 at the University of Pennsylvania and the Children's Hospital in Philadelphia for certain patients with chronic lymphocytic leukaemia (CLL),[84] and for patients with ALL in 2012.[85] Since then, CAR-T therapies have been developed further and several CAR-T therapies have been granted regulatory approval for use in a range of different types of cancer in the United States (US), Europe and other regions. The next section provides a brief overview of the timeline for, and the main current regulatory approvals applicable for CAR-T therapies in the US and Europe.

3.1 UNITED STATES: REGULATORY APPROVAL FOR CAR-T THERAPIES

In 2017, the first CAR-T therapies were given official regulatory approval for use in the US, by its regulatory body the Food and Drug Administration (FDA). The US FDA approved two types of CAR-T therapies in 2017, namely Kymriah and Yescarta.

[83] See discussion in: Jan Styczyński , 'A brief history of CAR-T cells: from laboratory to the bedside' (2020) 51(1) Acta Haematologica Polonica 2-5; see also: Memorial Sloan Kettering Cancer Center, 'CAR T Cells: Timeline of Progress' https://www.mskcc.org/timeline/car-t-timeline-progress accessed 31 August 2023.
For a discussion of the development of CAR-T therapies more generally, see: John Maher et al., 'Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRζ /CD28 receptor' (2002) 20(1) Nature Biotechnology 70–75 ; Memorial Sloan Kettering Cancer Center, 'FDA Approves First CAR T Cell Therapy for Leukemia' Cancer History Project (19 May 2021) https://cancerhistoryproject.com/research-milestone/fda-approves-first-car-t-cell-therapy-for-leukemia/ accessed 31 August 2023; Memorial Sloan Kettering Cancer Center, 'CAR T Cells: Timeline of Progress' https://www.mskcc.org/timeline/car-t-timeline-progress accessed 31 August 2023.
[84] David L Porter et al., 'Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia' (2011) 365(8) The New England Journal of Medicine 725–33.
[85]Stephan A Grupp et al., 'Chimeric antigen receptor-modified T cells for acute lymphoid leukemia' (2013) 368(16) The New England Journal of Medicine 1509-1518; Jan Styczyński, 'A brief history of CAR-T cells: from laboratory to the bedside' (2020) 51(1) Acta Haematologica Polonica 2-5.

Tisagenlecleucel, marketed under the brand name **Kymriah** which was granted FDA approval in August 2017.[86] Kymriah is approved for 'the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.''[87] It was also subsequently approved by the US FDA for 'adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma'.[88]

Axicabtagene ciloleucel, marketed under the brand name **Yecarta** was initially given FDA approval in October 2017.[89] Yescarta was initially approved by the FDA for 'use in adult patients with large B-cell lymphoma after at least two other kinds of treatment failed, including DLBCL, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.' [90] It was subsequently approved by the US FDA in 2022 for 'adult patients with large B-cell lymphoma (LBCL)

[86] U.S. Food and Drug Administration, 'FDA approval brings first gene therapy to the United States')3-August 2017) https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states accessed 31 August 2023.

[87] U.S. Food and Drug Administration, 'FDA approval brings first gene therapy to the United States')3-August 2017) https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states Maura C O'Leary et al., 'FDA Approval Summary: Tisagenlecleucel for Treatment of Patients with Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia' (2019) 25(4) Clinical Cancer Research 1142-1146.

[88] U.S. Food and Drug Administration, 'FDA approves tisagenlecleucel for adults with relapsed or refractory large B-cell lymphoma' (1 May 2018) https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-adults-relapsed-or-refractory-large-b-cell-lymphoma; See also: Kymriah, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah-tisagenlecleucel accessed 16th October 2023; Novartis, FDA approves Novartis Kymriah® CAR-T cell therapy for adult patients with relapsed or refractory follicular lymphoma (28th May 2022) https://www.novartis.com/news/media-releases/fda-approves-novartis-kymriah-car-t-cell-therapy-adult-patients-relapsed-or-refractory-follicular-lymphoma accessed 31 August 2023.

[89] U.S. Food and Drug Administration, 'FDA approves axicabtagene ciloleucel for large B-cell lymphoma' (25 October 2017) https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-axicabtagene-ciloleucel-large-b-cell-lymphoma#:~:text=FDA%20approves%20axicabtagene%20ciloleucel%20for%20large%20B%2Dcell%20lymphoma,-Share&text=On%20October%2018%2C%202017%2C%20the,%2C%20Kite%20Pharma%2C%20Inc. accessed 31 August 2023.

[90] U.S. Food and Drug Administration, 'FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma' https://www.fda.gov/news-events/press-announcements/fda-approves-car-t-cell-therapy-treat-adults-certain-types-large-b-cell-lymphoma accessed 30 August 2023.

that is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy'.[91]

In July 2020, the US FDA approved **Tecartus** (brexucabtagene autoleucel) for 'adult patients diagnosed with mantle cell lymphoma (MCL) who have not responded to or who have relapsed following other kinds of treatment,'[92] in certain contexts;[93] In October 2021, the US FDA subsequently approved it for 'adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia.'[94]

Abecma (idecabtagene vicleucel)[95] was approved by the US FDA in March 2021,[96] it is used 'for the treatment of multiple myeloma in patients who have received at least four kinds of treatment regimens that have not worked or have stopped working.'[97]

[91] U.S. Food and Drug Administration, 'FDA approves axicabtagene ciloleucel for second-line treatment of large B-cell lymphoma' (1 April 2022) https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-axicabtagene-ciloleucel-second-line-treatment-large-b-cell-lymphoma accessed 31 August 2023.

[92] 'FDA Approves First Cell-Based Gene Therapy For Adult Patients with Relapsed or Refractory MCL' (24 July 2020) https://www.fda.gov/news-events/press-announcements/fda-approves-first-cell-based-gene-therapy-adult-patients-relapsed-or-refractory-mcl accessed 31 August 2023.

[93] TECARTUS https://www.tecartus.com/ accessed 31 August 2023.

[94] 'FDA D.I.S.C.O. Burst Edition: FDA approval of Tecartus (brexucabtagene autoleucel) for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia' https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-tecartus-brexucabtagene-autoleucel-adult-patients-relapsed-or#:~:text=On%20October%201%2C%202021%2C%20the,cell%20precursor%20acute%20lymphoblastic%20leukemia accessed 31 August 2021.

[95] 'ABECMA (idecabtagene vicleucel)' https://www.fda.gov/vaccines-blood-biologics/abecma-idecabtagene-vicleucel accessed 31 August 2023.

[96]' FDA D.I.S.C.O. Burst Edition: FDA approval of ABECMA (idecabtagene vicleucel) the first FDA approved cell-based gene therapy for the treatment of adult patients with relapsed or refractory multiple myeloma' https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-abecma-idecabtagene-vicleucel-first-fda-approved-cell-based#:~:text=On%20March%2026%2C%202021%2C%20the,an%20anti%2DCD38%20monoclonal%20antibody. accessed 30 August 2023.

[97] 'Abecma' https://www.abecma.com/ accessed 31 August 2023.

Breyanzi (lisocabtagene maraleucel)[98] was approved by the US FDA in June 2022.[99] Breyanzi is approved for the treatment in adults of large B-cell lymphoma when at least two previous treatments have failed or have stopped working, in certain contexts.[100]

Carvykti (Ciltacabtagene autoleucel),[101] received US FDA approval in February 2022 for 'the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody'.[102]

3.2 European Medicines Agency: Regulatory Approval for CAR-T Therapies

At a European level, ATMPs (including CAR-T therapies) are regulated under various legal instruments including, Regulation 1394/2007/EC which sets out a regulatory framework specifically for ATMPs.[103]

[98] 'BREYANZI (lisocabtagene maraleucel)' https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel accessed 31 August 2023.
[99] 'FDA D.I.S.C.O. Burst Edition: FDA approval of Breyanzi (lisocabtagene maraleucel) for second-line treatment of large B-cell lymphoma' https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-breyanzi-lisocabtagene-maraleucel-second-line-treatment-large-b#:~:text=On%20June%2024%2C%202022%2C%20the,first%2Dline%20chemoimmunotherapy%20or%20relapse accessed 31 August 2023.
[100] See: Breyanzi https://www.breyanzi.com/ accessed 31 August 2023.
[101] 'CARVYKTI' https://www.fda.gov/vaccines-blood-biologics/carvykti accessed 31 August 2023.
[102] See: 'FDA D.I.S.C.O. Burst Edition: FDA approval of CARVYKTI (ciltacabtagene autoleucel) for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody' https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-carvykti-ciltacabtagene-autoleucel-treatment-adult-patients accessed 31 August 2023.
[103] See: Regulation No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004; However, other regulatory instruments are also of relevance, for an overview of the regulatory framework applicable to ATMPs more generally, see: Shada Warreth, and Elaine Harris, 'The Regulatory Landscape for ATMPs in the EU and US: a Comparison' (2020) 15(2) Level 3 available at https://doi.org/10.21427/PK3V-G445; Carolina Iglesias-Lopez et al. (2019) 'Regulatory Framework for Advanced Therapy Medicinal Products in Europe and United States' (2019) 10(921) Frontiers in Pharmacology doi: 10.3389/fphar.2019.00921

In Europe, the EMA approved **Kymriah**[104] and **Yescarta**[105] in August 2018. **Kymriah** is authorised by the EMA for treatment of : 'B-cell acute lymphoblastic leukaemia (ALL), in children and young adults up to 25 years of age whose cancer did not respond to previous treatment, has come back two or more times, or has come back after a transplant of stem cells; Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) in adults whose cancer has come back or did not respond after two or more previous treatments'.[106]

Yescarta is authorised by the EMA for the treatment of adult patients with relapsed or refractory: high-grade B-cell lymphoma (HGBL); diffuse large B-cell lymphoma (DLBCL); primary mediastinal large B-cell lymphoma (PMBCL); follicular lymphoma (FL).[107] It is authorised for use in these indications, in certain contexts.

The EMA more recently approved five other CAR T therapies, namely:

Tecartus (conditional marketing authorisation in December 2020) [108] which is authorised by the EMA for 'adults with mantle cell lymphoma (a cancer of B cells, a type of white blood cell) when the cancer has come back after two or more previous treatments, including a type of cancer medicine called a Bruton's tyrosine kinase (BTK) inhibitor; adults 26 years of age and older with acute lymphoblastic leukaemia (another cancer of B cells) when the cancer has come back or did not respond to previous treatments'.[109]

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[104] European Medicines Agency, 'Kymriah' https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah accessed 31 August 2023.
[105] European Medicines Agency, 'Yescarta' https://www.ema.europa.eu/en/medicines/human/EPAR/yescarta#:~:text=Yescarta%20is%20a%20medicine%20for,B%2Dcell%20lymphoma%20(DLBCL)%3B accessed 31 August 2023.
[106] European Medicines Agency, 'Kymriah' https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah accessed 31 August 2023.
[107] European Medicines Agency, 'Yescarta' https://www.ema.europa.eu/en/medicines/human/EPAR/yescarta accessed 31 August 2023.
[108] European Medicines Agency, 'Tecartus' https://www.ema.europa.eu/en/medicines/human/EPAR/tecartus#:~:text=Tecartus%20has%20been%20given%20'conditional,will%20be%20updated%20as%20necessary. accessed 31 August 2023.
[109] European Medicines Agency, 'Tecartus' https://www.ema.europa.eu/en/medicines/human/EPAR/tecartus accessed 31 August 2023.

Abecma (idecabtagene vicleucel) which received a conditional marketing authorisation from the EMA in August 2021.[110] It is authorised by the EMA to 'treat adults with multiple myeloma (a cancer of the bone marrow) when the cancer has come back (relapsed) and has not responded to treatment (refractory). It is used in adults who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and whose disease has worsened since the last treatment'.[111]

Breyanzi, (lisocabtagene maraleucel) which received marketing authorisation from the EMA in April 2022;[112] This is authorised by the EMA to treat adults with 'diffuse large B-cell lymphoma (DLBCL); high-grade B-cell lymphoma (HGBCL); primary mediastinal large B-cell lymphoma (PMBCL); follicular lymphoma grade 3B (FL3B).'[113] It is used where cancer is relapsed or refractory, in certain contexts.[114]

Carvykti (ciltacabtagene autoleucel) which received a conditional authorisation from the EMA in May 2022.[115] It is authorised by the EMA to treat adults with multiple myeloma which is relapsed and refractory, and used where adults 'have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and whose disease has worsened since the last treatment.'[116]

Finally, **Ebvallo (**tabelecleucel) received marketing authorisation from the EMA in December 2022.[117] Ebvallo, as noted, is an allogenic therapy. It is authorised by the

[110] European Medicines Agency, 'Abecma' https://www.ema.europa.eu/en/medicines/human/EPAR/abecma accessed 31 August 2023.
[111] European Medicines Agency, 'Abecma' https://www.ema.europa.eu/en/medicines/human/EPAR/abecma accessed 31 August 2023.
[112] European Medicines Agency, 'Breyanzi' https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi accessed 31 August 2023.
[113] European Medicines Agency, 'Breyanzi' https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi accessed 31 August 2023.
[114] European Medicines Agency, 'Breyanzi' https://www.ema.europa.eu/en/medicines/human/EPAR/breyanzi accessed 31 August 2023.
[115] European Medicines Agency, 'Carvykti' https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti accessed 31 August 2023.
[116] European Medicines Agency, 'Carvykti' https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti accessed 31 August 2023.
[117] European Medicines Agency, 'Ebvallo' https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo accessed 31 August 2023.

EMA 'to treat adults and children from 2 years of age who, after receiving an organ- or a bone marrow-transplantation, develop a blood cancer called Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD).'[118] It is used after patients receive at least one treatment when the condition is relapsed or refractory.[119] Ebvallo is not approved by US FDA currently.[120]

[118] European Medicines Agency, 'Ebvallo' https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo accessed 31 August 2023.
[119] European Medicines Agency, 'Ebvallo' https://www.ema.europa.eu/en/medicines/human/EPAR/ebvallo accessed 31 August 2023.
[120] See BioSpace, 'Atara Biotherapeutics Announces Plans to Submit Tab-cel® BLA in Q2 2024 Following FDA Agreement on Comparability' (19 September 2023) https://www.biospace.com/article/releases/atara-biotherapeutics-announces-plans-to-submit-tab-cel-bla-in-q2-2024-following-fda-agreement-on-comparability/ accessed 29th September 2023. This is correct at time of writing 16th October 2023.

4 CURRENT LANDSCAPE FOR ACCESS TO CAR-T THERAPIES FOR PATIENTS LIVING IN IRELAND

As noted, the EMA granted regulatory authorisation for both Kymriah and Yescarta CAR-T therapies in 2018. However, the first CAR-T therapy was not approved for public reimbursement and provided in Ireland until 2021. Following approval for reimbursement, as will be discussed below, the first adult CAR-T therapy provision commenced in Ireland in 2021 in St James's hospital, Dublin, and commenced in Ireland in 2022 for children at Children's Health Ireland, Crumlin.

Prior to CAR-T therapies being provided in Ireland, adult and child patients living in Ireland who needed CAR-T therapies had to travel abroad (generally they travelled to the UK or elsewhere) to avail of CAR-T therapy. This was enabled by the HSE Treatment Abroad Scheme (TAS) which is a very important scheme in such contexts. However, having to travel abroad for CAR-T therapy also created potential challenges for patients, and these aspects are discussed in section 6.

4.1 THE PATHWAY TOWARDS PUBLIC REIMBURSEMENT AND PROVISION OF CAR-T THERAPIES IN IRELAND

As noted, a key barrier in many countries to providing CAR-T therapies is the high cost of these therapies.[121] The Irish Health Service Executive (HSE) has an assessment process in place which considers the reimbursement of new drug technologies for provision in Ireland.[122]This assessment process considers a range of factors, including ensuring cost-effectiveness, and that such therapies are obtainable within budgetary

[121] See: Renaud Heine et al., 'Health Economic Aspects of Chimeric Antigen Receptor T-cell Therapies for Hematological Cancers: Present and Future' (2021) 5(2) Hemasphere 524.
[122] National Cancer Control Programme, 'Cancer Drugs Approved for Reimbursement' https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/new.html accessed 31 August 2023.

constraints. A finite public healthcare budget means that if very expensive products/therapies are funded a shortfall in funds for the provision of other therapies can result, and this gives rise to difficult ethical considerations.[123]

In general terms – and importantly, this section does not purport to offer a comprehensive overview of all aspects of the process involved –some of the key steps in the reimbursement process for new medicines relevant in this context, are as follows: The HSE is the body responsible for making decisions on the reimbursement of new drug technologies in Ireland.[124] When there is an application for consideration of reimbursement of a new medicine, the HSE's Corporate Pharmaceutical Unit (CPU) will commission the Irish National Centre for Pharmacoeconomics (NCPE) to appraise these.[125] In the case of oncology medicines, a report is sent from the NCPE to the HSE's CPU and the National Cancer Control Programme (NCCP).[126] Alongside the pharmacoeconomic process, the NCPE arranges a clinical evaluation to assess the clinical guidelines. Moreover, discussions which are generally confidential take place around pricing with the relevant parties and the company, and these take place throughout the process.[127] Once the clinical guidelines and NCPE pharmacoeconomic assessment report etc. are available, these are reviewed by the NCCP Technology Review Committee for oncology medicines. A recommendation is then made around

[123] See discussion in: European Cancer Patient Coalition, 'CAR-T Therapy: White Paper' (2022) at 5 https://ecpc.org/wp-content/uploads/2022/11/White-Paper-CAR-T-therapy.pdf accessed 31 August 2023; 'Tisagenlecleucel for B-Cell Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma — Ethics and Implementation Report' (2019) 8 (3d) CADTH at 2.3 https://www.cadth.ca/sites/default/files/pdf/car-t/op0538-tisagenlecleucel-ethics-and-implementation-jan2019.pdf accessed 31 August 2023.

[124] See: NCPE, 'Overview of the Drug Reimbursement Process' https://www.ncpe.ie/submission-process/overview-of-the-drug-reimbursement-process/ accessed 30 August 2023.

[125] See: NCPE, 'Overview of the Drug Reimbursement Process' https://www.ncpe.ie/submission-process/overview-of-the-drug-reimbursement-process/ accessed 30 August 2023.

[126] See: HSE 'NCCP TECHNOLOGY REVIEW COMMITTEE'https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/trc/nccp%20trc%202020.pdf for a more detailed overview of the general process, see: NCPE 'Process Flowchart' https://www.ncpe.ie/submission-process/process-flochart/ accessed 30 August 2023.

[127] HSE 'NCCP Technology Review Committee' https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/trc/nccp%20trc%202020.pdf accessed 30 August 2023.

the introduction of the medicine, and if a recommendation is positive, this is then brought for consideration and discussion at the HSE Drugs Group.[128]

Nine criteria are set out under Schedule 3, Part 3 of the *Health (Pricing and Supply of Medical Goods) Act* 2013, as amended, for the public reimbursement system to consider in assessing a drug/technology. [129] The NCPE pharmacoeconomic assessment considers three of these criteria in their assessment, namely the: (i) efficacy, effectiveness and added therapeutic benefit of the medicine/therapy (ii) cost effectiveness, and (iii) budget impact.[130] The remaining six criteria are considered by the HSE.[131]

Following initial consideration of Kymriah and Yescarta, the NCPE initially declined to recommend either Kymriah or Yescarta for reimbursement in Ireland based on various factors, including around cost-effectiveness of these therapies. At that time, the estimated cost to the HSE of providing Kymriah (per patient inclusive of rebate) was €301,762 – (NCPE assessment completed August 2019).[132] The estimated total cost to the HSE of Yescarta per patient based on the wholesaler price (and inclusive of

[128] For a full overview of this process, see: HSE 'NCCP Technology Review Committee' https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/trc/nccp%20trc%202020.pdf accessed 30 August 2023.
[129] This states: "The Executive shall have regard to: (a) the health needs of the public; (b) the cost-effectiveness of meeting health needs by supplying the item concerned rather than providing other health services; (c) the availability and suitability of items for supply or reimbursement, or both, under section 59 of the Act of 1970; (d) the proposed costs, benefits and risks of the item or listed item relative to therapeutically similar items or listed items provided in other health service settings and the level of certainty in relation to the evidence of those costs, benefits and risks; (e) the potential or actual budget impact of the item or listed item; (f) the clinical need for the item or listed item; (g) the appropriate level of clinical supervision required in relation to the item to ensure patient safety; (h) the efficacy (performance in trial), effectiveness (performance in real situations) and added therapeutic benefit against existing standards of treatment (how much better it treats a condition than existing therapies), and (i) the resources available to the Executive"
[130] National Centre for Pharmacoeconomics (NCPE) Ireland, 'Submission Process: Overview of the Drug Reimbursement Process' https://www.ncpe.ie/submission-process/overview-of-the-drug-reimbursement-process accessed 31 August 2023
[131] National Centre for Pharmacoeconomics (NCPE) Ireland, 'Submission Process: Overview of the Drug Reimbursement Process' https://www.ncpe.ie/submission-process/overview-of-the-drug-reimbursement-process accessed 31 August 2023.
[132] National Centre for Pharmacoeconomics, 'Cost-effectiveness of tisagenlecleucel (Kymriah®) for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse,' 5 https://ncpe.ie/wp-content/uploads/2019/08/Summary-Tisa-cel-pALL.pdf accessed 31 August 2023.

VAT/rebate) was €384,225 (NCPE assessment completed 21/02/2020).[133] The NCPE stated that neither should be 'considered for reimbursement unless cost effectiveness can be improved relative to existing treatments.'[134] It should be noted that such prices do not reflect the final prices subsequently paid, as this is generally subject to confidential negotiations.

Such therapies were subsequently reconsidered, and in 2021, the HSE Drugs Group recommended the reimbursement of Kymriah for certain indications, following consideration of factors including, a revised confidential commercial offer, and further clinical efficacy data.[135] In 2022, the HSE Drugs Group recommended reimbursement of Yescarta for certain indications, following additional clinical evidence and an enhanced confidential commercial proposal.[136] These two therapies are now available in Ireland, under specific criteria and for certain indications, and are publicly reimbursed in such contexts. The actual price paid for each therapy by the HSE is confidential – as noted, confidentiality in medicines price negotiations is common, and this is not unique to the Irish context.

Currently, Kymriah is approved for reimbursement (and hence available) in Ireland for reimbursement to treat diffuse large B cell lymphoma (DLBCL) after two or more systemic therapies. It is also approved in Ireland for reimbursement for the treatment

[133] National Centre for Pharmacoeconomics, 'Cost effectiveness of axicabtagene ciloleucel (Yescarta®) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy' 7 https://www.ncpe.ie/axicabtagene-ciloleucel-yescarta/ accessed 31 August 2023.
[134] NCPE, 'Tisagenlecleucel (Kymriah®) for pALL' https://www.ncpe.ie/tisagenlecleucel-kymriah-for-all/ accessed 31 August 2023; NCPE, 'Axicabtagene Ciloleucel (Yescarta®)' https://www.ncpe.ie/axicabtagene-ciloleucel-yescarta/ accessed 31 August 2023.
[135] HSE Drugs Group, 'April 2021 Minutes: Meeting 2021.04 Tuesday 13th April 2021' https://www.hse.ie/eng/about/who/cpu/drugs-group-minutes/hse-drugs-group-minutes-april-2021.pdf accessed 31 August 2023.
[136] HSE Drugs Group, 'January 2022 Minutes: Meeting 2022.01: Tuesday 11th January 2022' https://www.hse.ie/eng/about/who/cpu/drugs-group-minutes/hse-drugs-group-minutes-january-2022.pdf accessed 31 August 2023.

of B-cell acute lymphoblastic leukaemia (ALL), that is refractory and/or relapsed, in patients up to 25 years of age, in certain contexts.[137]

Yescarta is approved for reimbursement in Ireland to treat adults patients who have relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal B cell Lymphoma (PMBCL) and transformed follicular lymphoma (Tfl) after two or more systemic therapies.[138]

4.2 Provision of and Access to CAR-T Therapies for Patients in Ireland

In 2021, St James's Hospital in Dublin commenced as the first hospital in Ireland to provide CAR-T therapy to adult patients with the blood cancer lymphoma, specifically for patients with ALL and DLBCL, in certain circumstances. The first adult patient to receive an infusion of CAR-T therapy in Ireland, took place on 13th December 2021 in St James's hospital. [139] CAR-T therapy was first provided for paediatric patients in Ireland in Children's Health Ireland at Crumlin in 2022.[140] The ability to provide CAR-

[137] See: HSE Drugs Group, 'April 2021 Minutes: Meeting 2021.04 Tuesday 13th April 2021' https://www.hse.ie/eng/about/who/cpu/drugs-group-minutes/hse-drugs-group-minutes-april-2021.pdf accessed 31 August 2023; See also: (NCPE, 'Tisagenlecleucel (Kymriah®) for pALL' https://www.ncpe.ie/tisagenlecleucel-kymriah-for-all/ accessed 31 August 2023; NCPE, 'Tisagenlecleucel (Kymriah®) for DLBCL' https://www.ncpe.ie/tisagenlecleucel-kymriah-for-dlbcl/ accessed 31 August 2023).

[138] HSE Drugs Group, 'January 2022 Minutes: Meeting 2022.01: Tuesday 11th January 2022' https://www.hse.ie/eng/about/who/cpu/drugs-group-minutes/hse-drugs-group-minutes-january-2022.pdf accessed 31 August 2023 ; See also: NCPE, 'Axicabtagene Ciloleucel (Yescarta®)' https://www.ncpe.ie/axicabtagene-ciloleucel-yescarta/ accessed 31 August 2023.

[139] Eilish O'Regan, 'First patient in Ireland receives cell therapy for blood cancer at St James's Hospital' Independent.ie (13 December 2021) https://www.independent.ie/irish-news/health/first-patient-in-ireland-receives-cell-therapy-for-blood-cancer-at-st-jamess-hospital-41145728.html accessed 31 August 2023; Margaret Dunne, 'How CAR T-cell therapy is revolutionising cancer treatment' RTÉ (21 September 2022) https://www.rte.ie/brainstorm/2022/0921/1324579-car-t-cell-therapy-cancer-treatment/ accessed 31 August 2023; 'First patient in Ireland receives ground-breaking cell therapy for blood cancer at St James's Hospital' (St James's Hospital, 13 December 2021) https://www.stjames.ie/aboutus/news/2021/firstpatientinirelandreceivesground-breakingcelltherapyforbloodcanceratstjamesshospital.html accessed 31 August 2023.

[140] HSE, 'A revolutionary cancer treatment, CAR-T cell therapy now available to children in Ireland' (updated 6 May 2022) https://www.hse.ie/eng/services/news/media/pressrel/a-revolutionary-cancer-treatment-car-t-cell-therapy-now-available-to-children-in-ireland.html accessed 31 August 2023; 'A

T therapy for the first time in Ireland to patients who are clinically indicated for this therapy is a very positive development,[141] particularly, when we consider the potential such therapies hold for certain patients, who will generally have no other viable treatment avenues. The provision of this therapy in Ireland for the first time for adults and children was the result of collaboration across various relevant groups, including the NCCP, Department of Health, and the clinical and laboratory teams in St James' Hospital and Children's Health Ireland at Crumlin, and it brings important benefits for patients and their families.[142]

Nonetheless, potential challenges remain around CAR-T therapies in Ireland, both in terms of challenges for patients in accessing these therapies, and challenges at the national health services level in providing these therapies currently and in future, these are discussed further in section six.

revolutionary cancer treatment, CAR-T cell therapy now available to children in Ireland' (Children's Health Ireland at Crumlin, 27th April 2022) https://www.childrenshealthireland.ie/news/a-revolutionary-cancer-treatment-car-t-cell-therapy-now-available-to-children-in-ireland/ accessed 31 August 2023; Saoirse Mulgrew, 'Ground-breaking cancer treatment now available to children in Ireland: 'It marks a new era,' *Irish Independent* 27th April 2022 https://www.independent.ie/irish-news/health/ground-breaking-cancer-treatment-now-available-to-children-in-ireland-it-marks-a-new-era/41592528.html accessed 31 August 2023.

[141] See discussion in: HSE, 'New access to revolutionary cancer treatment for children' (29 April 2022) available at https://www.hse.ie/eng/about/our-health-service/making-it-better/new-access-to-revolutionary-cancer-treatment-for-children.html accessed 30 August 2023;St James's Hospital, 'First patient in Ireland receives ground-breaking cell therapy for blood cancer at St James's Hospital' https://www.stjames.ie/aboutus/news/2021/firstpatientinirelandreceivesground-breakingcelltherapyforbloodcanceratstjamesshospital.html accessed 30 August 2023.

[142] See discussion in: HSE, 'New access to revolutionary cancer treatment for children' (29 April 2022) https://www.hse.ie/eng/about/our-health-service/making-it-better/new-access-to-revolutionary-cancer-treatment-for-children.html accessed 30 August 2023; St James's Hospital, 'First patient in Ireland receives ground-breaking cell therapy for blood cancer at St James's Hospital' available at https://www.stjames.ie/aboutus/news/2021/firstpatientinirelandreceivesground-breakingcelltherapyforbloodcanceratstjamesshospital.html accessed 30 August 2023.

5 AVENUES FOR PATIENTS TO ACCESS CAR-T THERAPIES ABROAD PRIOR TO ITS AVAILABILITY IN IRELAND

Prior to CAR-T therapy being made available in Ireland, the only avenue for patients based in Ireland to obtain CAR-T therapies was by travelling abroad for such therapies. More generally, there are several main avenues for people living in Ireland to travel abroad to obtain medical treatment which can be reimbursed – in certain cases – depending on the circumstances applicable, which we will outline in this section. However, not all these avenues applied to CAR-T therapy in such contexts, for reasons we now turn to.

5.1 CAR-T THERAPY: APPLICABILITY OF THE EU CROSS BORDER DIRECTIVE?

Under European Union (EU) law, the EU Cross Border Directive (CBD) allows patients in one member state of the EU or European Economic Area (EEA) to access healthcare in another member state, if the treatment is *publicly available* in Ireland, in certain contexts.[143]

To obtain access to treatment under the CBD, a patient must be ordinarily resident in Ireland, and qualify for the healthcare they are having under the CBD as a public patient in Ireland.[144] An application must be made to the HSE prior to receiving the treatment abroad, which must be pre-authorised in many cases to be reimbursed.[145] Ordinarily, the patient must pay for treatment received up-front themselves, and can then later apply to the HSE for reimbursement up to the maximum cost of the treatment

[143] See: Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare.
[144] HSE, 'Getting healthcare through the Cross Border Directive Scheme' available at https://www2.hse.ie/services/schemes-allowances/cross-border-directive/how-to-get/
[145] Citizens Information, 'Cross-Border Healthcare Directive' https://www.citizensinformation.ie/en/health/eu-healthcare/cross-border-directive/ accessed 31 August 2023.

available in Ireland.[146] This can pose ethical issues when treatment is at a high cost, as some patients may be unable to afford this. The CBD does not cover the cost of travel or follow-up medication.[147] The CBD no longer applies for patients living in the Republic of Ireland to access healthcare in the United Kingdom following Brexit.[148]

Crucially, therapies/medicines are only available under the CBD in circumstances where the treatment available in other member states is *also* available in Ireland.[149] Thus, the CBD is not an avenue which enables patients to travel from Ireland to obtain CAR-T therapy elsewhere where that therapy is not available in Ireland, and therefore, this was not an applicable avenue for patients to access CAR-T therapies abroad prior to them being made available in Ireland 2021/2022, respectively.

5.2 Treatment Abroad Scheme

The HSE Treatment Abroad Scheme (TAS),[150] allows public patients ordinarily resident in Ireland to travel to another country in the EU, EEA, or Switzerland, for treatment which is *not provided in Ireland.*[151] The TAS was a key avenue under which such clinically indicated and approved patients could obtain CAR-T therapy abroad which was reimbursed, prior to its being made available in Ireland. For these patients,

[146] HSE, 'Apply for Reimbursement' https://www2.hse.ie/services/cross-border-directive/apply-for-cross-border-directive-repayment.html Accessed 31 August 2023.
[147] HSE, 'Cross Border Directive' https://www2.hse.ie/services/cross-border-directive/about-the-cross-border-directive.html accessed 31 August 2023.
[148] HSE, 'Cross Border Directive' https://www2.hse.ie/services/cross-border-directive/about-the-cross-border-directive.html accessed 31 August 2023.
Citizens Information, 'Cross-Border Healthcare Directive' https://www.citizensinformation.ie/en/health/eu-healthcare/cross-border-directive/ accessed 31 August 2023.
[150] The legal basis for the TAS is set out under EU law, see: Regulation (EC) No 883/2004 of the European Parliament and of the Council of 29 April 2004 on the coordination of social security systems. See also: Regulation (EEC) No 1408/71 of the Council of 14 June 1971 on the application of social security schemes to employed persons and their families moving within the Community; Regulation (EEC) No 574/72 of the Council of 21 March 1972 fixing the procedure for implementing Regulation (EEC) No 1408/71 on the application of social security schemes to employed persons and their families moving within the Community.
[151] See discussion in: HSE 'Treatment Abroad Scheme' https://www2.hse.ie/services/schemes-allowances/treatment-abroad-scheme/ accessed 30 August 2023.

such therapies were generally the only potential treatment option they may have had, which in some cases proved lifesaving.

Under the TAS scheme, all treatment must be pre-approved prior to travel for it to be reimbursed – additional treatments or consultations etc not pre-approved will not be covered.[152] The TAS can only provide reimbursement for *proven treatments,*[153] and therefore, it does not cover the costs, for example, of patients travelling abroad for participation in a clinical trial. The case of emerging therapies can be a challenge for patients, as in some instances, the only potential therapies available for a patient may be a clinical trial abroad. However, there are also broader ethical considerations, and other logistical/practical challenges to accessing emerging therapies abroad under a clinical trial, discussed further below.

Prior to CAR-T therapies being made available in Ireland, patients deemed clinically suitable for CAR-T therapy where it was not available in Ireland for their circumstances could, together with their treating consultant, submit an application for treatment abroad under the TAS. Applications are assessed under the TAS, and a decision is given in writing by letter.[154]

5.3 Participation in Clinical Trials Abroad

While it is possible in theory for someone from Ireland to be enrolled on a clinical trial for CAR-T therapies abroad, this is notably difficult in general.[155] Lalova et al., analysed access to cross-border clinical trials more generally in the EU, and found

[152] Citizens Information 'Treatment Abroad Scheme' https://www.citizensinformation.ie/en/health/eu_healthcare/treatment_abroad_scheme.html accessed 31 August 2023.
[153] HSE 'Treatment Abroad Scheme' https://www2.hse.ie/services/schemes-allowances/treatment-abroad-scheme/ accessed 30 August 2023.
[154] HSE 'Treatment Abroad Scheme' https://www2.hse.ie/services/schemes-allowances/treatment-abroad-scheme/ accessed 30 August 2023.
[155] For example, for a discussion of clinical trials in the UK and overseas patients, see: Cancer Research UK, 'Trials for people from outside the UK' https://www.cancerresearchuk.org/find-a-clinical-trial/how-to-join-a-clinical-trial/trials-for-people-outside-of-the-uk accessed 31 August 2023.

that 'cross-border participation in clinical trials occurs in practice, however very rarely.'[156] They stated that:

> '…the majority of patients that participate in clinical trials are recruited locally. Reasons for this include the fact that sponsors would seek to enable participation in the nearest hospital possible. Furthermore, clinical trials subjects have to comply with strict and frequent visits to the investigational site, and this was considered burdensome for foreign patients.'[157]

There may be issues around health insurance, and aftercare required following clinical trial participation which can raise complex issues for patients based outside the jurisdiction of the clinical trial.

[156] Teodora Lalova et al., 'Cross-Border Access to Clinical Trials in the EU: Exploratory study on needs and reality' (2020) 7 Frontiers in medicine https://doi.org/10.3389/fmed.2020.585722 accessed 31 August 2023.
[157] Teodora Lalova et al., 'Cross-Border Access to Clinical Trials in the EU: Exploratory study on needs and reality' (2020) 7 Frontiers in medicine https://doi.org/10.3389/fmed.2020.585722 accessed 31 August 2023.

6 Provision and Access to CAR-T Therapies for Patients based in Ireland: An Overview of Key Challenges and Policy Recommendations

CAR-T therapies offer significant current and future possibilities for the treatment of certain cancer types for adults and children. Where successful, such therapies can be curative for some, meaning such patients may no longer require ongoing cancer treatment. It is also likely that there will be an increase in the number of patients who may benefit from CAR-T therapies and other types of ATMPs in the coming years given the ongoing developments in the field, which may lead to an increased demand for such therapies. Moreover, although CAR-T therapies come with risks of side effects, it must be borne in mind, that currently for many clinically indicated patients accessing such therapies is their only remaining potential treatment option.

This section outlines some of the main challenges, potential opportunities and recommendations around providing CAR-T therapies in Ireland currently. At the outset we acknowledge that one key barrier to providing CAR-T therapies within public health contexts is the high cost of such therapies currently (discussed further below). This can result in difficult ethical considerations as tensions can arise between patients' needs in accessing these therapies, and national public health systems challenges in funding these therapies.

In recognition of these challenges and ethical issues, whilst also remaining cognisant that for many patients CAR-T therapies may be their only potential treatment avenue, in this section we focus first in the *short term* on how the current system can be developed to provide such therapies as far as possible to patients in Ireland and particularly, for those who have no other potential treatment option. In doing so, we focus on mapping and seeking to address some of the main legal, ethical and broader policy challenges around providing CAR-T therapies and related health-services in Ireland currently. Second, we focus on the *longer term* at the national health systems

level and on the need to develop a national strategy informed by multi-disciplinary perspectives which would in the longer term develop further more sustainable pathways to provide CAR-T therapies in Ireland.

Finally, as a caveat, this section provides an overview of some of the main challenges and issues arising, however, it does not purport to provide an exhaustive list of all challenges or all policy issues that arise in such contexts.

6.1 Accessing CAR-T Therapies in Ireland: Key Potential Challenges For Patients

Since 2021 and 2022, adult and child patients in certain circumstances can access certain CAR-T therapies in Ireland. This is a very positive development. However, potential challenges remain *for individual patients around accessing CAR-T therapies* within the current context and are examined here.

6.1.1 Reimbursement Decisions and Provision of CAR-T Therapies for Patients living in Ireland: Timeline Between EMA Authorisation and Decisions/Consideration for Provision in Ireland

To date, two main types of CAR-T therapies are approved for reimbursement in Ireland, Yescarta and Kymriah, which are approved for certain indications.[158]

However, there are several other CAR-T therapies - at the time of writing – approved for use in Europe by the EMA,[159] but not currently available in Ireland. Ireland is not unique in this context; various complex factors including the high costs of CAR-T

[158] On 10th August 2023, the NCPE issued a rapid review of Tecartus for use for 'Adults 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia'. This NCPE rapid review recommended a full health technology assessment (HTA) of this therapy to 'assess the clinical effectiveness and cost effectiveness of brexucabtagene autoleucel compared with the current standard-of-care.' See: NCPE, 'Brexucabtagene Autoleucel (Tecartus®). HTA ID: 23045' https://www.ncpe.ie/brexucabtagene-autoleucel-tecartus-hta-id-23045/ accessed 31 August 2023.
[159] This is correct as of 16th October 2023.

therapies mean that not all CAR-T therapies that are authorised by the EMA for use are accessible in all European countries.[160]

Moreover, the timeline for approving CAR-T therapies for public reimbursement has, to date, been longer in Ireland than in some other European countries. For example, Kymriah was approved for public reimbursement in Ireland in 2021 for certain indications, three years after it was approved by the EMA in 2018. Whilst for paediatric patients, Yescarta was approved for reimbursement for certain indications in Ireland in 2022. In contrast, in the UK, the NHS confirmed it would fund and provide Kymriah for certain indications in September 2018, ten days after it was approved by the EMA.[161] The first patient in the UK commenced receiving this therapy in November 2018.[162] The NHS approved Yescarta for reimbursement in October 2018 on a limited basis under the Cancer Drugs Fund.[163] The first patient received Yescarta in the UK in December 2018.[164] Yescarta was granted approval for routine use in certain circumstances by the National Institute for Health and Care Excellence (NICE) in the

[160] European Cancer Patient Coalition, 'CAR-T Therapy: White Paper' (2022), 3 https://ecpc.org/wp-content/uploads/2022/11/White-Paper-CAR-T-therapy.pdf accessed 30 August 2023.
[161] Cancer Research UK, 'NHS England to fund personalised blood cancer immunotherapy' (5 September 2018) https://news.cancerresearchuk.org/2018/09/05/nhs-england-to-fund-personalised-blood-cancer-immunotherapy/?_gl=1%2A23zk3e%2A_gcl_au%2ANzYyNzA4NjA5LjE2OTY3MjYyNTU.%2A_ga%2AMTI5Mzk3OTQ2OC4xNjk2NzI2MTk3%2A_ga_58736Z2GNN%2AMTY5NjcyNjE5Ni4xLjEuMTY5NjcyNjI1NC4wLjAuMA..&_ga=2.136096056.862747503.1696726197-1293979468.1696726197 accessed 31 August 2023; See also: NHS England, 'NHS England announces groundbreaking new personalized therapy for children with cancer' (5 September 2018) https://www.england.nhs.uk/2018/09/nhs-england-announces-groundbreaking-new-personalised-therapy-for-children-with-cancer/ accessed 31 August 2023.
[162] Cancer Research UK, 'First patient receives CAR T cell therapy on NHS' (31 January 2019) https://news.cancerresearchuk.org/2019/01/31/first-patient-receives-car-t-cell-therapy-on-nhs/ accessed 31 August 2023.
[163] Rachel Arthur, 'Gilead's Yescarta set to become England's first routinely available personalized immunotherapy for lymphoma' BioPharmaReporter (26 January 2023) https://www.biopharma-reporter.com/Article/2023/01/26/gilead-s-yescarta-set-to-become-england-s-first-routinely-available-personalized-immunotherapy-for-lymphoma accessed 31 August 2023. https://www.biopharma-reporter.com/Article/2023/01/26/gilead-s-yescarta-set-to-become-england-s-first-routinely-available-personalized-immunotherapy-for-lymphoma
[164] Fraiser Kansteiner, 'After years of back-and-forth, Gilead's CAR-T Yescarta sways England's cost watchdog NICE' FiercePharma (26 January 2023) https://www.fiercepharma.com/pharma/after-years-back-and-forth-gilead-and-kites-car-t-yescarta-woos-uk-cost-watchdog-nice accessed 31 August 2023.

UK in January 2023.[165] In such contexts, this report recognises that there are a range of complex factors which affect reimbursement and also the availability of such therapies under national public health systems. Moreover, we acknowledge there are differences between the UK and Irish systems including around population size, health systems etc. which may impact such contexts.

Nonetheless, a key challenge currently is that patients in Ireland may in some instances have access to fewer types of CAR-T therapies within Ireland, and/or access to certain CAR-T therapies in more restrictive circumstances than applicable in other countries.[166] Furthermore, such therapies in the past were not made available in Ireland until a later point in time than in some other countries.[167] A concern for the future, is that if CAR-T therapies continue to develop at the current pace, if the high costs of these therapies persists, and if the reimbursement avenues and processes remain unchanged in Ireland, these issues could be exacerbated.

Importantly, we acknowledge that there are significant resource and institutional considerations relevant to the reimbursement and roll-out of CAR-T therapies in any public health system, including, their high costs under current commercial pathways. Thus, other pathways to develop and deliver more affordable CAR-T therapies (and other ATMPs) and strategies to increase their availability in Ireland in the longer term must also be considered and are discussed further below.

Under the current approach timeliness of decisions around whether CAR-T therapies will be reimbursed in Ireland is vital for patients in the short term. There are a range of

[165] Rachel Arthur, 'Gilead's Yescarta set to become England's first routinely available personalized immunotherapy for lymphoma' BioPharmaReporter (26 January 2023) http//www.biopharma-reporter.com/Article/2023/01/26/gilead-s-yescarta-set-to-become-england-s-first-routinely-available-personalized-immunotherapy-for-lymphoma accessed 31 August 2023.
[166] For example, in April 2023 NHS England introduced changes to expand the criteria for access to such therapies in England in certain contexts, see NHS England, 'NHS to roll out personalised CAR-T cancer therapies to hundreds more people' (27th April 2023) available at https://www.england.nhs.uk/2023/04/nhs-to-roll-out-personalised-car-t-cancer-therapies-to-hundreds-more-people/ (31st August 2023).
[167] Although, on this latter aspect, we acknowledge that before such therapies were provided in Ireland, where such therapies were clinically indicated, patients could apply to travel abroad to obtain CAR-T therapies under the TAS.

factors which can impact the time it takes for decisions on whether newly EMA approved CAR-T therapies will be reimbursed and provided in Ireland. Existing literature on reimbursement timelines/decisions for medicines more generally (not specific to CAR-T therapies) in Ireland, has highlighted the potential for delays to occur at various stages of the process which can impact decisions/considerations on when or whether medicines will be reimbursed in Ireland. These include, for instance, delays between when medicines are authorised by the EMA and when the Health Technology Assessment process is commenced in Ireland.[168] There can also be delays for some medicines at the price negotiations stage.[169] Moreover, and specific to CAR-T therapies, there are challenges to conducting HTAs for CAR-T therapies which have been highlighted in the literature, including assessing the cost-effectiveness of CAR-T therapies.[170] For example, CAR-T therapy as a treatment modality is relatively recent, therefore, there is only limited evidence on the long-term outcomes of these therapies, which is an important consideration within traditional pharmacoeconomic assessments. Nonetheless, it is vital for patients, where possible, that decisions on whether Ireland will reimburse approved CAR-T therapies can take place as quickly as is practicable after the EMA authorises such therapies in Europe.

[168]For a general discussion of the Health Technology Assessment process for medicines and timelines in the Irish context, see: Emma Connolly et al, 'Health Technology Assessment of Drugs in Ireland: An Analysis of Timelines' (2020) 4(2) Pharmacoecon Open. 287, 293 where the authors indicate more generally that: "… most companies chose to submit an RR within a few months of the MA. However, there were several outliers in the sample where the applicant company waited for more than a year before submitting to the NCPE. The reason for this is unclear but may be because the applicant company chose to submit to other European countries first."

[169] This is discussed as a potential issue for drug reimbursement decisions more generally in Ireland, in: Mazars, Review of the Governance Arrangements and the Resources currently in place to support the Health Service Executive reimbursement and pricing decision-making process (January 2020), 46 https://assets.gov.ie/258773/70942321-d13b-49b4-b24d-28e097076ba5.pdf 31 August 2023.

[170] For example, see discussion in: Doug Coyle et al, 'HTA Methodology and Value Frameworks for Evaluation and Policy Making for Cell and Gene Therapies' (2020) 21(9) Eur. J. Health Econ 1421–1437; See also: Niamh Carey et al., 'Tisagenlecleucel for Relapsed/Refractory Acute Lymphoblastic Leukaemia in the Irish Healthcare Setting: Cost-Effectiveness and Value of Information Analysis' (2022) 38(1) International Journal of Technology Assessment in Health Care e56; Niamh Carey et al., 'Cost-utility and value of information analysis of tisagenlecleucel for relapsed/refractory diffuse large B-cell lymphoma in the Irish healthcare setting' (2023) 11(1) Journal of Market Access Health Policy 2166375. doi: 10.1080/20016689.2023.2166375.

Recommendation 1: Timelines around Decisions on Reimbursement/Provision of CAR-T therapies in Ireland following European Medicines Agency authorisation of CAR-T therapies: *This report recommends the processes and decisions on whether CAR-T therapies will be publicly reimbursed and provided in Ireland are conducted as quickly as possible after new therapies are authorised by the European Medicines Agency. The timeliness of such decisions is particularly important where such therapies are likely to be the only clinically indicated treatment option available to certain patients. In this context, it is also recommended that a deeper study of the potential challenges which may affect the timeline for such decisions/considerations in Ireland is undertaken, and where relevant, deeper consideration is given around any potential avenues to address these challenges.*

6.1.2 Out of Pocket Expenses for Patients Travelling within Ireland for CAR-T therapies

At the time of writing,[171] CAR-T therapies are provided in Ireland in Dublin for adult and paediatric patients. There are plans to provide such therapies in Galway in future. Currently, some patients may need to travel long distances for CAR-T therapy if they are based outside Dublin. Following treatment, the patient and an accompanying adult must generally stay within a certain range of the hospital for health reasons. From a broader health equity perspective this can create additional financial burdens for patients/families.[172] Moreover, as discussed above, patients may not have access to their wider support networks during this time. We acknowledge that this issue is not specific to CAR-T therapies or to cancer care.

Recommendation 2: Financial Assistance for Patients Travelling Significant Distances within Ireland to obtain CAR-T Therapies: *Where CAR-T therapies are*

[171] 16th October 2023

[172] There are charities which will provide support to patients towards accommodation and other expenses due to need to travel to receive cancer care. For example, the Irish cancer society has a range of supports available on a limited basis – see Irish Cancer Society, 'Financial Support' https://www.cancer.ie/cancer-information-and-support/cancer-support/getting-organised/financial-support accessed 31 August 2023.

provided for some patients at a significant distance to their home, where they and a support person need to travel and obtain accommodation to receive this therapy, it is recommended that further consideration is given to whether, or to what extent, State supports could be extended to such patients and their families to reduce financial burdens.

6.1.3 Regional Centres of Excellence for the Provision of CAR-T Therapy

Relatedly, having a small number of regional centres of excellence around Ireland, where feasible, could potentially facilitate more patients to obtain CAR-T therapies in Ireland closer to home.[173] This would allow such patients to remain closer to support networks. It would reduce the likelihood of families being separated during the process and reduce the financial burdens on patients. However, it is also acknowledged that the provision of CAR-T therapies is highly specialised, and thus, setting up such services would require careful consideration based on clinical context/needs, and also considerable State support/commitments.

Recommendation 3: Regional Centres of Excellence for the Provision of CAR-T Therapies*: Developing additional regional centres of excellence for the provision of CAR-T therapies in Ireland should be considered, where this may be practicable and feasible. Developing such services would require State commitments, including in terms of additional funding, training, facilities, and personnel to ensure these services can be developed, and that all centres are operating at the required best practice international standards. This should be considered as part of an overall national policy approach to the provision of CAR-T therapy (and ATMPs more generally) in Ireland (discussed below).*

[173] For example, in the UK context there are a small number of specialist centres located in England, Wales and Scotland which provide CAR-T therapies for patients, see: Cancer Research UK, 'CAR T-cell therapy' available at https://www.cancerresearchuk.org/about-cancer/treatment/immunotherapy/types/CAR-T-cell-therapy accessed 31st August 2023.

6.1.4 Accessing CAR-T Therapy Abroad for Patients living in Ireland where such CAR-T therapies are not available in Ireland.

The TAS has been a vital avenue for patients living in Ireland to obtain access to CAR-T therapies abroad where these were not provided in Ireland. Having said that, where patients need to travel abroad for CAR-T therapies, this can give rise to a range of challenges, including: Such patients may be exposed to additional risks during travel, including, the risk of contracting infections which could pose additional challenges. Depending on the patient's health condition, it may be difficult for a patient to travel abroad.

Having to travel abroad for treatment more generally can also give rise to a range of broader social/psychological issues for patients. For example, studies have found that local access to treatment improved the morale of adult patients as they had more time to focus on their health, remained close to their support network, and financial stresses were not accentuated by the need to travel.[174] Treatment abroad can also be isolating for the patient as they are away from their broader family and other support networks, where research shows the importance of social support networks for cancer patients.[175]

Furthermore, all patients (including adults) travelling abroad for CAR-T therapy require an accompanying adult to travel with them as a condition of receiving CAR-T therapy abroad. That accompanying person and the patient are generally required to stay near the hospital for a period of time after discharge from treatment for clinical reasons. This could potentially pose challenges for some patients, and having to travel and

[174] 'Tisagenlecleucel for B-Cell Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma — Ethics and Implementation Report' (2019) 8 (3d) CADTH, 31 https://www.cadth.ca/sites/default/files/pdf/car-t/op0538-tisagenlecleucel-ethics-and-implementation-jan2019.pdf accessed 31 August 2023.

[175] Yasemin Yildirim Usta, 'Importance of social support in cancer patients' (2012) 13(8) Asian Pacific Journal of Cancer Prevention 3569-72; Barbara L Andersen and Caroline Dorfman, 'The Importance of Social Support for People with Cancer' Society of Behavioral Medicine https://www.sbm.org/healthy-living/the-importance-of-social-support-for-people-with-cancer#:~:text=Those%20who%20feel%20supported%20report,and%20the%20lengthy%20recovery%20thereafter accessed 31 August 2023.

source accommodation near the hospital can increase the financial burden on families/patients.[176]

In the case of paediatric patients, having to go abroad for treatment could cause disruption to family life as one parent/guardian may need to travel with the child for treatment while the other parent/guardian remains to continue working/caring for remaining children. It could also mean separating parent(s) from their partners and other children and separating the child who needs CAR-T therapy from one parent/guardian and/or their siblings. Furthermore, practical difficulties could arise for single parents where there may not be an additional caregiver to care for their other children while their child is receiving CAR-T therapy. The literature suggests that families may also have concerns about the success of the treatment, finances, and scheduling treatment around work, school and the other siblings' schedule which can be particularly difficult where parents are also trying to provide a sense of normalcy and routine.[177] In such contexts, Callahan et al., noted the need for support for the family where there is a need to travel abroad due to the psychosocial and financial issues,[178] and recommend that psychosocial support should begin at the time of referral.[179] Alongside this, in some instances, patients may need to travel abroad for healthcare to a jurisdiction where there are language barriers for patients/their

[176] Colleen Callahan, Diane Baniewicz and Amy Barry, 'CAR T-cell therapy for children: Meeting patient and family needs' (2020) 21(2) Hematology/Oncology Today https://www.healio.com/news/hematology-oncology/20200116/car-tcell-therapy-for-children-meeting-patient-and-family-needs# accessed 31 August 2023; Colleen Callahan et al., 'Pediatric Survivorship: Considerations Following CAR T-Cell Therapy' (2019) 23(2) Clin J Oncol Nurs. 35-41.

[177] Colleen Callahan, Diane Baniewicz and Amy Barry, 'CAR T-cell therapy for children: Meeting patient and family needs' (2020) 21(2) Hematology/Oncology Today https://www.healio.com/news/hematology-oncology/20200116/car-tcell-therapy-for-children-meeting-patient-and-family-needs# accessed 31 August 2023; Colleen Callahan et al., 'Pediatric Survivorship: Considerations Following CAR T-Cell Therapy' (2019) 23(2) Clin J Oncol Nurs. 35-41.

[178] Colleen Callahan, Diane Baniewicz and Amy Barry, 'CAR T-cell therapy for children: Meeting patient and family needs' (2020) 21(2) Hematology/Oncology Today https://www.healio.com/news/hematology-oncology/20200116/car-tcell-therapy-for-children-meeting-patient-and-family-needs# accessed 31 August 2023

[179] Colleen Callahan, Diane Baniewicz and Amy Barry, 'CAR T-cell therapy for children: Meeting patient and family needs' (2020) 21(2) Hematology/Oncology Today https://www.healio.com/news/hematology-oncology/20200116/car-tcell-therapy-for-children-meeting-patient-and-family-needs# accessed 31 August 2023

families.[180] More generally where patients have treatment abroad, challenges may arise in certain contexts in terms of needing to return to the provider hospital for follow up appointments, and/or around access to follow-on treatment in their home country.[181] Moreover, it can be additionally difficult for families where a child or adult patient travel abroad and they experience side effects or that therapy is unsuccessful.

Recommendation 4: Accessing CAR-T Therapy Abroad for Patients living in Ireland where such CAR-T therapies are not available in Ireland: *The Treatment Abroad Scheme (TAS) was a very important scheme for enabling patients to access CAR-T therapies especially prior to these being provided in Ireland in 2021 and 2022. However, ideally, where it is possible, and feasible, given the additional challenges faced by patients needing to travel abroad to obtain CAR-T therapies, CAR-T therapies should be provided in Ireland for patients ordinarily residing here.*

Nonetheless, CAR-T therapies are evolving rapidly, and not all CAR-T therapies authorised by the EMA are approved for reimbursement and provided in Ireland. Access to such therapies may often be the only remaining potential avenue certain patients have for treatment. Accordingly, this report recommends that the TAS continues to consider patients for CAR-T therapies abroad on a case-by-case basis where these therapies are clinically indicated, where these are not available in Ireland, and where such patients have no other viable treatment option. In such instances, and as far as practicable, this report also recommends consideration around to what extent financial support can be offered to families/patients who need to travel abroad to access CAR-T therapies to assist with the costs of travel abroad and accommodation.

[180] This challenge is highlighted, more generally, albeit in the clinical trial context in: Teodora Lalova et al., 'Cross-Border Access to Clinical Trials in the EU: Exploratory study on needs and reality' (2020) 7 Frontiers in medicine https://doi.org/10.3389/fmed.2020.585722 accessed 31 August 2023.

[181] Teodora Lalova et al., 'Cross-Border Access to Clinical Trials in the EU: Exploratory study on needs and reality' (2020) 7 Frontiers in medicine https://doi.org/10.3389/fmed.2020.585722 accessed 31 August 2023.

6.1.5 The Current Process for CAR-T Therapies in Ireland: Manufacturing of the Final Product for Infusion

Currently, the collection of cells from patients and the infusion of the final CAR-T therapy is conducted in Ireland. However, the manufacturing of the CAR-T product takes place outside Ireland. This can create additional challenges in terms of cryopreservation and storage of cells and logistical challenges for the transport of the cells outside the country and the transport of the final product back into the hospital setting in Ireland for infusion into the patient.[182] As noted above, there is generally a timeline of approximately four weeks between cell collection and final product infusion into the patient. Although this is a quick turnaround given the complexity of the process involved, any time lag between collection and infusion at this stage can present challenges for patients who are generally severely ill, and the patient's health may deteriorate in this time between cell collection and final planned infusion of the CAR-T therapy.[183]

In an ideal scenario, the manufacturing element of this CAR-T therapy process would be conducted in the same jurisdiction as the collection takes place, ideally in a closely adjacent site.[184] This would reduce storage and transport risks and would likely reduce the timelines between collection and infusion.

Having this manufacturing process take place in Ireland, for the existing EMA approved CAR-T therapies available here would likely require entities currently holding the relevant marketing authorisation for CAR-T therapies to commence such processes in Ireland, and would be subject to meeting relevant regulatory requirements and having the appropriate legal authorisations in place. In a broader

[182] See discussion in: Lorenzo Giorgioni, et al, 'CAR-T State of the Art and Future Challenges, A Regulatory Perspective' (2023) 24 Int. J. Mol. Sci. 11803 at 3.4.1.
[183] Lorenzo Giorgioni, et al, 'CAR-T State of the Art and Future Challenges, A Regulatory Perspective' (2023) 24 Int. J. Mol. Sci. 11803 at 3.4.1
[184] See also discussion in: Lorenzo Giorgioni, et al, 'CAR-T State of the Art and Future Challenges, A Regulatory Perspective' (2023) 24 Int. J. Mol. Sci. 11803 at 3.4.

national discussion, the conditions required to allow this to happen should be further examined.

Furthermore, the development and manufacturing of new CAR-T therapies in Ireland in industry led or academic-led settings in Ireland, could also potentially be used to achieve this in the longer term (see discussion below).

Recommendation 5: The Process for CAR-T Therapies in Ireland: Manufacturing of the Infusion: *We recommend detailed consideration is given around developing and facilitating conditions needed to encourage the manufacturing step of the CAR-T therapy for existing therapies to take place in Ireland, and ideally, where possible for this to take place in close proximity to the treating hospital(s). This would reduce the time involved for the CAR-T therapy process from cell collection to re-infusion, reduce the logistical challenges of transporting and freezing/thawing these cells/products abroad, and would likely result in some reduction in costs. However, it would need to be underpinned by the required resources to ensure sufficient additional personnel, training, and large-scale infrastructural supports, including space and specialist facilities required. In the shorter term, further development of the existing expertise and skills already available regarding key aspects, such as aseptic techniques for processing and cryopreservation of cells for haemopoietic stem cell transplantation and CAR-T therapy in Ireland should also be considered.*

As will be discussed below, in terms of future developments, the EU pharmaceutical legislation proposes a decentralised manufacturing route for ATMPs. Subject to how this proposal develops at the EU level, it may present an opportunity to facilitate a direct pathway towards manufacturing existing therapies in Ireland.

6.1.6 Patients Undergoing CAR-T Therapies: Access to Fertility Preservation Services

At the time of writing, patients who undergo CAR-T therapies will generally require other cancer therapies, including chemotherapy prior to obtaining CAR-T therapies, and may experience side effects, including fertility issues following treatment. These

patients may need access to fertility preservation services, including storage of their gametes for later use (i.e., egg or sperm). There is a funded fertility preservation service available for adults undergoing cancer treatment in certain circumstances in Ireland.[185]

In the case of adolescent children, there are some services for fertility preservation available in Ireland for male patients who are undergoing cancer treatment. However, for adolescent female children fertility preservation is more complex and invasive. Fertility preservation is also more complex for pre-pubescent children who are undergoing cancer treatment. In some cases, such patients living in Ireland would need to travel to the UK or elsewhere to avail of fertility preservation services.[186] The need to travel abroad with a seriously ill child for fertility preservation services can place significant additional burdens on families/patients. It could also create additional financial issues as fertility services are not covered under the TAS.

In 2018, a pilot project 'The Childhood Cancer Fertility Project" commenced comprising the Irish Cancer Society, Merrion Fertility Clinic, the National Maternity Hospital, and Children's Health Ireland, and was funded by the Irish Cancer Society with further support provided by the National Cancer Control Programme. The project aims to provide fertility preservation services for children in Ireland,[187] including '[a] structured fertility health service for children, adolescent and young adult cancer patients headed by Merrion Fertility Clinic that will make it possible for patients to be routinely referred for the assistance they need in a timely manner'.[188]

[185] Irish Cancer Society, 'Fertility preservation for cancer patients: Quality of Life in survivorship' (Policy Paper July 2020), 8 https://www.cancer.ie/sites/default/files/2020-08/Fertility%20preservation__policy_doc_August2020.pdf accessed 31 August 2023.
[186] Irish Cancer Society, 'Helen Groarke and Dr Lucia Hartigan provide a progress update on our Childhood Cancer Fertility Project for Childhood Cancer Awareness Month' (26 September 2021) https://www.cancer.ie/about-us/news/childhood-cancer-fertility-project-update accessed 31 August 2023.
[187] Irish Cancer Society, 'Childhood Cancer Fertility Project' https://www.cancer.ie/cancer-information-and-support/childrens-cancer/childhood-cancer-fertility-project accessed 31 August 2023.
[188] Irish Cancer Society, 'Childhood Cancer Fertility Project' https://www.cancer.ie/cancer-information-and-support/childrens-cancer/childhood-cancer-fertility-project accessed 31 August 2023.

Recommendation 6(1): Patients Undergoing CAR-T Therapies: Access to Fertility Preservation Services: *For adult and children undergoing cancer therapies including CAR-T therapies, we recommend consideration around how fertility preservation services are provided in Ireland. In particular, a full review of the current landscape for fertility preservation services for children in the oncology context is needed to ensure such patients can obtain access to funded fertility preservation services which align with best international practice, in Ireland.*

Relatedly, more generally, there is no tailored legislative framework for assisted human reproduction (AHR) in Ireland, despite recommendations highlighting the need for this and the significant gap around the legal and ethical issues arising around AHR more generally.[189] Most recently, the *Health (Assisted Human Reproduction) Bill* 2022 was published.[190] However, at the time of writing, this Bill has not progressed or passed into law, and a significant regulatory gap remains. This affects a range of aspects of AHR with implications which go beyond the oncology fertility context. A tailored legal regulatory framework for AHR generally in Ireland which also addresses the potential legal and ethical issues that may arise in the oncology fertility preservation context for adults and children, including around the storage of gametes, is needed.[191]

Recommendation 6(2): Patients Undergoing CAR-T Therapies: Access to Fertility Preservation Services: *Fertility preservation, including in the oncology context, presents a range of complex legal and ethical issues and it is vital that these issues, are considered and provided for as soon as possible, as part of a broader regulatory approach to Assisted Human Reproduction (AHR). A regulatory framework for AHR is urgently needed in Ireland.*

[189] The need for a legal framework for AHR more generally was highlighted in: Commission on Assisted Reproduction, 'Report of the Commission on Assisted Human Reproduction' (April 2005) https://www.lenus.ie/bitstream/handle/10147/46684/1740.pdf?sequence=1 accessed 31 August 2023.
[190] See Health (Assisted Human Reproduction) Bill 2022.
[191] For a detailed discussion of the legal and ethical issues which arise in the oncofertility context for children, see: Neil Maddox and Claire McGovern, 'Fertility Preservation for Children with Cancer: Legal and Ethical Challenges' (19 July 2022) https://ssrn.com/abstract=4167110 accessed 31 August 2023.

6.2 Providing Access to CAR-T Therapies for Patients in Ireland: Current and Longer-Term Health-Systems Opportunities and Challenges

Turning to the broader national health systems challenges around providing Advanced Therapy Medicinal Products (ATMPs) and specifically, CAR-T therapies, whilst such therapies have significant potential for cancer care, however, there are health systems challenges around delivering them in the short and longer term. As noted, research in the field is advancing rapidly, and there will likely be an increase in the numbers of patients who could benefit from ATMPs, including CAR-T therapies in future. There is a real risk that countries which do not consider how they will develop such technologies in a sustainable and affordable manner, will fall behind in the provision of CAR-T therapies. Some of the key challenges from a national health systems perspective are considered in this section, which also sets out recommendations on key issues for consideration as part of a broader approach to address these in the longer term.

6.2.1 CAR-T Therapies: Challenges and the Need for Sustainable Avenues to provide CAR-T Therapies

A key barrier to providing CAR-T therapies for many public health systems is the high cost of such therapies under existing commercial led routes.[192] In the US, the list prices for CAR-T therapies are typically over $400,000USD per patient per infusion.[193]

[192] See discussion in: Edward R. Scheffer Cliff et al., 'High Cost of Chimeric Antigen Receptor T-Cells: Challenges and Solutions' (2023) American Society of Clinical Oncology Educational Book 43 (11th July 2023), which estimates such costs as in excess of $400,000USD https://ascopubs.org/doi/full/10.1200/EDBK_397912 accessed 16 October 2023; C Chabannon, et al., 'CAR-T cells: the narrow path between hope and bankruptcy?' (2017) 52(12) Bone Marrow Transplantation1588–1589; Emanuele Ostuni et al., 'Commercialising CAR-T Therapies' in *The Evolution of a Revolution. In Second Generation Cell and Gene-based Therapies* 747-775 (Academic Press 2020); Tao Ran et al., 'Cost of decentralized CAR T-cell production in an academic nonprofit setting' (2020) 147(12) International Journal of Cancer 3438-3445 ; European Cancer Patient Coalition, 'CAR-T Therapy: White Paper' (2022) https://ecpc.org/wp-content/uploads/2022/11/White-Paper-CAR-T-therapy.pdf accessed 31 August 2023.

[193] Edward R. Scheffer Cliff et al., 'High Cost of Chimeric Antigen Receptor T-Cells: Challenges and Solutions' (2023) American Society of Clinical Oncology Educational Book 43 (11th July 2023), 1; See also Denise Roland, 'FDA Approves Pioneering Cancer Treatment With $475,000 Price Tag' The Wall

The prices that European countries can negotiate for access to CAR-T therapies are generally lower than in the US.[194] Nonetheless, the costs in Europe remain very high. For example, the total estimated cost to the HSE of Yescarta inclusive of rebate and VAT in Ireland based on proposed wholesale price in 2020 was €384,222, as reported in the NCPE's February 2020 assessment.[195] The proposed estimated costs of Kymriah per patient per infusion based on the NCPE's 2019 assessment was €301,762.[196] Importantly, these are not the final prices paid by the HSE to access such therapies –the final prices for medicines/therapies are generally subject to confidential negotiations within public health systems. Such figures are used here only to give a general illustration of the initial estimated costs per patient per infusion. These costs also do not include the indirect costs involved in providing the therapies to patients, including costs of hospital care etc. Due to various factors, including the high costs of CAR-T therapies and complexity in terms of logistical issues, some countries have been unable to provide CAR-T therapies.[197] Such high costs could also raise issues in terms of reimbursement in the Irish context. Under Schedule 3, Part 3 of the Health Act 2013 two factors for consideration on whether technologies/medicines can be reimbursed in Ireland, are 'the resources available' and 'the potential or actual budget impact of the item.'[198]

Street Journal (updated 30 August 2017) https://www.wsj.com/articles/fda-approves-first-gene-therapy-in-u-s-1504108512 accessed 31 August 2023.

[194] Marion Subklewe, Michaelvon Bergwelt-Baildon, and Andreas Humpe, 'Chimeric antigen receptor T cells: a race to revolutionize cancer therapy' (2019) 46(1) Transfusion Medicine and Hemotherapy 15-24.

[195] See: NCPE, 'Cost effectiveness of axicabtagene ciloleucel (Yescarta®) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy' 7 https://ncpe.ie/wp-content/uploads/2020/02/Summary-Axi-Cel-Final-1-1.pdf accessed 31 August 2023.

[196] See: NCPE, 'Cost-effectiveness of tisagenlecleucel (Kymriah®) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy' https://ncpe.ie/wp-content/uploads/2019/09/Summary-Tisa-Cel-DLBCL.pdf accessed 31 August 2023.

[197] Adam Zamecnik, 'Access to CAR-T therapies in Central and Eastern Europe in "catch-up" mode compared to the West' (29 April 2022) Pharmaceutical Technology https://www.pharmaceutical-technology.com/features/access-to-car-t-therapies-in-central-and-eastern-europe-in-catch-up-mode-compared-to-the-west/ accessed 31 August 2023; European Cancer Patient Coalition, 'CAR-T Therapy: White Paper' (2022) https://ecpc.org/wp-content/uploads/2022/11/White-Paper-CAR-T-therapy.pdf accessed 31 August 2023.

[198] Schedule 3, Part 3 of the Health (Pricing and Supply of Medical Goods) Act 2013.

Thus, despite the potential benefits of such therapies for individual patients, these current high costs can give rise to difficult ethical considerations. These ethical issues include the potential opportunity costs involved if such costs remain this high – as funding such therapies may mean less funding is available for other healthcare therapies/interventions within a national public health system.[199] However, if such therapies cannot be provided under public health systems this also gives rise to significant ethical issues when we consider individual patients for whom access to such therapies (where these are clinically indicated) may present their only potential for treatment, or in some cases, of curative therapy.

Thus, in the longer term more sustainable avenues are necessary to reduce the high cost of such therapies. These issues are particularly significant as the demand for CAR-T therapies and other ATMPs will likely increase in future. Two main avenues are suggested in relevant literature around how such costs may be reduced for CAR-T therapies: i) novel reimbursement mechanisms, and ii) by looking at other sustainable avenues to develop and produce such therapies. Alongside this, the report highlights the need for transparency in the prices paid currently by European States for such therapies. Moreover, there is an ongoing need to engage with avenues which may reduce costs and logistical complexities under existing pathways which are also considered here.

6.2.1.1 Novel Reimbursement Models for CAR-T Therapies

One avenue proposed within the literature to address some the challenges around the high prices in the CAR-T therapy context, is via developing alternative or novel reimbursement models for such therapies, including mechanisms that spread the cost over time, rather than payment of the upfront cost of the therapy prior to, or at the time of, the patient receiving it. Such models also often consider outcomes of the therapies.

[199] See discussion in: European Cancer Patient Coalition, 'CAR-T Therapy: White Paper' (2022) at 5 https://ecpc.org/wp-content/uploads/2022/11/White-Paper-CAR-T-therapy.pdf accessed 31 August 2023; 'Tisagenlecleucel for B-Cell Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma — Ethics and Implementation Report' (2019) 8 (3d) CADTH at 2.3 https://www.cadth.ca/sites/default/files/pdf/car-t/op0538-tisagenlecleucel-ethics-and-implementation-jan2019.pdf accessed 31 August 2023.

A study by Jørgensen et al., in 2020, which was also examined by a recent PwC/IPHA Pathfinder study for the adoption of cell and gene therapies in Ireland,[200] highlighted several key avenues used by five European States (the United Kingdom, France, Italy, Spain, Germany) for pricing/reimbursing Kymriah and Yescarta CAR-T therapies, including: [201]

- *Outcomes model based on future evidence*: where pricing is based on the evidence development and the future pricing is linked to the longer-term evidence on patient outcomes resulting from the use of such therapies including future clinical trials (a variation of this approach was adopted in the UK and France);
- *Outcomes models where rebates to the payer are applied which often will depend on patient outcomes*, patient survival is often a key outcome measured in such contexts (Germany);
- *Outcome based staged payment model* which aim to spread the cost over several years, and payment can be dependant at each stage on patient outcomes (a model like this applied in Spain and Italy).[202]

Jørgensen, Hanna and Kefalas conclude by stating that:

> 'Kymriah® and Yescarta® serve as relevant and interesting examples of how innovative, high-cost therapies with data uncertainty at launch, and with the potential to deliver significant patient and healthcare system benefits, can secure

[200] PwC and IPHA, 'Pathfinder Study for the Adoption of Cell and Gene Therapies in Ireland' (May 2021) 26 https://www.ipha.ie/wp-content/uploads/2021/05/CGT-Pathfinder-Study-May-2021.pdf accessed 31 August 2023.

[201] See: Jesper Jørgensen, Eve Hanna and Panos Kefalas, 'Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries' (2020) 8(1) Journal of Market Access & Health Policy 1715536 https://doi.org/10.1080/20016689.2020.1715536 accessed 31 August 2023.

[202] See: Jesper Jørgensen, Eve Hanna and Panos Kefalas, 'Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries' (2020) 8(1) Journal of Market Access & Health Policy 1715536 https://doi.org/10.1080/20016689.2020.1715536 accessed 31 August 2023. These are discussed in PwC and IPHA, 'Pathfinder Study for the Adoption of Cell and Gene Therapies in Ireland' (May 2021) 26 https://www.ipha.ie/wp-content/uploads/2021/05/CGT-Pathfinder-Study-May-2021.pdf accessed 31 August 2023.

adoption. The developments, particularly in Germany, Italy, and Spain, suggest that the door for OBR is opening in large parts of continental Europe, which is exciting. Still, it is important to highlight that there is no 'one size fits all' solution, as different countries have different HTA methodologies and processes, and different preferences and priorities...'[203]

Another model, identified in a recent PwC/IPHA Pathfinder study, is the use of 'blended annuity style payments with rebates', as adopted in the US context, whereby the price is paid over several years in instalments, with rebates tied to patient outcomes over time.[204]

Examining different types of reimbursement models for CAR-T therapies may alleviate some funding issues for public health systems. However, greater research is needed on the extent to which such reimbursement strategies can reduce the final current costs of CAR-T therapies. Under such proposed approaches, a concern that has been raised is whether a similar overall price is charged if patients have positive outcomes, and a key change could be (in some instances) to spread the high costs over a longer period of time,[205] and/or to lead to a potential reduction of costs where therapies are not successful.

Recommendation 7(1): Novel Reimbursement Models for CAR-T Therapies: *A detailed study is needed around the use of novel reimbursement models for CAR-T therapies.* [206] *This should also consider the potential benefits/limitations such*

[203] Jesper Jørgensen, Eve Hanna and Panos Kefalas, 'Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries' (2020) 8(1) Journal of Market Access & Health Policy 1715536 at 9.
[204] PwC and IPHA, 'Pathfinder Study for the Adoption of Cell and Gene Therapies in Ireland' (May 2021) 26 https://www.ipha.ie/wp-content/uploads/2021/05/CGT-Pathfinder-Study-May-2021.pdf accessed 31 August 2023.
[205] See also: Tao Ran, Stefan Eichmüller, Patrick Schmidt et al.,'Cost of decentralized CAR T-cell production in an academic nonprofit setting' (2020) 147(12) International Journal of Cancer 3438–3445 https://doi.org/10.1002/ijc.33156 accessed 31 August 2023.
[206] These are discussed in the recent: PwC and IPHA, 'Pathfinder Study for the Adoption of Cell and Gene Therapies in Ireland' (May 2021) 26 https://www.ipha.ie/wp-content/uploads/2021/05/CGT-Pathfinder-Study-May-2021.pdf accessed 31 August 2023; See also: Jesper Jørgensen, Eve Hanna and Panos Kefalas, 'Outcomes-based reimbursement for gene therapies in practice: the experience of

approaches could offer to reduce the overall high costs of CAR-T therapies for public health systems.

Alongside and within the context of novel reimbursement approaches, transparency around the prices paid for CAR-T therapies should be considered within in the EU context. As discussed above, the actual prices that European States pay to access CAR-T therapies and other medicines, are often negotiated within confidential commercial discussions and the final prices not subsequently disclosed. Greater transparency in the prices paid by various EU States to access such therapies, could potentially assist states in negotiations around the prices to access such therapies. Indeed, the World Health Assembly passed a resolution in 2019 which urged Member States to take measures around the transparency of medicines/health technologies, including "to take appropriate measures to publicly share information on the net prices of health products."[207]

Recommendation 7(2): Transparency around Pricing: *At an EU level, greater transparency around how much each EU State is paying to access CAR-T therapies should be considered. Making such information publicly available across EU States would provide greater information for all States and the public.[208] It would also be important to consider the need for transparency in pricing as part of a discussion on novel reimbursement mechanisms.*

recently launched CAR-T cell therapies in major European countries' (2020) 8(1) Journal of Market Access & Health Policy 1715536 https://doi.org/10.1080/20016689.2020.1715536 accessed 31 August 2023.

[207] Resolution on improving the transparency of markets for medicines, vaccines, and other health products. Geneva: Seventy-second World Health Assembly; 2019. (WHA72.8) https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_R8-en.pdf accessed 30 August 2023; See discussion in: Mara K Perehudoff and Ellen t'Hoen, 'What is the evidence on legal measures to improve the transparency of markets for medicines, vaccines and other health products (World Health Assembly resolution WHA72.8)?'(WHO Regional Office for Europe; 2021) https://www.ncbi.nlm.nih.gov/books/NBK572579/#ch3.s6 accessed 16 October 2023.

[208] Katrina Perehudoff, 'European governments should align medicines pricing practices with global transparency norms and legal principles' (2022) 16 Lancet Europe Regional https://doi.org/10.1016/j.lanepe.2022.100375 accessed 30 August 2023.

6.2.1.3 Future Sustainable Pathways to Develop and Produce CAR-T Therapies

In the longer term, additional and more sustainable pathways are also needed to develop and provide CAR-T therapies, and ideally, to deliver these at lower costs to public health systems. This would require a detailed understanding and investigation of the pathways available and a national strategy to consider key aspects which needed in such contexts. Prior to discussing some of the key elements that require further consideration within such a national strategy, this section provides a brief overview of some of the main avenues that could be considered to deliver more sustainable pathways for longer term production of CAR-T therapies. This is not an exhaustive list of all potential strategies.

1) *Manufacturing of CAR-T Therapies in Ireland via Existing Providers & Decentralised Manufacturing*

As discussed above, developing the conditions required to allow for the manufacturing of CAR-T therapies to occur in Ireland could reduce some of the costs of providing CAR-T therapies. It would reduce also the time and the logistical issues with the processing element of CAR-T therapies occurring abroad.[209] However, under the current regulatory framework it would require any site setting up in Ireland to have its own relevant manufacturing authorisations under the applicable regulatory frameworks for ATMPs.

The EU proposed Pharmaceutical Legislation Reforms which were published in April 2023, provide for new measures around the de-centralised manufacturing of ATMPs. Under that proposal a central manufacturer can have decentralised manufacturing sites for ATMPs set up in close proximity to the patients, and each site will not require a separate manufacturing authorisation (but will be a registered manufacturer and will

[209] See discussion in Tao Ran et al., 'Cost of Decentralized CAR T-Cell Production in an Academic Nonprofit Setting'(2020) 147(12) International Journal of Cancer 3438–3445, https://doi.org/10.1002/ijc.33156 accessed 30 August 2023 which suggests it could reduce the time to 12-14 days.

need to comply with relevant applicable standards, including the Good Manufacturing Practices principles). This proposal, if adopted in this current form, could enable the manufacturing process to take place for existing CAR-T therapies at de-centralised sites within the jurisdiction in which the CAR-T therapy is provided in.[210]

Recommendation 8(1): Manufacturing of CAR-T Therapies in Ireland via existing providers & Decentralised Manufacturing: *As discussed above an investigation is needed in relation to potential pathways for manufacturing of CAR-T therapies in Ireland, and the extent to which this may be possible under the current system and may reduce overall costs of providing CAR-T therapies, and address other challenges. As part of this, an assessment is needed around the infrastructural needs, including personnel, facilities, expertise, and funding needed to facilitate this.*

For the reasons highlighted above, and subject to the development of the proposed EU's pharmaceutical legislation in relation to the de-centralised manufacturing of these types of therapies, a deeper study is needed in relation to potential legal/regulatory pathways for decentralised manufacturing of CAR-T therapies in Ireland for existing therapies, and the extent to which this avenue could reduce the costs of providing CAR-T therapies. For all potential pathways, an assessment is needed around the personnel, facilities, expertise, and funding etc needed to facilitate this.

2) *Development of Academic CARs in Ireland*

Another avenue to be considered, is the development of academic CARs in Ireland. This is whereby academic centres or other research groups develop their own CAR-T therapies, which may initially be offered to individual patients in a tailored personalised manner, often as an investigational medicinal product under a clinical trial framework.[211] The development of CAR-T therapies within academic centres of excellence, usually affiliated to a university or hospital, presents opportunities in this

[210] See, recital 109, Art 33, Art 34 of 2023/0132 (COD) Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC available at https://eur-lex.europa.eu/legal-content/EN/TXT/DOC/?uri=CELEX:52023PC0192 accessed 31 August 2023.
[211] See Regulation EU/536/214, article 2(5).

field, subject to the relevant best practice international standards being in place. Arnaudo states that:

> 'Academic CAR-Ts represent a viable opportunity for producing and administering in-house CGTP/ATMPs to patients under the strict safety conditions required for clinical trials, at sustainable costs, and with promising results of efficacy, because of the simpler delivery processes.'[212]

Moreover, the origins of CAR-T therapies can be traced to such academics CARs, Mitchell, Kenderian and Rajkumar highlighted previously:

> 'long before pharmaceutical companies took control of CAR-T, medical centers made these treatments. Cancer centers like the University of Pennsylvania, the National Cancer Institute, Memorial Sloan Kettering Cancer Center, Fred Hutchinson Cancer Center, Baylor University, and others figured out how to engineer CAR-T cells and ran the initial trials to test them. Drug companies were later involved mainly as a means to scale up production.'[213]

Arnaduo also states that:

> "The in-house academic route is proving to be of particular interest to healthcare systems in many EU countries that have publicly owned (or privately owned but affiliated) infrastructures integrated with academic centers of excellence, in view of establishing national networks of CAR-Ts R&D activities."[214]

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[212] Luca Arnaudo, 'On CAR-Ts, decentralized in-house models, and the hospital exception: Routes for sustainable access to innovative therapies" (2022) Journal of Law and the Biosciences 1-19, 13 available at https://academic.oup.com/jlb/article/9/2/lsac027/6712359

[213] David Mitchell, Saad Kenderian & S. Vincent Rajkumar, 'Letting Academic Medical Centers Make CAR-T Drugs Would Save Billions', STAT, November 20, 2019, https://www.statnews.com/2019/11/20/car-t-drugs-aca demic-medical-centers-save-billions/ accessed 30 August 2023; See also: Karlo Perica et al., 'Building a CAR Garage: Preparing for the Delivery of Commercial CAR T Cell Products at Memorial Sloan Kettering Cancer Center' (2018) 24 Biology of Blood and Marrow Transplant 1135–1141– as cited in Luca Arnaudo, 'On CAR-Ts, decentralized in-house models, and the hospital exception: Routes for sustainable access to innovative therapies" (2022) Journal of Law and the Biosciences 1-19, 13.

[214] Luca Arnaudo, 'On CAR-Ts, decentralized in-house models, and the hospital exception: Routes for sustainable access to innovative therapies" (2022) Journal of Law and the Biosciences 1-19, 14.

There is debate around the exact potential costs associated with the production of CAR-T therapies in academic non-profit settings, However, some studies indicate production in academic settings could be considerably lower than current costs of the therapies. For example, Ran et al have suggested direct costs for manufacturing production of CAR-T therapies in a non-profit academic settings could range from €35,000-€60,000.[215]

Arnaudo argues that: 'Academic CAR-Ts represent a viable opportunity for producing and administering in-house CGTP/ATMPs to patients under the strict safety conditions required for clinical trials, at sustainable costs, and with promising results of efficacy, because of the simpler delivery processes.'[216]

Recommendation 8(2): Development of Academic CARs in Ireland: *In the longer term, and as part of a national plan discussed below, consideration is needed around the potential for greater development of academic CARs in Ireland. From the outset, the development of such academic CARs should also be shaped by, the key goal of achieving accessible CAR-T therapies, and policies should be embedded to achieve this, including, for example, where relevant via socially responsible intellectual property licensing strategies and clauses.[217] To develop further academic CARs in Ireland would require sustained investment in academic research, translational*

[215] This study was based on 2018 costs and developed using costs involved in the production of CAR-T therapies in-house in a German academic context. Ran et al., note that there are initial outlay costs and personnel requirements to develop CAR-T therapies in-house, outlining the "[m]ain cost components included personnel and technician salaries, expenditure on equipment, a clean room, as well as production materials." This also does not appear to include IP licensing costs, if relevant. See discussion in: Tao Ran et al., 'Cost of Decentralized CAR T-Cell Production in an Academic Nonprofit Setting' (2020) 147(12) International Journal of Cancer 3438–3445; For a critique of this approach, see: Michael Schmitt et al., 'Comments on "Cost of decentralized CAR T cell production in an academic non-profit setting.' (2021) 148(2) Int J Cancer. 514-515; See also: Tao Ran et al., 'Comments on "Cost of decentralized CAR T cell production in an academic non-profit setting' (2021) 148(2) Int J Cancer. 516-517.

[216] Luca Arnaudo, 'On CAR-Ts, decentralized in-house models, and the hospital exception: Routes for sustainable access to innovative therapies" (2022) Journal of Law and the Biosciences 1-19, 13.

[217] International examples of such polices, include: Netherlands Federation of University Medical Centers, 'Ten principles for Socially Responsible Licensing' (June 2019) https://www.nfu.nl/sites/default/files/2020-08/19.4511_Ten_principles_for_Socially_Responsible_Licensing_v19-12-2019.pdf accessed 30 August 2023; See discussion in:

medicine, suitably qualified personnel and appropriate facilities for such research in Ireland, including funding for clinical trials.

3) Hospital Exemption Mechanism & CAR-T Therapies

Relatedly, the 'hospital exemption' mechanism (HE) under EU law allows hospitals to produce tailored personalised therapies for individual patients in certain circumstances where there is an *unmet need*.[218] This mechanism is provided for by Article 28(2) of Regulation 1394/2007/EC (which amends Article 3(7) of Directive 2001/83/EC).[219] It allows for the production of ATMPs which includes CAR-T therapies, outside of the centralised marketing authorisation pathway for ATMPs.[220] CAR-T therapies can be produced under this pathway, provided they are produced as tailored individualised therapies for patients, carried out on a non-routine basis, and produced for use under the professional responsibility of a medical practitioner.[221]

In practical terms, where the HE operates, CAR-T therapies are manufactured via research 'in hospitals, universities or start-up companies where the medicine is prescribed for patients under the care of a medical practitioner.'[222] The therapy must be delivered to patients by the clinician in the relevant hospital, having been produced on an individualised tailored manner. Such HE based therapies must be produced to the required safety standards as assessed by the national regulatory competent

[218] Manel Juan et al., 'Is Hospital Exemption an Alternative or a Bridge to European Medicines Agency for Developing Academic Chimeric Antigen Receptor T-Cell in Europe? Our Experience with ARI-0001' (2021) 32 Human Gene Therapy 19–20 https://doi.org/10.1089/hum.2021.168 accessed 31 August 2023; Luca Arnaudo, 'On CAR-Ts, decentralized in-house models, and the hospital exception. Routes for sustainable access to innovative therapies' (2022) 9(2) Journal of Law and the Biosciences https://doi.org/10.1093/jlb/lsac027 accessed 30 August 2023.

[219] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

[220] See discussion in: Fermín Sánchez-Guijo et al., 'Role of Hospital Exemption in Europe: position paper from the Spanish Advanced Therapy Network (TERAV)' (2023) 58 Bone Marrow Transplant 727–728.

[221] Art 28(2) Regulation (EC) No 1394/2007.

[222] Health Products Regulatory Authority (HPRA), 'Guide to Hospital-Based Advanced Therapy Medicinal Products' (28 February 2013) http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/aut-g0091-guide-to-hospital-based-advanced-therapy-medicinal-products-v1.pdf?sfvrsn=4 accessed 30 August 2023.

authority. In Ireland, the competent authority is the Health Products Regulatory Authority (HPRA), which has produced guidelines on the use of the HE within the ATMPs context in Ireland.[223]

The use of the HE mechanism for CAR-T therapies offers two main advantages. First, where hospitals can produce such therapies in-house, it allows medical practitioners to tailor treatments to individual patient needs and provide access to therapies for patients who have no other alternative therapy. This could, for example, enable hospitals to tailor products for patients suffering from rare cancers, where there is no commercial product available. In the Spanish context, Sánchez-Guijo et al. state that the main uses of ATMPs developed using the HE in Europe are:

> "…to provide treatments for patients not included or ineligible for participating in clinical trials or where ATMPs were not considered suitable for commercial development. Hospital Exemption is therefore an essential tool to ensure timely access to safe, effective, and legally regulated treatments for patients with rare diseases or those lacking effective treatments or better therapeutic alternatives."[224]

In terms of increasing access for patients with unmet needs, Sánchez-Guijo et al. state that:

> "…the most positive consequence [of the use of HE to develop CAR-T therapies] is the increased access of advanced therapies to our patients. The main reasons for this are, amongst others, the fact that they may cover indications not yet approved for commercial CARTs and other ATMPs, the expedited manufacturing time (and at a lower cost) of an academic product,

[223] HPRA, 'Guide to Hospital-Based Advanced Therapy Medicinal Products' (28 February 2013) http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/aut-g0091-guide-to-hospital-based-advanced-therapy-medicinal-products-v1.pdf?sfvrsn=4 accessed 30 August 2023.
[224] Fermín Sánchez-Guijo, et al., 'Role of Hospital Exemption in Europe: position paper from the Spanish Advanced Therapy Network (TERAV)' (2023) 58 Bone Marrow Transplant 727–728.

> and that they may provide treatment for diseases where pharmaceutical companies are not focused on. Besides, Hospital Exemption clause alleviates the worrying difficulties of supplies to European countries of ATMPs manufactured outside the EU."[225]

Thus, the HE may offer an avenue for patients to access CAR-T therapies in certain circumstances where there are no other therapies available to them.

Second, CAR-T therapies provided under the HE scheme can potentially be provided for a lower cost than existing CAR-T therapies.[226] Trias et al., highlight that: "although ATMPs development following the HE pathway does not pursue saving costs but rather to provide a solution for patients for whom no treatment alternatives are available, it is worth noting the reduced cost associated with developing and manufacturing HE-ATMPs." [227] For example, the price of ARI-001, a CAR-T therapy produced via the HE in the Spanish public healthcare system is one third of the price of CAR-Ts produced under commercial pathways available in Spain.[228]

However, there are challenges to using the HE scheme in Europe,[229] which include: the lack of harmonisation in the EU around the legal application of the HE scheme in

[225] Fermín Sánchez-Guijo et al., 'Role of Hospital Exemption in Europe: position paper from the Spanish Advanced Therapy Network (TERAV)' (2023) 58 Bone Marrow Transplant 727–728.
[226] Luca Arnaudo, 'On CAR-Ts, decentralized in-house models, and the hospital exception. Routes for sustainable access to innovative therapies' (2022) 9(2) Journal of Law and the Biosciences https://doi.org/10.1093/jlb/lsac027 accessed 30 August 2023.
[227] Esteve Trias et al., 'The Hospital Exemption Pathway for the Approval of Advanced Therapy Medicinal Products: An Underused Opportunity? The Case of the CAR-T ARI-0001' (2022) 57 Bone Marrow Transplantation 157.
[228] Esteve Trias, Manel Juan et al., 'The Hospital Exemption Pathway for the Approval of Advanced Therapy Medicinal Products: An Underused Opportunity? The Case of the CAR-T ARI-0001' (2022) 57 Bone Marrow Transplantation 157.
[229] Esteve Trias et al., 'The Hospital Exemption Pathway for the Approval of Advanced Therapy Medicinal Products: An Underused Opportunity? The Case of the CAR-T ARI-0001' (2022) 57 Bone Marrow Transplantation 157. See also: Report from the Commission to the European Parliament and the Council in accordance with Article 25 of Regulation (EC)2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52014DC0188 accessed 30 August 2023, at 4.2.

each Member State, which leads to 'differences in interpretation and of implementation of the European legislation hamper transnational collaboration in HE-ATMPs';[230] alongside this ATMP manufacturing requires 'human, logistic and financial resources, which, together with regulatory challenges, commonly poses a great barrier for public facilities, but also for private investors.'[231] The use of CAR-T therapies under HE, may also give rise to certain ethical questions in terms of potential risks/benefits to patients and the uncertainties which can arise in such contexts, such factors require careful consideration.

Recommendation 8(3): The Use of the Hospital Exemption (HE) for CAR-T Therapies for Patients with unmet needs: *The HE mechanism under Article 28 of the EU ATMP Regulation enables a pathway to develop in-house CAR-T therapies in certain circumstances on an individualised basis for patients where there is an unmet need. This report recommends detailed consideration is given around to what extent the HE pathway could be used for the provision of CAR-T therapies in Ireland in such circumstances, which would map the potential opportunities and challenges/limitations of using the HE mechanisms in such contexts.*

a. *As part of such a study, at a regulatory level, greater study is needed around the parameters within which the HE mechanism can be used in Ireland for ATMPs, including, how the 'unmet' need requirement could be interpreted in Ireland for CAR-T therapies. Consideration should be given to the experiences of other EU countries where the HE exemption is utilised to develop CAR-T therapies in cases of 'unmet need'.*
b. *Moreover, a detailed assessment is needed around the current facilities available and the broader additional resources (including funding,*

[230] Alliance for Regenerative Medicine, Recommendations for the use of Hospital Exemption 2020. http://alliancerm.org/wp-content/uploads/2020/10/ARM-position-on-HE-final-Oct-2020.pdf accessed 30 August 2023; Philippe Van Wilder, 'Advanced therapy medicinal products and exemptions to the regulation 1394/2007: how confident can we be? An exploratory analysis' (2012) 3(12) Frontiers in Pharmacology https://doi.org/10.3389/fphar.2012.00012 accessed 30 August 2023.
[231] Esteve Trias et al., 'The Hospital Exemption Pathway for the Approval of Advanced Therapy Medicinal Products: An Underused Opportunity? The Case of the CAR-T ARI-0001' (2022) 57 Bone Marrow Transplantation 157.

personnel, facilities, and expertise) that would be required to develop the use of the HE.

6.2.2 Legal and Ethical Considerations around current and alternative sustainable pathways for providing CAR-T Therapies

A range of legal and ethical considerations arise in relation to the development and provision of CAR-T therapies to patients, many of these issues have already been discussed where relevant within this report. However, two different legal/ethical issues warrant deeper consideration in particular as part of a broader discussion of CAR-T therapies, namely: 1) the role of intellectual property rights and licensing policies in relation to the development of, and downstream access to CAR-T therapies; and 2) the need to consider broader legal/ethical issues including issues around informed consent, best interests of the child, and other ethical issues which can arise in relation to the provision of CAR-T therapies, particularly for emerging CAR-T therapies. This section again does not purport to offer a comprehensive overview of such issues, instead it offers a brief introduction to some of the key aspects within each context to encourage greater consideration of such issues as part of a broader policy discussion in this field.

CAR-T Therapies and Intellectual Property Rights

First, a range of legal factors can impact the incentives for and downstream access to health-technologies more generally, one factor is the role of intellectual property rights, including patents. A patent right in general terms allows rightsholders to exclude (or stop) others from using that technology without the rightsholder(s)' permission for 20 years, and under the relevant international law, patents must be made available in all fields of technologies including for health-technologies.[232] Patents, and other intellectual property rights such as trade secrets, can have different types of effects

[232] Art 27(2), TRIPS Agreement.

within different areas, and there is considerable debate around such potential effects. On the one hand the potential role of intellectual property rights as an incentive for research and development within the health field is often noted, on the other hand, depending on how patents (and other IPRs) are used over IP protected technologies, such rights can impact the price and downstream access to such technologies.[233] Thus, careful consideration of such issues is needed, which is specific to the technology and field in question.

In the CAR-T therapy context, there are also questions around to what extent certain aspects of CAR-T therapies should be/are patentable in Europe.[234] For example, Art 53(c) of the European Patent Convention 1973, as amended, states that: 'European patents shall not be granted in respect of: c) methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.'

Similar legal provisions apply in other jurisdictions which also limit the patentability of methods of treatment.[235] However, in practice this exclusion from patentability and what qualifies as a 'method of therapy' is often interpreted narrowly including in Europe. Furthermore, many 'technologies' which may relate to CAR-T therapies could also likely be patentable. To date, a range of patents have been granted within the CAR-T therapy field.[236] Such issues, alongside the extent to which patents (and

[233] For a general discussion of such issues, albeit in the context of COVID-19 health-technologies, see: Aisling McMahon, 'Global equitable access to vaccines, medicines and diagnostics for COVID-19: The role of patents as private governance' (2021) 47 Journal of Medical Ethics 142-148.
[234] See discussion, in: Luis Gil Abinader and Jorge L Contreras, 'The Patentability of Genetic Therapies: CAR-T and Medical Treatment Exclusions Around The World' (2019) 34(4) American University International Law Review 705.
[235] Luis Gill Abinader and Jorge L Contreras, 'The Patentability of Genetic Therapies: CAR-T and Medical Treatment Exclusions Around the World' (2019) 34(4) American University International Law Review 705.
[236] On patents within the CAR-T therapy field more generally, see Björn Jürgens & Nigel S Clarke, 'Evolution of CAR T-cell immunotherapy in terms of patenting activity' (2019) 37(4) Nat Biotechnol. 370-375.

patentability) can impact development and access to such therapies warrant deeper consideration at a national and international level.

Moreover, where such patents and other IPRs apply over CAR-T therapies or related technologies, greater consideration is needed around how such rights are used, and the potential role of intellectual property policies to shape the uses of such IPRs. In particular, consideration is needed around the extent to which licensing policies can be used to embed requirements related to increasing broader downstream accessibility of such technologies.[237] Such factors require greater consideration at a national and international level.

Recommendation 9(1): Legal and Ethical Considerations around the Provision of CAR-T Therapies: - **Intellectual Property Rights and the Development of and Access to CAR-T Therapies:** *Consideration should be given around to what extent intellectual property rights are operating in relation to CAR-T therapies in the current context, and in particular, consideration should be given on the extent to which such rights apply over relevant aspects of CAR-T therapies and related technologies, and how such rights may be impacting research and development in the field - in terms of incentivising research, and/or acting as a barrier to access and development of such therapies. Moreover, where relevant, consideration should be given to the potential role for intellectual property licensing policies/principles to encourage socially responsible uses of intellectual property rights over patentable technologies which relate to the provision of CAR-T therapies.*

[237] For a discussion of some of these issues, see: Aisling McMahon, "Accounting for Ethical Considerations in the Licensing of Patented Biotechnologies and Health-Related Technologies: A Justification" in Naomi Hawkins (eds), *Patenting Biotechnological Innovation: Eligibility, Ethics and Public Interest* (Edward Elgar 2022); see also: Jorge Contreras, "'In the Public Interest' - University Technology Transfer and the Nine Points Document – An Empirical Assessment" (2022) Utah Law Faculty Scholarship 339.

Second, a key legal and ethical principle in providing medical treatment, as enshrined in various national and international policies/laws, is the need to ensure informed consent of patients for medical treatment. For adults, provided a patient is competent (i.e., they have capacity to make a medical treatment decision) they must provide adequate informed consent for treatment– this means they should be informed of the treatment process and, as far as possible, of the relevant risks and alternatives to that treatment that may be available. On that basis, they should make an informed decision around whether they wish to have the medical treatment.

For children, appropriate consent for treatment is also needed, in such instances if the child is under 16, generally a parent or guardian can provide consent for treatment and the 'best interests' of the child should be considered. The child's view should also generally be considered (where this is possible, e.g. depending on their age and circumstances) as part of this process.[238] Where a child is over 16 years, Section 23 of the Non-Fatal Offences Against the Person Act 1997, allows the young person aged 16 -17 years to give consent to medical treatment, however, this does not include an entitlement to refuse such treatment *per se.* In the case of disagreements over medical treatment for children, in certain contexts an application can be made to the court[239] however, such contexts are rare in practice, and where this occurs the 'best interests' test is also applied.[240] These factors are important considerations in providing medical therapies, more generally.

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[238] On the right of a children to be heard in the healthcare setting generally, see: Ursula Kilkelly and Mary Donnelly, 'The Child's Right to be heard in the Healthcare Setting: Perspectives of children, parents and health professionals' (2006) https://www.lenus.ie/bitstream/handle/10147/45520/8185.pdf?sequence=1&isAllowed=y accessed 31 August 2023; See also HSE National Consent Policy 73 https://www.hse.ie/eng/about/who/national-office-human-rights-equality-policy/consent/hse-national-consent-policy.pdf accessed 31 August 2023.

[239] 'National Consent Policy Part Two: Children and Minors' https://www.tusla.ie/uploads/content/NationalConsentPolicyPart2.pdf accessed 31 August 2023.

[240] See discussion albeit in the UK context, in: Nuffield Council on Bioethics, 'Disagreements in the care of critically ill children' (Bioethics Briefing Note 2019) available at https://www.nuffieldbioethics.org/publications/disagreements-in-the-care-of-critically-ill-children accessed 31 August 2023:see also: Neera Bhatia, 'Disagreements in the care of critically ill children: emerging issues in a changing landscape' (Literature Review, Nuffield Council on Bioethics 2018) https://www.nuffieldbioethics.org/assets/pdfs/Bhatia-N-2018-Disagreements-in-care-of-critically-ill-children-emerging-issues.pdf accessed 31 August 2023.

In terms of consent, having sufficient information to inform patients of potential treatments/risks is crucial - for approved CAR-T therapies, there are studies which can inform clinicians and patients of the risks and potential benefits of treatment. This in turn allows more information to be provided to patients/families to consider such therapies and potential risks. However, there are still, in some instances, more limited data, especially in relation to long term outcomes of CAR-T therapies which can present some uncertainties, but more studies are emerging in such contexts.

Ethical issues also arise around emerging CAR-T therapy including those being developed under clinical trials, hospital exemptions etc.[241] Again here, adequate consent is required for adults and for children who are deemed clinically suitable for, and are being considered for participation in clinical trials. This can also present difficult ethical considerations.[242] For example, a terminally ill patient may not be clinically indicated for an approved CAR-T therapy, and they may be in a situation where they have tried other treatments which have not been successful. They may have no other viable treatment option remaining. In such instances, availing of a product under a clinical trial (if one becomes available that they are deemed clinically suitable for) may present a last treatment option for a patient. However, undergoing such therapies may also present potential risks/uncertainties, and the therapy may not be successful. In some cases, the patient's health may also deteriorate from the time when they are initially considered suitable for a clinical trial and the point at which the trial starts. Thus, complex ethical considerations can arise which need to carefully considered. Many of these issues are not specific to CAR-T therapies and are similar

[241] For a discussion of some of the ethical issues in relation to access to novel treatments, see: Nuffield Council on Bioethics Briefing Note, 'Patient access to experimental treatments' (2018) available at https://www.nuffieldbioethics.org/publications/experimental-treatments/introduction/ethical-issues-arising-from-the-use-of-experimental-treatments accessed 31 August 2023.

[242] See discussion in: Tisagenlecleucel for B-Cell Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma — Ethics and Implementation Report' (2019) 8 (3d) CADTH at 2.4 https://www.cadth.ca/sites/default/files/pdf/car-t/op0538-tisagenlecleucel-ethics-and-implementation-jan2019.pdf accessed 31 August 2023.

to those encountered for other emerging and innovative therapies within the broader clinical trial contexts, but nonetheless warrant consideration.

Recommendation 9(2): Legal and Ethical Considerations around the Provision of CAR-T Therapies: Consent and Ethical Issues in Provision of Emerging CAR-T Therapies - *CAR-T therapies offer significant potential in the cancer care context including, in some contexts leading to remission for some patients who have no other treatment option. However, and particularly for new and emerging CAR-T therapies, as with other emerging health-technologies, there may be uncertainties and risks for individual patients. Detailed consideration is needed around the legal and ethical considerations in providing CAR-T therapies in certain contexts, including considerations around informed consent, best interests of the child, and developing policies around ethical issues that may arise in the HE, academic CAR and other emerging therapy contexts.*

6.2.3 National Strategy for the Development of CAR-T Therapies

Recommendation 10: Overall, to deliver on current patient needs and to enable the development of sustainable pathways for future CAR-T therapies, it is recommended that a national strategy for the development and provision of ATMPs (including CAR-T therapies) is developed. Such a national plan for Ireland is needed as soon as possible.[243] A national policy of this nature ideally

[243] A national strategy/plan in this area has also been recommended by other recent reports, including: NUI Galway, 'The Benefits of An All-Island Dedicated Centre for ATMP (Advanced Therapy Medicinal Product) Manufacturing' 9 https://www.universityofgalway.ie/atmpstrategy/downloads/All-Island-Dedicated-Centre-for-ATMP-Manufacturing.pdf accessed 30 August 2023; IPHA and PWC, 'Pathfinder Study for the Adoption of Cell and Gene Therapies in Ireland (May 2021), 28 https://www.ipha.ie/wp-content/uploads/2021/05/CGT-Pathfinder-Study-May-2021.pdf accessed 30 August 2023, which called for a 'A CGT adoption policy, guided by a White Paper led by the Department of Health, which draws together proposals for tackling the related strands of assessment, access and reimbursement.'
Moreover, other countries such as the UK have adopted consolidated national approaches to ATMPs, see: NHS England, 'Accelerated Access Collaborative: Early Stage Support for ATMPs & HITs Programme Update' https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2022/03/AAC-Early-Stage-Support-for-ATMPs-and-HITs-Programme-Update.pdf accessed 30 August 2023; Ceri Roberts

should involve a multi-disciplinary approach, which would include consideration of a range of issues including the scientific, clinical, manufacturing, funding, ethical, regulatory and legal opportunities and challenges in this context. As part of this strategy deeper consideration should be given to the following key aspects which are discussed briefly here. However, importantly this is not an exhaustive list of issues:

- **Training and Retention of Relevant Personnel to develop and deliver CAR-T therapies in Ireland:** CAR-T therapies require multi-disciplinary teams to provide all stages of the care from the laboratory stages (bench) to bedside. It is recommended that any national policy would consider the current expertise in Ireland at the basic science research, laboratory, manufacturing and health-practitioner levels, and consider what would be needed in this context to provide CAR-T therapies (and other ATMPs) at a larger scale in Ireland, in addition to existing service delivery, to ensure we are training and retaining sufficient personnel to develop and deliver CAR-T therapies and other ATMPs in Ireland.
- **Space for the development and provision of CAR-T therapies in Ireland:** The provision of CAR-T therapies (and other ATMPs), particularly, as such therapies develop and will likely be provided for other health conditions in future, will require continued investment and provision of adequate space and facilities, including space for laboratory, clinical and storage facilities for the development of these therapies.
- **Academic Research & Funding of CAR-T therapies:** Support for the development of internationally leading academic research is vital in this field. This would develop the potential around academic CAR-T therapies in Ireland and would provide further opportunities in terms of developing more sustainable pathways for CAR-T therapy provision in the longer term. There is a need for significant funding and investment to support basic and translational science

and Rachel Bell, 'UK at the forefront of advanced therapies' (26 August 2021) European Pharmaceutical Review https://www.europeanpharmaceuticalreview.com/article/161176/uk-at-the-forefront-of-advanced-therapies/ accessed 30 August 2023.

and clinical work in the ATMP field, including in the CAR-T therapy context in Ireland.

- **Manufacturing Facilities for CAR-T therapies and other ATMPs in Ireland:** There is a need to consider the manufacturing facilities for ATMP production in Ireland which are vital to support the development and manufacturing of CAR-T therapies in Ireland.[244]
- **Clinical Trials:** Consideration is needed around the clinical trial landscape in Ireland,[245] to understand opportunities and potential challenges to conducting clinical trials in Ireland for ATMPs including CAR-T therapies, and to enable relevant stakeholders to access funding required to develop clinical trials in this field. Moreover, consideration is needed around ensuring protected research time for clinicians and hospital staff to enable their participation in clinical trials and translational research.[246]
- **Biobanking:** There is a need to consider the landscape for biobanking in the CAR-T therapy and in the broader ATMP context in Ireland, and the required additional resources that would be needed to expand this at the highest international standards which will be critical for longer term translational research in the area (including, for example consideration around the funding, personnel and facilities needed etc,). Broader legal and ethical considerations should also be considered in such contexts.

[244] NUI Galway, 'The Benefits of An All-Island Dedicated Centre for ATMP (Advanced Therapy Medicinal Product) Manufacturing' 23 https://www.universityofgalway.ie/atmpstrategy/downloads/All-Island-Dedicated-Centre-for-ATMP-Manufacturing.pdf accessed 30 August 2023, which states that there is "unanimous support for the development of appropriately funded and managed cGMP cell manufacturing facility with a focus on supporting the translational research of academic and commercial centres"

[245] See also: NUI Galway, 'The Benefits of An All-Island Dedicated Centre for ATMP (Advanced Therapy Medicinal Product) Manufacturing' 24 https://www.universityofgalway.ie/atmpstrategy/downloads/All-Island-Dedicated-Centre-for-ATMP-Manufacturing.pdf accessed 30 August 2023.

[246] Protected research time for clinicians and hospital staff in the broader ATMP context in Ireland, is also recommended by: NUI Galway, 'The Benefits of An All-Island Dedicated Centre for ATMP (Advanced Therapy Medicinal Product) Manufacturing' 13 https://www.universityofgalway.ie/atmpstrategy/downloads/All-Island-Dedicated-Centre-for-ATMP-Manufacturing.pdf accessed 30 August 2023

- **Data Collection:** Consideration should be given to the establishment of a central database for the collection of data in relation to patients who receive ATMPs including CAR-T therapies. This would facilitate greater knowledge sharing on the parameters effecting outcomes for such patients and also provide greater insight into the short- and long-term effects of these types of therapies. Broader relevant legal and ethical considerations including around data protection etc should also be considered in such contexts.
- **Regulatory Mechanisms for CAR-T Therapies:** A deeper study is needed around how to enhance the regulatory pathways to develop CAR-T therapies in Ireland, any potential gaps or challenges in the current system, and how to address these. In this context, engagement with the national regulatory authority, the HPRA, and in particular with their Innovation Office is recommended.

7 CONCLUSION AND SUMMARY OF RECOMMENDATIONS

CAR-T therapies offer significant current and future potential for the treatment of certain types of cancers for adult and paediatric patients. Where successful, such therapies can be curative for some patients, meaning that such patients no longer require cancer treatments. Moreover, although CAR-T therapies come with risk of side effects for patients, it must also be borne in mind, that for many patients accessing such therapies, when clinically indicated will be their only potential and viable treatment option, and these therapies can be lifesaving for certain patients. Nonetheless, this can present a range of ethical issues which must be carefully considered.

Given ongoing research and developments in the field, it is likely that there will be an increase in the number of patients who may benefit from CAR-T therapies and other Advanced Therapy Medicinal Products (ATMPs) in the coming years. Accordingly, this could lead to an increased demand for such therapies in Ireland and elsewhere. Yet, there is also a real risk that countries which do not consider strategies for how they will develop CAR-T therapies and other ATMPs in a sustainable and affordable manner in future, will fall behind in the provision and development of such therapies.

Against the current backdrop, this section outlines and summarises the ten main recommendations made in this report which focus on seeking to address some of the main legal, ethical, and broader policy challenges around providing CAR-T therapies in Ireland. At the outset, we acknowledge that a key barrier to providing CAR-T therapies currently is the high cost of such therapies under current commercial avenues. Due to such costs, a difficult tension arises between individual patients needs in accessing these therapies, and the national public health systems challenge in funding these therapies at these high costs given the finite public health budget and other healthcare needs.

In recognition of this challenge and cognisant that for many patients CAR-T therapies are their only potential treatment option, in this section we focus first on the current system can be developed and improved to provide these therapies as far as possible to patients where they are clinically indicated. Second, we focus on the health systems level and *on the longer term* need to build a national strategy to develop more sustainable pathways to provide affordable CAR-T therapies in Ireland in future.

7.1 Recommendations to Address Current Challenges for Patients in Accessing CAR-T Therapies and Related Services in Ireland.

Recommendation 1: Timelines around Decisions on Reimbursement/Provision of CAR-T therapies in Ireland following European Medicines Agency authorisation of CAR-T therapies: *This report recommends the processes and decisions on whether CAR-T therapies will be publicly reimbursed and provided in Ireland are conducted as quickly as possible after new therapies are authorised by the European Medicines Agency. The timeliness of such decisions is particularly important where such therapies are likely to be the only clinically indicated treatment option available to certain patients. In this context, it is also recommended that a deeper study of the potential challenges which may affect the timeline for such decisions/considerations in Ireland is undertaken, and where relevant, deeper consideration is given around any potential avenues to address these challenges.*

Recommendation 2: Financial Assistance for Patients Travelling Significant Distances within Ireland to obtain CAR-T Therapies: *Where CAR-T therapies are provided for some patients at a significant distance to their home, where they and a support person need to travel and obtain accommodation to receive this therapy, it is recommended that further consideration is given to whether, or to what extent, State supports could be extended to such patients and their families to reduce financial burdens.*

Recommendation 3: Regional Centres of Excellence for the Provision of CAR-T Therapies: *Developing additional regional centres of excellence for the provision of CAR-T therapies in Ireland should be considered, where this may be practicable and feasible. Developing such services would require State commitments, including in terms of additional funding, training, facilities, and personnel to ensure these services can be developed, and that all centres are operating at the required best practice international standards. This should be considered as part of an overall national policy approach to the provision of CAR-T therapy (and ATMPs more generally) in the Republic of Ireland (discussed below).*

Recommendation 4: Accessing CAR-T Therapy Abroad for Patients living in Ireland where such CAR-T therapies are not available in Ireland: *The Treatment Abroad Scheme (TAS) was a very important scheme for enabling patients to access CAR-T therapies especially prior to these being provided in Ireland in 2021 and 2022. However, ideally, where it is possible, and feasible, given the additional challenges faced by patients needing to travel abroad to obtain CAR-T therapies, CAR-T therapies should be provided in Ireland for patients ordinarily residing here.*

Nonetheless, CAR-T therapies are evolving rapidly, and not all CAR-T therapies authorised by the EMA are approved for reimbursement and provided in Ireland. Access to such therapies may often be the only remaining potential avenue certain patients have for treatment. Accordingly, this report recommends that the TAS continues to consider patients for CAR-T therapies abroad on a case-by-case basis where these therapies are clinically indicated, where these are not available in Ireland, and where such patients have no other viable treatment option. In such instances, and as far as practicable, this report also recommends consideration around to what extent financial support can be offered to families/patients who need to travel abroad to access CAR-T therapies to assist with the costs of travel abroad and accommodation.

Recommendation 5: The Process for CAR-T Therapies in Ireland: Manufacturing of the Infusion: *We recommend detailed consideration is given around developing and facilitating conditions needed to encourage the manufacturing step of the CAR-T*

therapy for existing therapies to take place in Ireland, and ideally, where possible for this to take place in close proximity to the treating hospital(s). This would reduce the time involved for the CAR-T therapy process from cell collection to re-infusion, reduce the logistical challenges of transporting and freezing/thawing these cells/products abroad, and would likely result in some reduction in costs. However, it would need to be underpinned by the required resources to ensure sufficient additional personnel, training, and large-scale infrastructural supports, including space and specialist facilities required. In the shorter term, further development of the existing expertise and skills already available regarding key aspects, such as aseptic techniques for processing and cryopreservation of cells for haemopoietic stem cell transplantation and CAR-T therapy in Ireland should also be considered.

As will be discussed below, in terms of future developments, the EU pharmaceutical legislation proposes a decentralised manufacturing route for ATMPs. Subject to how this proposal develops at the EU level, it may present an opportunity to facilitate a direct pathway towards manufacturing existing therapies in Ireland.

Recommendation 6: Patients Undergoing CAR-T Therapies: Access to Fertility Preservation Services:

1) *For adult and children undergoing cancer therapies including CAR-T therapies, we recommend consideration around how fertility preservation services are provided in Ireland. In particular, a full review of the current landscape for fertility preservation services for children in the oncology context is needed to ensure such patients can obtain access to funded fertility preservation services which align with best international practice, in Ireland.*
2) *Fertility preservation, including in the oncology context, presents a range of complex legal and ethical issues and it is vital that these issues, are considered and provided for as soon as possible, as part of a broader regulatory approach to Assisted Human Reproduction (AHR). A regulatory framework for AHR is urgently needed in Ireland.*

7.2 Providing Access to CAR-T Therapies for Patients in Ireland: Health-Systems Opportunities and Challenges

Recommendation 7: Costs of CAR-T Therapies

1) ***Novel Reimbursement Models for CAR-T Therapies:*** *A detailed study is needed around the use of novel reimbursement models for CAR-T therapies.*[247] *This should also consider the potential benefits/limitations such approaches could offer to reduce the overall high costs of CAR-T therapies for public health systems.*

2) ***Transparency on Pricing: Transparency around Pricing:*** *At an EU level, greater transparency around how much each EU State is paying to access CAR-T therapies should be considered. Making such information publicly available across EU States would provide greater information for all States and the public.*[248] *It would also be important to consider the need for transparency in pricing as part of a discussion on novel reimbursement mechanisms.*

Recommendation 8: Sustainable Pathways to Develop and Produce Affordable CAR-T Therapies

1) **Manufacturing of CAR-T Therapies in Ireland via existing providers and Decentralised Manufacturing:** *As discussed above an investigation is needed in relation to potential pathways for manufacturing of CAR-T therapies in Ireland, and the extent to which this may be possible under the current system*

[247] These are discussed in the recent: PwC and IPHA, 'Pathfinder Study for the Adoption of Cell and Gene Therapies in Ireland' (May 2021) 26 https://www.ipha.ie/wp-content/uploads/2021/05/CGT-Pathfinder-Study-May-2021.pdf accessed 31 August 2023; See also: Jesper Jørgensen, Eve Hanna and Panos Kefalas, 'Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries' (2020) 8(1) Journal of Market Access & Health Policy 1715536 https://doi.org/10.1080/20016689.2020.1715536 accessed 31 August 2023.

[248] Katrina Perehudoff, 'European governments should align medicines pricing practices with global transparency norms and legal principles' (2022) 16 Lancet Europe Regional https://doi.org/10.1016/j.lanepe.2022.100375 accessed 30 August 2023.

and may reduce overall costs of providing CAR-T therapies, and address other challenges. As part of this, an assessment is needed around the infrastructural needs, including personnel, facilities, expertise, and funding needed to facilitate this.

For the reasons highlighted above, and subject to the development of the proposed EU's pharmaceutical legislation in relation to the de-centralised manufacturing of these types of therapies, a deeper study is needed in relation to potential legal/regulatory pathways for decentralised manufacturing of CAR-T therapies in Ireland for existing therapies, and the extent to which this avenue could reduce the costs of providing CAR-T therapies. For all potential pathways, an assessment is needed around the personnel, facilities, expertise, and funding etc needed to facilitate this.

2) **Development of Academic CARs in Ireland:** *In the longer term, and as part of a national plan discussed below, consideration is needed around the potential for greater development of academic CARs in Ireland. From the outset, the development of such academic CARs should also be shaped by, the key goal of achieving accessible CAR-T therapies, and policies should be embedded to achieve this, including, for example, where relevant via socially responsible intellectual property licensing strategies and clauses.*[249] *To develop further academic CARs in Ireland would require sustained investment in academic research, translational medicine, suitably qualified personnel and appropriate facilities for such research in Ireland, including funding for clinical trials.*

[249] International examples of such polices, include: Netherlands Federation of University Medical Centers, 'Ten principles for Socially Responsible Licensing' (June 2019) https://www.nfu.nl/sites/default/files/2020-08/19.4511_Ten_principles_for_Socially_Responsible_Licensing_v19-12-2019.pdf accessed 30 August 2023; See discussion in:

3) **The Use of the Hospital Exemption (HE) for CAR-T therapies for Patients with unmet needs:** *The HE mechanism under Article 28 of the EU ATMP Regulation enables a pathway to develop in-house CAR-T therapies in certain circumstances on an individualised basis for patients where there is an unmet need. This report recommends detailed consideration is given around to what extent the HE pathway could be used for the provision of CAR-T therapies in Ireland in such circumstances, which would map the potential opportunities and challenges/limitations of using the HE mechanisms in such contexts.*

   a. *As part of such a study, at a regulatory level, greater study is needed around the parameters within which the HE mechanism can be used in Ireland for ATMPs, including, how the 'unmet' need requirement could be interpreted in Ireland for CAR-T therapies. Consideration should be given to the experiences of other EU countries where the HE exemption is utilised to develop CAR-T therapies in cases of 'unmet need'.*
   b. *Moreover, a detailed assessment is needed around the current facilities available and the broader additional resources (including funding, personnel, facilities, and expertise) that would be required to develop the use of the HE.*

Recommendation 9: Legal and Ethical Considerations around the Provision of CAR-T Therapies:

1) **Intellectual Property Rights and the Development of and Access to CAR-T Therapies:** *Consideration should be given around to what extent intellectual property rights are operating in relation to CAR-T therapies in the current context, and in particular, consideration should be given on the extent to which such rights apply over relevant aspects of CAR-T therapies and related technologies, and how such rights may be impacting research and development in the field - in terms of incentivising research, and/or acting as a barrier to*

access and development of such therapies. Moreover, where relevant, consideration should be given to the potential role for intellectual property licensing policies/principles to encourage socially responsible uses of intellectual property rights over patentable technologies which relate to the provision of CAR-T therapies.

2) **Consent and Ethical Issues in Provision of Emerging CAR-T Therapies:** *CAR-T therapies offer significant potential in the cancer care context including, in some contexts leading to remission for some patients who have no other treatment option. However, and particularly for new and emerging CAR-T therapies, as with other emerging health-technologies, there may be uncertainties and risks for individual patients. Detailed consideration is needed around the legal and ethical considerations in providing CAR-T therapies in certain contexts, including considerations around informed consent, best interests of the child, and developing policies around ethical issues that may arise in the HE, academic CAR and other emerging therapy contexts.*

Recommendation 10: Overall, to deliver on current patient needs and to enable the development of sustainable pathways for future CAR-T therapies, it is recommended that a national strategy for the development and provision of ATMPs (including CAR-T therapies) is developed. Such a national plan for Ireland is needed as soon as possible.[250] *A national policy of this nature ideally*

[250] A national strategy/plan in this area has also been recommended by other recent reports, including: NUI Galway, 'The Benefits of An All-Island Dedicated Centre for ATMP (Advanced Therapy Medicinal Product) Manufacturing' 9 https://www.universityofgalway.ie/atmpstrategy/downloads/All-Island-Dedicated-Centre-for-ATMP-Manufacturing.pdf accessed 30 August 2023; IPHA and PWC, 'Pathfinder Study for the Adoption of Cell and Gene Therapies in Ireland (May 2021), 28 https://www.ipha.ie/wp-content/uploads/2021/05/CGT-Pathfinder-Study-May-2021.pdf accessed 30 August 2023, which called for a 'A CGT adoption policy, guided by a White Paper led by the Department of Health, which draws together proposals for tackling the related strands of assessment, access and reimbursement.'
Moreover, other countries such as the UK have adopted consolidated national approaches to ATMPs, see: NHS England, 'Accelerated Access Collaborative: Early Stage Support for ATMPs & HITs Programme Update' https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2022/03/AAC-Early-Stage-Support-for-ATMPs-and-HITs-Programme-Update.pdf accessed 30 August 2023; Ceri Roberts

should involve a multi-disciplinary approach, which would include consideration of a range of issues including the scientific, clinical, manufacturing, funding, ethical, regulatory and legal opportunities and challenges in this context. As part of this strategy deeper consideration should be given to the following key aspects which are discussed briefly here. However, importantly this is not an exhaustive list of issues:

- **Training and Retention of Relevant Personnel to develop and deliver CAR-T therapies in Ireland:** *CAR-T therapies require multi-disciplinary teams to provide all stages of the care from the laboratory stages (bench) to bedside. It is recommended that any national policy would consider the current expertise in Ireland at the basic science research, laboratory, manufacturing and health-practitioner levels, and consider what would be needed in this context to provide CAR-T therapies (and other ATMPs) at a larger scale in Ireland, in addition to existing service delivery, to ensure we are training and retaining sufficient personnel to develop and deliver CAR-T therapies and other ATMPs in Ireland.*
- **Space for the development and provision of CAR-T therapies in Ireland:** *The provision of CAR-T therapies (and other ATMPs), particularly, as such therapies develop and will likely be provided for other health conditions in future, will require continued investment and provision of adequate space and facilities, including space for laboratory, clinical and storage facilities for the development of these therapies.*
- **Academic Research & Funding of CAR-T therapies:** *Support for the development of internationally leading academic research is vital in this field. This would develop the potential around academic CAR-T therapies in Ireland and would provide further opportunities in terms of developing more sustainable pathways for CAR-T therapy provision in the longer term. There is a need for significant funding and investment to support basic and translational science*

and Rachel Bell, 'UK at the forefront of advanced therapies' (26 August 2021) European Pharmaceutical Review https://www.europeanpharmaceuticalreview.com/article/161176/uk-at-the-forefront-of-advanced-therapies/ accessed 30 August 2023.

and clinical work in the ATMP field, including in the CAR-T therapy context in Ireland.

- **Manufacturing Facilities for CAR-T therapies and other ATMPs in Ireland:** *There is a need to consider the manufacturing facilities for ATMP production in Ireland which are vital to support the development and manufacturing of CAR-T therapies in Ireland.*[251]
- **Clinical Trials:** *Consideration is needed around the clinical trial landscape in Ireland,*[252] *to understand opportunities and potential challenges to conducting clinical trials in Ireland for ATMPs including CAR-T therapies, and to enable relevant stakeholders to access funding required to develop clinical trials in this field. Moreover, consideration is needed around ensuring protected research time for clinicians and hospital staff to enable their participation in clinical trials and translational research.*[253]
- **Biobanking:** *There is a need to consider the landscape for biobanking in the CAR-T therapy and in the broader ATMP context in Ireland, and the required additional resources that would be needed to expand this at the highest international standards which will be critical for longer term translational research in the area (including, for example consideration around the funding, personnel and facilities needed etc). Broader legal and ethical considerations should also be considered in such contexts.*

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[251] NUI Galway, 'The Benefits of An All-Island Dedicated Centre for ATMP (Advanced Therapy Medicinal Product) Manufacturing' 23 https://www.universityofgalway.ie/atmpstrategy/downloads/All-Island-Dedicated-Centre-for-ATMP-Manufacturing.pdf accessed 30 August 2023, which states that there is "unanimous support for the development of appropriately funded and managed cGMP cell manufacturing facility with a focus on supporting the translational research of academic and commercial centres"

[252] See also: NUI Galway, 'The Benefits of An All-Island Dedicated Centre for ATMP (Advanced Therapy Medicinal Product) Manufacturing' 24 https://www.universityofgalway.ie/atmpstrategy/downloads/All-Island-Dedicated-Centre-for-ATMP-Manufacturing.pdf accessed 30 August 2023.

[253] Protected research time for clinicians and hospital staff in the broader ATMP context in Ireland, is also recommended by: NUI Galway, 'The Benefits of An All-Island Dedicated Centre for ATMP (Advanced Therapy Medicinal Product) Manufacturing' 13 https://www.universityofgalway.ie/atmpstrategy/downloads/All-Island-Dedicated-Centre-for-ATMP-Manufacturing.pdf accessed 30 August 2023

- **Data Collection:** *Consideration should be given to the establishment of a central database for the collection of data in relation to patients who receive ATMPs, including CAR-T therapies. This would facilitate greater knowledge sharing on the parameters effecting outcomes for such patients and also provide greater insight into the short- and long-term effects of these types of therapies. Broader relevant legal and ethical considerations, including around data protection etc should also be considered in such contexts.*
- **Regulatory Mechanisms for CAR-T Therapies:** *A deeper study is needed around how to enhance the regulatory pathways to develop CAR-T therapies in Ireland, any potential gaps or challenges in the current system, and how to address these. In this context, engagement with the national regulatory authority, the HPRA, and in particular with their Innovation Office is recommended.*

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