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Availability and financing of CAR-T cell therapies: A cross-country comparative analysis

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ABSTRACT

Chimeric antigen receptor T-cell therapies (CAR-T therapies) are a type of advanced therapy medicinal product (ATMP) that belong to a new generation of personalised cancer immunotherapies. This paper compares the approval, availability and financing of CAR-T cell therapies in ten countries. It also examines the implementation of this type of ATMP within the health care system, describing the organizational elements of CAR-T therapy delivery and the challenges of ensuring equitable access to all those in need, taking a more systems-oriented view. It finds that the availability of CAR-T therapies varies across countries, reflecting the heterogeneity in the organization and financing of specialised care, particularly oncology care. Countries have been cautious in designing reimbursement models for CAR-T cell therapies, establishing limited managed entry arrangements under public payers, either based on outcomes or as an evidence development scheme to allow for the study of real-world therapeutic efficacy. The delivery model of CAR-T therapies is concentrated around existing experienced cancer centres and highlights the need for high networking and referral capacity. Some countries have transparent and systematic eligibility criteria to help ensure more equitable access to therapies. Overall, as with other pharmaceuticals, there is limited transparency in pricing, eligibility criteria and budgeting decisions in this therapeutic area.

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1. Introduction

1.1. CAR-T therapy: background

Chimeric antigen receptor (CAR) T-cell therapies (CAR-T therapies) are Advanced Therapy Medicinal Products (ATMPs) that belong to a new generation of personalised cancer immunotherapies, where specialists collect the patients' own immune cells and modify them to target cancer cells. Current commercially available CAR-T therapies treat haematological cancers, including B-cell acute lymphoblastic leukaemia (ALL), diffuse large B-cell lymphoma (DLBCL), Mantle cell lymphoma (MCL) and multiple myeloma. In March 2022, more than 30% of all approved ATMPs in the United Kingdom (UK) and European Union (EU) were CAR-T therapies [1]. Over 63% of newly developed CAR-T treatments target proteins of haematological cancers, with 37% targeting solid tumours. The top three tumour types tested in clinical research are gastrointestinal (10%), breast (6%) and nervous system (6%) [2].

CAR-T cell therapies involve modifying T-cells, which are white blood cells that play a crucial role in the immune system. T-cells naturally target specific foreign particles (antigens) and are vital in fighting infections and cancer. The cellular memory of the immune response can persist and control disease over time [3]. Scientists can program T-cells to identify specific proteins, such as the CD19 or B-cell maturation antigen (BCMA), present on the surface of cancer cells. This is achieved by adding a new piece of genetic code to create a chimeric antigen receptor (CAR). T-cells with a CAR (CAR-T cells) can then recognise cancer cells and attack them more effectively [4].

This technology offers promising effects such as high and long-term remission rates, including improved survival [5–7]. However, it also carries risks like cytokine release syndrome (CRS) or neurotoxicity, making careful planning and well-coordinated multidisciplinary collaboration essential for successful treatment [8]. Additionally, the uncertainty surrounding the long term effects of these novel therapies, coupled with their high costs, raise concerns about their system-wide implementation [9]. (Box 1)

1.2. CAR-T therapies available on the market

In 2017, the Food and Drug Administration (FDA) in the United States (USA) approved the first CAR-T cell therapy (Kymriah®) for adult patients with certain types of lymphoma and for children and young adults with acute lymphoblastic leukaemia (ALL) who have not responded to other treatments. As of July 2022, there were six CAR-T therapies authorised by the FDA, the European Medicines Agency (EMA) and some of them by Health Canada and the Swiss Agency for Therapeutic Products (Swissmedic). Table 1 provides an overview of authorised CAR-T cell therapies, the diseases they target, and eligible patients.

All CAR-T therapies are indicated for patients who have completed at least two rounds of systematic therapy and/or have refractory cancers (i.e. *cancers that are resistant at the beginning of treatment or become resistant during treatment)* or are in their second (or subsequent) relapses. While these therapies are generally for adults, Novartis's Kymriah® is also authorised for treating paediatric patients with ALL.

Since these CAR-T products are produced on demand, their accessibility depends on success in overcoming several challenges. First, whether manufacturing agreements are in place and sufficient infrastructure for manufacturing is available in the region. Second, whether therapy delivery centres and the necessary staff with the necessary skills are available. Third is financial accessibility - whether these expensive treatments can be covered by public payer mechanisms and any limitations on the number of therapies that can be reimbursed by public funds. Extensive research has shown that not all ATMPs, including recently approved CAR-T products, are made available to patients for a number of reasons. Pricing and reimbursement are the first obstacles to accessibility [10].

Against this backdrop, the objective of this analysis is to explore the involvement of selected health systems in providing CAR-T therapies to patients, specifically with regard to accessibility and delivery challenges. The main elements of interest are: (1) to identify the financing models applied to CAR-T therapies – given their costs – and explore the potential implications of full coverage for pharmaceutical budgets; (2) to understand the infrastructural capacities and delivery models in different settings; and (3) to draw lessons for policymakers involved in decision-making around ATMPs.

2. Methods

2.1. Framework

This study was initiated through the Health Systems and Policy Monitor (HSPM) Network, hosted by the European Observatory on Health Systems and Policies [11]. Following a research pitch by network members at the HSPM 2020 annual meeting, a rapid review of published and grey literature was conducted, focusing on the period between

Table 1
Overview of authorised CAR-T therapies as of November 2022.

CAR-T Technology	Product name	Company	Authorised by FDA	Authorised by EMA	Authorised by Health Canada	Authorised by Swissmedic	Disease	Eligible patients
Tisagenlecleucel	Kymriah®	Novartis	30 May 2017	23 August 2018	September 2018	18 October 2018	B-cell acute lymphoblasticleukemia (ALL), Diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL)	ALL - up to 25 years, Other conditions - Adults
Axicabtagene ciloleucel	Yescarta®	Kite Pharma / Gilead	18 October 2017	23 August 2018	February 2019	17 April 2019	Diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma and follicular lymphoma (FL)	Adults
Brexucabtagene autoleucel	Tecartus®	Kite Pharma / Gilead	24 July 2020	14 December 2020	August 2021	25 August 2021	Mantle-cell lymphoma	Adults
Lisocabtagene maraleucel	Breyanzi®	Juno Therapeutics / BMS	02 May 2021	4 April 2022	May 2022	28 March 2022	Diffuse large B-cell lymphoma	Adults
Idecabtagene vicleucel	Abecma®	Bluebird Bio / BMS	26 March 2021	18 August 2021	May 2021	20 August 2021	Multiple myeloma	Adults
Ciltacabtagene autoleucel	Carvykti®	Janssen	28 February 2022	26 May 2022	N/A	N/A	Multiple myeloma	Adults

Note: N/A – not authorised as of 1 November 2022.

August 2018 (time of EMA market approval for the first CAR-T therapy) and September 2020 (see Annex 1). It aimed to identify key themes around the availability and delivery of CAR-T therapies towards informing the conceptualization of the analytical framework for the cross-country comparison.

The resulting framework comprises five main components (see Fig. 2): i) the authorization of CAR-T therapies and their availability; ii) funding mechanisms; iii) the potential expenditure on CAR-T therapy in relation to total pharmaceutical budget; iv) the delivery model and availability of referral networks; and v) equity considerations, particularly regarding whether eligibility criteria for treatment have been established.

2.2. Questionnaire and data collection

As detailed information on the above dimensions is rarely publicly available, a standardised questionnaire was developed based on the framework presented in Fig. 2 to collect relevant data from national experts in the HSPM network countries (see Annex 2). The national experts were initially contacted in August 2020 and asked to complete the survey, reviewing national documents, and drawing on their own experience and that of professional experts. The questionnaire was explicitly limited to two commercial CAR-T therapies, Kymriah® and Yescarta®, as a reasonable period of time had elapsed between market access (2018) and the time of the survey. Completed questionnaires were returned for Belgium, Canada, England, Hungary, Italy, Latvia, Malta, Norway, Spain, and Switzerland by March 2021.

To estimate the financial impact that CAR-T therapies could have on pharmaceutical budgets (item iii of the framework), country experts were asked to provide available information on official drug prices and the estimated number of patients to be treated annually, with 2020 as a baseline year (Table 3). On this basis, cost projections were put in relation to national pharmaceutical expenditure published in the OECD Health Statistics to provide an idea of the magnitude of costs of CAR-T therapies [12]. We did not distinguish between paediatric patients with the B-cell acute lymphoblastic leukaemia (ALL) or adult patients with DLBCL. In addition, we did not include estimates for associated costs such as hospital care or bridging/conditioning therapy as shown in the patient pathway (Box 1 or Annex 3). According to some estimates, these costs can reach up to EUR 40 000 per case [9]. A comprehensive budget impact analysis was beyond the scope of this study.

The analysis and validation of the survey results was completed by December 2021, followed by a second round of rapid literature review. The objective of the second review was to complement initial findings with newly published work, given the rapid development in the field of gene and cell therapies in oncology. It was undertaken using the same search strategy (see Annex 1) and included literature published between January 2020 and May 2022.

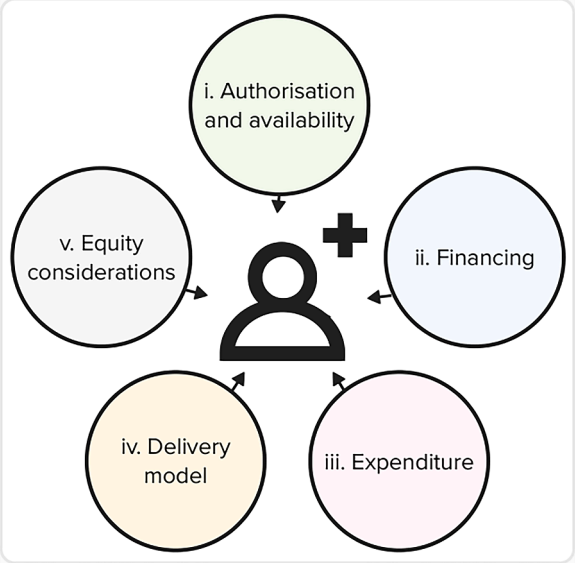

Fig. 2. Framework for analyzing CAR-T therapy across countries.

3. Results

3.1. Availability of CAR-T therapies

Most available commercial CAR-T therapies have been approved by the FDA, the EMA, Health Canada, and Swissmedic (Table 1).

EU regulations for the authorization of orphan drugs, including CAR-T therapies, apply for all Member States and applied to the United Kingdom (England) until the end of 2020. Consequently, the approved indications for Kymriah® and Yescarta® are identical throughout EU Member States. Kymriah® is indicated for treating B-cell acute lymphoblastic leukaemia (ALL) in patients up to 25 years and Diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma; while Yescarta® is indicated for the treatment of DLBCL and Primary mediastinal large B-cell lymphoma (PMBCL). In all the countries studied, CAR-T therapy is first offered to those who have not responded to two or more previous treatments. Age limits apply in certain countries: in Italy, the age limit for treatment of DLBCL with Yescarta® is limited to 70 years, and with Kymriah® to 75 years [13]. Health Canada approved the two products with similar terms with the exception of paediatric ALL patients, who have to be at least three years old in order to undergo CAR-T therapy with Kymriah®.

However, despite the blanket applicability of the centralised EMA approval, CAR-T therapies had not been launched in all European countries in the sample at the time of writing. For example, Latvia doesn't deliver or reimburse this treatment at all; Hungary and Malta do

Box 1
Example of a patient pathway with CAR-T therapy

Treatment with CAR-T cells includes multiple steps and involves numerous health system stakeholders. A generalised overview of how the patient and the health system interact in the complex provision of a single CAR-T therapy session is illustrated in Fig. 1 (more detailed illustration in Annex 3). Generally, if a patient is deemed eligible for CAR-T treatment, they will be referred to the therapy provider. The administration of CAR-T therapies is possible in designated cancer centres. Due to the high toxicity of the treatments, these centres must be able to ensure immediate care in the case of any adverse event (such as CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), other infections, and cytopenias). The actual therapy occurs over several stages: first, the treatment facility performs leukapheresis (*collection of patient's T lymphocytes),* then sends the cells to the CAR-T manufacturing site. While the individual's cells are being reprogrammed in the lab, the patient receives a bridging therapy, followed by a conditioning therapy prior to the reinfusion of the reprogrammed CAR-Ts. After the administration of the medical product, the patient remains in the facility, or at least in close proximity, in order to be monitored. After approximately 30 days of management by the therapy provider, the patient is released to the referring oncologist.

not systematically provide CAR-T therapies, but have covered treatment administered abroad on occasion. In the case of Malta, the bilateral agreement allows haematology patients requiring an ATMP to be treated in the UK [10]. Furthermore, at the time of writing (July 2022), adult patients with DLBCL in Norway could not receive Kymriah® or Yescarta® within the country.

3.2. Financing CAR-T therapies

Due to their potential to address unmet medical needs and promising treatment outcomess, countries are increasingly opting to reimburse these therapies, despite their high cost and scarcity of sufficient evidence at launch. This is often achieved through a conditional coverage, which involves further exploration of risk-sharing schemes already used for reimbursing other cancer medicines [14–16]. Based on the survey responses, managed entry agreements (MEAs) proved to be common for the reimbursement for CAR-T, with 1) individual performance-based MEAs and 2) coverage with evidence development (CED) schemes based on population data mentioned most frequently. In individual performance-based MEAs, the assessment of outcomes was linked to payment schemes, where payment only occurs if the desired response is achieved. CED requires the collection of evidence at the population level to inform reappraisal or pricing and reimbursement negotiations [17]. (Table 2)

In Switzerland, health insurers and hospitals have entered into tariff agreements that define the terms of CED for CAR-T therapies in addition to the diagnosis-related-group (DRG) flat rate. The reimbursement of CAR-T therapies is temporarily included in the benefits basket provided by health insurers, until further evidence is developed. The exact price for the therapies remains confidential. However, it is known that health insurers, hospitals and pharmaceutical companies may negotiate price reductions on a case by case basis [18,19].

The Belgian National Institute for Health and Disability Insurance (NIHDI-INAMI-RIZIV) Drug Reimbursement Commission (CRM) proposed a population-based CED reimbursement scheme for CAR-T therapies but with three staged payments. (Table 2)

Table 2
Overview of reimbursement mechanisms in selected countries.

	Kymriah®		Yescarta®	
	MEA (outcome-based or CED)	Standard reimbursement	MEA (outcome-based or CED)	Standard reimbursement
Belgium	✓ CED (in 3-staged payments)		✓ CED (in 3-staged payments)	
Canada	✓ CED		✓ CED	
Hungary	Public payer reimbursement program under development			
Italy	✓ Outcome-based (in 3-staged payments)		✓ Outcome-based (in 3-staged payments)	
Latvia	There is a possibility of reimbursement for treatment abroad, no further details available			
Malta	Treatment for haematology patients reimbursed in the UK			
Norway		✓		N/A
Spain	✓ Outcome-based (in 2-staged payments)		✓ Outcome-based (in 2-staged payments)	
Switzerland	✓ CED		✓ CED	
United Kingdom (England)	✓ CED		✓ CED	

Note: N/A – not available. CED – coverage with evidence development, MEA – managed entry agreement.

The details of MEAs signed in Canada are unknown, although recommendations for further price reductions and direct interprovincial agreements were issued by the Canadian Agency for Drugs and Technologies in Health (CADTH). Accordingly, the responsibility for funding and providing CAR-T therapies, falls on provincial governments. In Ontario, Canada, funding for CAR-T therapy is regularly negotiated to meet demand and comes from the provincial cancer agency, Cancer Care Ontario [20] (now part of Ontario Health), which receives its budget from the provincial ministry of health. Since August 2020 the provincial government of Alberta has been partnering with the Alberta Cancer Foundation on a CAD 15 million (EUR 9 million) program to offer CAR-T therapy in the province.

In England, due to the high uncertainty and limited clinical data available, the National Institute for Health and Care Excellence (NICE) did not recommend Kymriah® and Yescarta® for routine use due to the high level of uncertainty and limited clinical data available, but instead approved access to these treatments through the Cancer Drugs Fund (CDF), which was also linked to the generation of evidence on real-world evidence of effectiveness [21]. In January 2023 (after the closing date of the survey underpinning this paper), NICE recommended Yescarta® for routine use in adults with DLBCL and at a list price of GBP 208 451 (approx. EUR 245 000), following a review of real-world data to address clinical uncertainties remaining from the original technology appraisal [22]. Final approval of Kymriah® for children and young adults with ALL followed in April 2024 at a list price of 282 000 GBP (approx. 332 000 EUR) per infusion [23]. Both listed prices are publicly available, but there is a confidential discount applied to them [22,23].

In Italy, the MEAs for CAR-T therapies take the form of "payment by result" and are generally limited to 18 months. For treatment with Kymriah®, the payments are processed in three steps: at the beginning of treatment, 6 months and 12 months (only in case of a remission). For Yescarta® they occur at 6, 9 and 12 months after administration of treatment. CAR-T therapies are funded for eligible patients by the Fund for Innovative Drugs; the innovation status of Kymriah® was valid from August 2019 to August 2022 and for Yescarta® from November 2019 to November 2022. CAR-T therapies are considered innovative due to their therapeutic need, added value, and robust scientific evidence. Drugs with this status can be made available to patients immediately, even without formal inclusion in reimbursement lists through regional hospital therapeutic schedules [24]. After the innovative status of the products comes to an end, the financial responsibility for the treatments will fall to the regional budgets (which provide health services to its population) [24]. Monitoring of pharmaceutical effectiveness through registries is a longstanding tradition in Italy [25]. This allows for the evaluation of the therapy performance in clinical practice. In the case of CAR-T therapies, it supports the implementation of MEAs and enables further evidence development based on the real-world data [26].

The Spanish National Health System reimburses Kymriah® in two outcome-based staged payments: the first one (50%–52% of the full list price) takes place upon treatment administration, whereas the second one (50%–48%) occurs after 18 months, given that the patient has achieved and sustained the expected response to the treatment. For Yescarta® the payment scheme is similar: two-staged payments, where the first (36% of the full list price) happens upon the therapy delivery and the second (64%) 18-months later linked to the patient's survival. Other details concerning the MEA remain confidential [27,28]. In terms of further investigation of treatment effectiveness, different solutions were established. In Spain, the individual CAR-T patients' data are collected in the web-based VALTERMED registry, developed by Spanish Ministry of Health, which should help to determine the therapeutic value in real-world settings [29].

3.3. Estimated expenditure on CAR-T therapy

It is important to note that price agreements between industry and payers are mostly confidential; therefore, only list prices or rough estimates of costs are available. In most cases, these costs include only the prices for the CAR-T product itself, but not the treatment pathway (Table 3). Italy and Spain listed a price of EUR 320 000 for Kymriah® and EUR 327 000 for Yescarta® without specifying additional treatment costs or terms for the staged payments. In Belgium, Kymriah® costs EUR 280 000 (ex-factory list price) on the day of administration, plus payments of EUR 20 000 at 6 and 12 months. Yescarta® has been reimbursed with the price EUR 287 000 (ex-factory list price) on the day of administration, plus payments of EUR 20 000 at 12 and 20 months [30]. In Norway, the Kymriah® Single Technology Assessment report mentions the public price for tisagenlecleucel at NOK 3 167 606 [approx. EUR 317 000] [31]. Publicly available information on prices for CAR-T therapies in Switzerland also indicates similarly high levels – around CHF 300 000 (approx. EUR 270 000).

Overall, the total cost of CAR-T therapy, accounting only for the pharmaceutical products and based on the official ex-factory prices, corresponds to an average of EUR 45.4 million (EUR 6.3 million to EUR 89.6 million), or 0.28% (0.20% to 0.37%) of pharmaceutical expenditure annually (using 2020 as a reference year, Table 3).

3.4. Delivery model

CAR-T therapies are provided at designated cancer centres, which are often embedded in the system of institutions (mainly large tertiary hospitals) or part of a network of collaborating centres (university hospitals). The number of treatment locations in the selected countries are shown in Table 4.

Generally, the number of centres qualified to provide CAR-T therapies ranges between 0.02 and 0.05 per 100 000 inhabitants in the selected countries. With the current capacity, Switzerland, Belgium and England treat more patients per 100 000 than the other countries in the sample (1.09, 0.44 and 0.42 per 100 000 population, respectively) (Table 4). Yet, for further assumptions of performance in CAR-T therapies delivery, disease prevalence needs to be considered. In Norway, the only provider of CAR-T therapies is the Radium Hospital (part of the Oslo University Hospital), which has also become the centre for the development of non-commercial CAR-T products (see Discussion). By 2022, ten centres in only four provinces in Canada - Ontario, Quebec, Alberta, and Nova Scotia - could provide CAR-T therapies to their residents or those referred from other provinces.

In five out of the seven surveyed countries which provide CAR-T therapies, referral networks have been established. These mostly build on existing national referral systems, e.g., for stem-cell transplantation, to organise the referral of patients for CAR-T therapies (Belgium, Canada, England, Italy, Spain). In Italy, institutions from the National Cancer Network "Alliance Against Cancer" (*Alleanza Contro il Cancro, ACC*) have organised themselves as a referral network.

The delivery model for CAR-T therapy relies on tertiary care providers and related laboratory and hospital infrastructure. To be able to manage potential severe risks associated with the administration of these treatment, the designated CAR-T therapy centres have to fulfil strict quality and safety criteria, and in most cases should 1) have accreditations from the Joint Accreditation Committee of the International Society for Cell & Gene Therapy (JACIE) and the European Society of Blood and Marrow Transplantation (EBMT); 2) be certified as the national transplant centre; 3) have an intensive care and resuscitation unit; for the allogeneic transplant: include clinical unit, unit of collection and processing unit and 4) offer a multidisciplinary team suitable for the clinical management of the patient and possible complications [36]. These criteria are similar throughout the studied countries and defined at national level.

3.5. Equity considerations

In addition to the eligibility criteria defined by the manufacturer and (national) regulators [37,38], some countries have established national clinical or expert panels to grant approval and prioritise patients. Based on the studied countries, these criteria mainly refer to clinical indications rather than other characteristics. For instance, in the English National Health Service (NHS), capacity has not been a problem for young patients with ALL. However, for lymphoma patients, a National CAR-T Clinical Panel (NCCP) had to prioritise adult patients before the final evaluation in 2023 due to the limited financial resources of the system. This meant that not all patients who could benefit from the therapy were able to do so. After January 2023, the role of the NCCPs became more about providing expert clinical advice on CAR-T therapies, ensuring the clinical eligibility of patients, monitoring the outcomes of these patients at different stages of treatment, and prioritising patients

Table 3
Estimated expenditure on CAR-T therapies, based on list prices of Kymriah® and numbers of patients treated in 2020.

Country	Approx. price per treatment, local currency[a]	Approx. price for treatment, EUR[b]	Number of patients treated	Approx. CAR-T budget, total, EUR, mln	Pharmaceutical expenditure, EUR[c], mln	Share of the CAR-T budget in general pharmaceutical expenditure, %,
Belgium	320 000 EUR	320 000	51	16.3	5754.3	0.28
Canada	NA	320 000	153	49.0	24,602.3	0.20
Hungary					2717	0.00
Italy	320 000 EUR	320 000	236[d]	75.5	28,227	0.27
Latvia					502.1	0.00
Malta					310.8	0.00
Norway	3 167 606 NOK	316 761	20[e]	6.3	2796.4	0.23
Spain	320 000 EUR	323 500	160[f]	51.8	18,117.6	0.29
Switzerland	300 000 CHF	307 000	95[g]	29.2	7957.7	0.37
United Kingdom (England)	NA	320 000	280[e]	89.6	29,849.6	0.30

Note: NA - not available.

[a] For Canada and England a price of 320 000 EUR was used for the calculations because no data on price was available upon the survey conduction;.

[b] Local prices were changed to EUR, given the average exchange rate in 2020, provided by European Central Bank: 1 CAD = 0.6 EUR, 1 CHF = 0.9 EUR, 1 GBP = 1.1 EUR, 1 HUF = 0.003 EUR, 1 NOK = 0.1 EUR. [32];.

[c] OECD Health Statistics [12], 2020, for Malta – Eurostat, 2020;.

[d] [33];.

[e] for Norway and the UK (England) - an estimate of patients eligible for treatment, but not patients received treatment;.

[f] [34];.

[g] [35].

Table 4
Delivery of CAR T therapies in selected countries, 2020.

Country	Number treatment centres	Number of centres per 100 000 population	Total population, mln. [a]	Referral Network (Yes / No)	Total number of patients	Number of patients per 100 000 population
Belgium	4	0.03	11.54	✓	51	0.44
Canada	10 [b]	0.03	37.74	✓	153[c]	0.41
Hungary	The first national centre at the Central Hospital of Southern Pest National Institute of Haematology and Infectious Diseases to be opened in 2023	NA	9.71			
Italy	20[c]	0.03	59.07	✓	236	0.40
Latvia		NA	1.88			
Malta		NA	0.52			
Norway	1	0.02	5.41		20	0.37
Spain	8[d]	0.02	47.33	✓	160	0.34
Switzerland	4	0.05	8.7		95	1.09
United Kingdom (England)	12	0.02	67.33	✓	280	0.42

[a] World Bank, 2020;.
[b] Of which 4 are in Ontario, 3 in Quebec, 2 in Alberta, and 1 in Nova Scotia;.
[c] [33];.
[d] [34].
Note: NA (not available).

for treatment according to the capacity of the centres and the distribution of patients [39].

In Italy, the eligibility criteria formalise the requirements used in clinical trials conducted by the pharmaceutical companies and listed in the Italian Medicines Agency's reports. Although this ensures that patients who are likely to benefit from the treatment are prioritised, it may inadvertently exclude diverse patient populations that don't meet strict clinical criteria.

To receive CAR-T therapy in Spain, prospective patients must apply to the national expert group, which evaluates eligibility on a case-by-case basis. In 2020, a total of 265 treatment applications for CAR-T therapy were received from 138 hospitals covering all 17 Spanish regions. Of these, 242 requests were granted access to the therapy. However, as shown in Tables 3 and 4, only 160 patients actually received treatment [34]. This gap may indicate challenges with capacity or logistics as well as potential decline in the clinical status of patients that could hinder the administration of therapy.

4. Discussion

This study has identified a number of trends regarding the availability and affordability of CAR-T therapies in different countries along the five areas of i) availability, ii) financing, iii) potential pharmaceutical expenditure, iv) delivery, and v) equity. The following sections each focus on one area.

4.1. Availability is inconsistent across member states

Despite the centralised approval by the EMA, CAR-T therapies are currently not reimbursed in some EU Member States within our sample, specifically Hungary, Latvia and Malta. Additionally, the reimbursement of Kymriah® and Yescarta® is limited in countries outside our sample, such as Bulgaria, Czechia, Denmark, Iceland, Slovenia and Sweden [10]. In Denmark, reimbursement decisions for both Kymriah® and Yescarta® for Diffuse Large B-cell Lymphoma (DLBCL) were negative, aimed at controlling expenditure. Similarly, in Sweden, Kymriah® is not reimbursed for DLCBL [10]. The reimbursement landscape for newer CAR-T therapies, such as Tecartus® and Abecma® (see Table 1), is even more restricted, with only France, Germany, Italy, and Spain having made any arrangements [10].

Inconsistent availability may be due to several factors: the health system's inability to provide the therapy due to its high cost (as seen in the reimbursement), a lack of necessary infrastructure in the laboratory and/or hospital setting, the absence of specialised knowledge, and unpredictable demand, especially in smaller countries like Malta. Additionally, pharmaceutical companies may choose not to launch their products in certain countries. The newly proposed EU Pharmaceutical Regulation [40] and Pharmaceutical Directive [41] (April 2023) aim to incentivise the industry to launch therapies in all EU countries within two years. This incentive includes extended market exclusivity and seeks to create a single European market for medicines. It is unclear whether these changes will impact the accessibility of ATMPs across Member States, as the development of these products is costly and time-consuming, requiring enhanced delivery capacity, and affordability issues would still need to be addressed.

The proposal also introduces measures to improve the application of the hospital exemption rule for ATMPs, including measures for collectng and reporting safety and efficacy data. Currently, the application of this rule varies between Member States [42]. A more consistent use of 'hospital exemptions' could help address the high cost of commercial products [42] and encourage the development of 'local' treatments, further tackling unmet need [43].

4.2. Development of 'local' treatments can enhance CAR-T accessibility

One way to increase the availability and affordability of these innovative technologies is to reduce their cost by investing in the development of 'local' CAR-T therapies. Taking advantage of the existing 'hospital exemption' authorisation pathway in European regulation, university hospitals in several countries, including Belgium, Canada, Italy, Norway, Spain and Switzerland, are actively engaged in this effort.

A notable example is CAR-T ARI-0001, developed by the Hospital Clínic in Barcelona for patients over 25 with lymphoblastic leukemia resistant to conventional treatments [43]. The Spanish Agency for Medicines and Health Products (AEMPS) approved its use in February 2021 [44]. Its price has been set at EUR 89 270 and it has been included in the Spanish reimbursement package since June 2021 [45]. The product was granted a conditional licence for three years, subject to a follow-up annual report and re-evaluation of the data for a further five-year renewal. (44) Although this example illustrates the possibilities of such developments, in Spain there are limitations to making the therapy available to patients from other hospitals, as national legislation only grants the licence to the hospital developer, whereas the European Regulation limits the use of these products to the same Member State in which they were developed.

In addition, the Radium Hospital in Norway became a ground for the

development and manufacturing of non-commercial CAR-T therapies with first results to undergo the trials [46]. In Italy, additional funding was designated to research hospitals (*Istituti di Ricovero e Cura a carattere Scientifico, IRCCS*) belonging to the Italian Alliance Against Cancer (ACC) oncologic network and involved in the development of new oncologic CAR-T therapies [47].

4.3. Conditional reimbursement is the primary financing model for CAR-T treatments

Financing policies for ATMPs in different countries can reflect purchasing power, health system priorities, experience, and available capacities and/or the population's clinical needs. Due to the initially high cost of developing CAR-T therapies as well as the treatment costs along the patient pathway (see Annex 3), healthcare payers are largely relying on conditional reimbursement to fund these treatments. This is also relevant given the high upfront price for the potential of having a "one shot therapy".

To determine reimbursement, many of the countries in the sample (Belgium, Canada, Italy, Spain, Switzerland, England) use forms of MEAs. These MEAs may include milestone- or outcome-based contracts to account for the uncertainties in clinical evidence but rather they ensure value for money and help to facilitate a process by which real-world evidence is generated. Individual performance-based agreements, which are present in Italy and Spain, concern ensuring that only eligible patients receive treatment, sometimes with assessment of outcomes to determine treatment continuation (appropriate use) or linked to payment schemes (paying only if response achieved or refund if response not achieved) [16,48].

In Belgium, Canada, and England the MEAs cover CAR-T treatments on the basis of evidence collection to inform re-appraisal or pricing re-negotiations. Furthermore, payment models for CAR-T therapies can be distinguished as a one-time (one-shot) payment or staged payments spread over time regardless of MEAs. One-shot payments are less common in the financing of expensive and complex treatments because their costs occur up front, whereas benefits accrue over a lifetime [17,49].

In terms of funding, most countries have used their public/statutory healthcare budget, while others have used special funds created for specific disease areas, such as the *Cancer Drugs Fund* (CDF) in the UK or *Fund for Innovative Oncology Drugs* in Italy. The extent to which such funds ensure better access to appropriate medicines while making best use of health system resources remains controversial. One of the challenges is that such funds may be short-term and divert resources specifically to cancer, raising questions about the equity of the resource allocation within the broader context of population health needs [50].. Furthermore, they may not deliver meaningful value to individual patients and society as a whole if they fund drugs based on uncertain evidence of effectiveness (see also the discussion on MEAs, above) [51]. Nevertheless, these funds allow existing data gaps on uncertainties surrounding these medicines to be filled by supporting data collection activities, including ongoing clinical trials in parallel with publicly funded observational research [52]. Recognising these issues, the establishment of the *Innovative Medicines Fund* in the UK (in addition to the *Cancer Drugs Fund*) was intended to ensure that cancer and non-cancer patients have equal opportunities to benefit from the latest clinical developments through managed access at a reasonable price [53].

4.4. Concentrated delivery further enables collaboration and data collection

Generally, two to six centres per 10 million residents were established for the CAR-T therapy provision in the surveyed countries. This covers treatments for the range of 9–57 patients per 1 million residents a year. Also, many countries in the sample have established networks for CAR-T therapy providers so that the relatively small number of patients being treated will be concentrated among a small number of experienced providers. These referral networks have the potential to serve other purposes beyond managing patient care. They can establish working groups to collaborate and share expertise across institutions with the objective of improving the effectiveness of CAR-T therapy, as for example in the aforementioned ACC Italian referral network and working group.

At the supranational level, the European Society of Blood and Marrow Transplantation (EBMT) and the International Society for Cell & Gene Therapy (ISCT) play an important role in assessing and approving the standards of treatment in clinics or administration centres through the Joint Accreditation Committee of ISCT and EBMT (JACIE), which applies not only to blood or marrow transplantation but also to CAR-T therapies. Besides that, the EBMT initiated data collection on treatments and outcomes for the patients treated with commercial CAR-T therapies, with the notion that outcomes reporting and treatment data management will provide necessary input for the analysis of treatment efficacy and possible future improvements. The use of registry data supports Post Authorisation Safety (PAS) studies for the manufacturers but also advises the health authorities on value and reimbursement decisions. EBMT requires that data on treatment be reported within one month of treatment and at the follow up visits which are expected at day 100, 6 months and annually for 15 years. By June 2022, the registry contained data on over 3 250 patients treated with CAR-T products and collected through EBMT [54].

4.5. Affordability, availability, clear eligibility criteria and location of treatment centres are linked to equity concerns

This study identified countries that have established eligibility criteria for CAR-T therapies, focusing on clinical indications only. However, the decision-making criteria of expert groups assessing patient eligibility is variably transparent and the limited number of treatment centres poses a challenge for the potential recipients of the CAR-T therapies [18,55,56]. Furthermore, given the severity of the side effects associated with CAR-T therapy, patients must stay for at least four weeks at the treatment centre or in close proximity to minimise harm to patients. For patients who live further away from the nearest CAR-T therapy centre, this requirement imposes another burden and may limit access [55–57]. Therefore, disparities within a country, whether based on urban or rural differences, or even on region (e.g. Italy) or province (e.g. Canada), can exacerbate geographical inequities in access. Furthermore, the limited affordability of these therapies necessitates adherence to strict eligibility criteria based on potential benefit-to-cost ratios for public coverage. As a result, only patients most likely to benefit from the treatment are selected, which can exacerbate inequities [9,58,59].

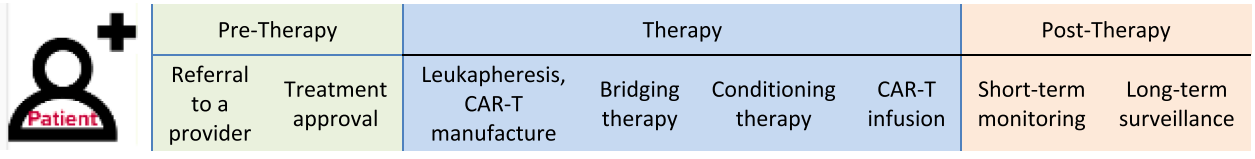

Fig. 1. The main steps in a patient's journey with CAR-T therapy.
Source: authors' version based on [62,63].

4.6. New CAR-T therapies may address health system challenges

All currently approved CAR-T treatments (including the studied products of Kymriah® and Yescarta®) are based on the autologous process, in which CAR-T cells are generated from the patient's own immune cells. Over 80% of therapies in development fall into this category [2]. Autologous CAR-T cells are manufactured on demand basis and are truly personalised treatments. However, the manufacturing process increases the cost and time required to prepare, deliver and administer these products, which limits their large-scale clinical application as seen above. A potential solution to these limitations is offered by allogeneic donor-derived CAR-T products, so-called "off-the-shelf" cells. Currently, only 8% of CAR-T clinical trials are investigating these [2,60]. These advances are being explored with the support of new gene editing and cellular engineering tools [60]. With the extensive ongoing research in this area, the CAR-T market will look very different in the decades to come.

4.7. Study limitations

The number of analysed countries was limited to ten and only two CAR-T therapies were investigated in detail. The latter was limited by the short time frame since these treatments have been available on the market. Furthermore, the information collected relied on the responses from country experts and available literature and only encompasses publishable data (e.g., not the exact terms of MEAs or the extent of confidential discounts on price). In addition, the rough calculations on budget impact were limited by the simplicity of the approach. The results are not indicative of real costs or real shares in expenditure, they do not reflect staged payments done over the timespan, nor do they include treatment administration costs in hospital, e.g., hospital stay, apheresis or managing adverse events. Moreover, the national sources report significantly lower net expenditures on this type of pharmaceuticals. For instance, Italy's expenditure was EUR 16.7 million [33] and Belgium's was EUR 3 million [61], which is considerably lower than our estimates.

Future analysis could include a wider list of countries for comparison, newer CAR-T therapies, and the views of clinicians and patients regarding whether current eligibility criteria and reimbursement decisions reflect the real need for this therapy to be used in practice. It was beyond the scope of our analysis to determine whether Directive 2011/24/EU (on patients' rights in cross-border healthcare) has been used in the context of CAR-T therapy but there may be potential to explore this possibility further, although the movement of severely ill patients across borders poses significant challenges.

Based on the results of this research, further analysis could focus on capturing the policy landscape regarding the regulation, financing, and delivery of ATMPs at the national or regional level.

5. Conclusion

In summary, we studied some of the challenges in providing CAR-T therapies related to availability and financing across countries. CAR-T therapies are a relatively novel form of therapy, yet their promising effects are drawn from studies with smaller samples and a higher degree of uncertainty. For this reason, it is important to carefully monitor the long-term benefits of these therapies and compare them with the high promises made by the pharmaceutical industry. To address these uncertainties while still ensuring access to these therapies, countries have implemented conditional coverage. Until now, countries have cautiously designed reimbursement models for CAR-T treatments, often establishing evidence-development schemes or outcome-based MEAs to study the efficacy and impact of the therapies in real-world settings. To address the high prices, some health systems have invested in the research and development of academic therapies derived from the application of ATMPs under the hospital exemption in Europe.

To ensure equal access for all, regardless of their proximity to delivery centres, it is important to maintain transparent and systematised eligibility criteria. Additionally, improving the organization and clarity of the clinical pathway phases can help distribute accountability for the quality and safety of CAR-T therapies among the various stakeholders involved in the process, including the treatment centre, the manufacturing plant and the patients. In addition, the establishment of strong networks and referral systems has the potential for collaboration and sharing of expertise to improve the outcome of CAR-T therapies.

Due to the multi-dimensional nature of the CAR-T clinical pathway, exchanging knowledge and learning from current best practices can improve therapy provision within the healthcare system and ultimately benefit relevant populations.

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CRediT authorship contribution statement

Yulia Litvinova: Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis. **Sherry Merkur:** Writing – review & editing, Writing – original draft, Validation, Methodology, Data curation, Conceptualization. **Sara Allin:** Validation, Investigation, Data curation. **Ester Angulo-Pueyo:** Validation, Investigation, Data curation. **Daiga Behmane:** Validation, Investigation, Data curation. **Enrique Bernal-Delgado:** Validation, Investigation, Data curation. **Miriam Dalmas:** Validation, Investigation, Data curation. **Antonio De Belvis:** Validation, Investigation, Data curation, Conceptualization. **Nigel Edwards:** Validation, Investigation, Data curation. **Francisco Estupiñán-Romero:** Validation, Investigation, Data curation. **Peter Gaal:** Validation, Investigation, Data curation. **Sophie Gerkens:** Validation, Investigation, Data curation. **Margaret Jamieson:** Validation, Investigation, Data curation. **Alisha Morsella:** Validation, Investigation, Data curation, Conceptualization. **Dario Picecchi:** Writing – review & editing, Validation, Investigation, Data curation. **Hilde Røshol:** Validation. **Ingrid Sperre Saunes:** Validation, Investigation, Conceptualization. **Terry Sullivan:** Investigation, Data curation. **Balázs Szécsényi-Nagy:** Validation. **Inneke Van De Vijver:** Validation. **Ricciardi Walter:** Validation, Methodology, Investigation, Data curation. **Dimitra Panteli:** Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

None.

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Supplementary materials

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