Accepted article: Gagelmann N, Sureda A, Montoto S, et al. Access to and affordability of CAR-T cell therapy in multiple myeloma: an EBMT position paper. Lancet Haematol 2022. <https://www.thelancet.com/journals/lanhae/home>

**Access to and affordability of CAR-T cell therapy in multiple myeloma: an EBMT position paper**

Nico Gagelmann M.D.,1 Prof Anna Sureda M.D. ,2 Silvia Montoto M.D.,3 John Murray,4 Natacha Bolaños,5 Michelle Kenyon,6 Meral Beksac M.D.,7 Prof Stefan Schönland M.D.,8 Patrick Hayden M.D.,9 Hans Scheurer,10 Kate Morgan,10 Laurent Garderet M.D.,11 Donal P. McLornan M.D.,12 Annalisa Ruggeri M.D.13

1 University Medical Center Hamburg-Eppendorf, Hamburg, Germany

2 Institut Català d'Oncologia, Hospital Duran i Reynals, Barcelona, Spain

3 St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK

4 The Christie NHS Foundation Trust, Manchester, UK

5 Lymphoma Coalition Europe, Paris, France

6 Department of Haematology, King's College Hospital NHS Foundation Trust, London, UK

7 Department of Hematology, Ankara University, Ankara, Turkey

8 Medical Department V, Heidelberg University Hospital, Heidelberg, Germany

9 Department. of Hematology, Trinity College Dublin, St. James's Hospital, Dublin, Ireland

10 Myeloma Patients Europe, Brussels, Belgium

11 Service d'Hématologie et thérapie cellulaire, Hôpital Pitié-Salpêtrière, AP-HP, Paris, France

12 Department of Haematology and Stem Cell Transplantation, University College Hospital, London

13 Hematology and BMT Unit, San Raffaele scientific Institute, Milano, Italy

**Corresponding author:** Nico Gagelmann M.D., University Medical Center Hamburg-Eppendorf, Martinistr 52, 20246 Hamburg, Germany, phone +49-40-7410-54851, email nico.gagelmann@posteo.de

**Text:** 4524

**Contribution:** N.G. and A.R. generated hypotheses, designed the framework, formulated key positions, and wrote the first draft of the manuscript. S.M., J.M., N.B., M.K., M.B., S.S., P.H., H.S., K.M., L.G., A.S., and D.ML. reviewed the framework and first draft of the manuscript, formulated positions, and wrote the manuscript. All authors approved of the final version of the manuscript.

**Data sharing:** Selected literature data will be made available upon email request to the corresponding author.

**Role of funding source:** No funding received.

**Ethics committee approval:** Not applicable.

**Summary**

Chimeric antigen receptor (CAR-) T cell therapy represents a promising immunotherapeutic approach in the treatment of multiple myeloma, and the recent approval of the first two CAR-T products may result in improved outcomes. However, it remains a complex and expensive technology, which poses challenges to healthcare systems as well as society in general, especially in times of crises. This potentially accelerates pre-existing inequalities as access to CAR-T varies, both between countries depending on the level of economic development, and within countries due to structural disparities in access to quality healthcare, a parameter strongly correlated with socioeconomic status, ethnicity, and lifestyle. Here, we identify two important issues: (1) affordability, and (2) access to CAR-T treatment. This position paper from clinical investigators, clinicians, nurses, and patients from the European Society for Blood and Marrow Transplantation proposes solutions as part of an innovative collaborative strategy to make CAR-T accessible to all multiple myeloma patients.

**Introduction**

Multiple myeloma accounts for approximately 15% of all hematological cancers. The incidence in Europe is estimated to be between 4.0 and 6.0 per 100.000 per year with a median age at diagnosis of 72 years.1 Although there have been remarkable improvements in treatment, especially over the last decade, with the introduction of immunotherapy, almost all patients ultimately relapse, with very poor outcomes seen in patients whose disease is refractory to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies.2,3 Chimeric antigen receptor (CAR-) T cell therapy is a promising new immunotherapeutic approach that has shown remarkable results in patients with advanced relapsed multiple myeloma.4,5 The first two constructs, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), have been approved by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).6,7.

There is currently considerable geographical variation in outcomes,8 and CAR-T cell therapy, being a complex and therefore expensive procedure, may potentially exacerbate this inequality.9 This variation is strongly influenced by two major factors: (1) structural disparities in access to quality health care, a parameter strongly related to the economic development of individual countries; and (2) population composition including variations due to socioeconomic status, ethnicity, race and lifestyle. For multiple myeloma patients, particularly, significant barriers to treatment already exist for different ethnicities, patients with lower income but also patients living in rural areas.10 This inequality has been accelerated with the advent of newer, more expensive treatments that may help to control disease and improve outcome but also pose more treatment burden with new (financial) toxicities over years or even decades,11,12 repeated required hospital admission due to infusion and others.12,13 In our view, CAR-T cell therapy will pose another significant risk to create even more imbalances. Therefore, it seems to us that clearly identifying these disparities by engaging in discussion with all relevant stakeholders will ultimately lead to better care and improved outcomes for all myeloma patients in need of this new immunotherapy, regardless of their backgrounds.

The European Society for Blood and Marrow Transplantation (EBMT) has long been committed to improving education and access-to-care for all patients, families, and donors in Europe by working in close collaboration with international societies. This has been accelerated by the creation of the Nurses Working Group, the Patient Advocacy Committee (PAC) and the Equality, Diversity, and Inclusion (EDI) committee. Furthermore, beyond the Cellular Therapy and Immunobiology Working Party (CTIWP) of EBMT, the recent creation of the subcommittee for CAR-T cell therapy in plasma cell disorders within the Chronic Malignancies Working Party (CMWP) was an initiative to increase awareness and to provide ‘real world’ evidence to guide clinical practice in order to improve care in patients with multiple myeloma receiving CAR-T across Europe. Previous surveys from research groups,14 position papers such as those from the European Hematology Association on fair pricing of innovative medicines,15 and recent practice recommendations for multiple myeloma from the American Society for Translantation and Cellular Therapy have strengthened our common-sense based approach that specifically for CAR-T in multiple myeloma,16 a real collaborative effort is required to tackle the real challenges inherent to this new treatment of this already very complex disease course. In this sense, the following work is meant to be a call for collaboration across continents and societies.

This manuscript reflects the position of the members of the CMWP, PAC, EDI, Nurses Working Group, and the CTIWP of EBMT regarding current challenges. Apart from the medical challenges of using CAR-T in MM patients, we believe that two important issues require attention: (1) the affordability of treatment both for countries and for individual patients; and (2) access to specialised centres or CAR-T service networks for multiple myeloma (Figure 1). This position paper is intended to draw attention to possible interventions as part of a wider strategy to define a common vision and to identify the actions that will be required to make CAR-T accessible to all MM patients in need.

**Search strategy and selection criteria**

We searched PubMed using the terms “multiple myeloma”, “chimeric antigen receptor” “access”, “cost”, “quality of life”, “telemedicine”, and “patient reported outcome”. We included articles in peer-reviewed journals published in the English language between August, 2018, and March, 2022. In addition, for patient resources, online sources were identified through a comprehensive search of common search engines using the aforementioned terms. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review by N.G. and A.R. References and position statements were then circulated to all panel members for critical evaluation. References and position statements could then be added and underwent subsequent discussion within the whole panel.

**Affordability**

European countries vary in both wealth and spending priorities.17 In addition, countries have differing regulatory environments, and hospitals must meet these specific requirements before establishing CAR-T cell therapy programs. Though figures are not publicly available, the cost of production and of the scaling up of infrastructure for CAR-T are much more expensive than for the typical drug manufacturing process. Apart from the CAR-T cell product itself, there are other significant costs. Because of the unique toxicity profile of CAR-T cells, the price of the inpatient hospital admission for their administration must include the costs of intensive care and expensive medications, such as tocilizumab, in addition to the standard costs of hospitalization.

Various measures exist to evaluate cost-effectiveness. Quality-adjusted life years (QALYs) per euro spent are designed to assess the impact of a given therapy both on the expected lifespan of a patient as well as on health-related quality of life during this gain in left expectancy.18,19 However, although QALYs are well established outcome measures, it must be acknowledged that they can only, at best, represent an approximation and that they are also dependent upon patients’ living conditions. Other outcomes of interest usually include total life-years (LYs) gained, equal value life-years gained (evLYG), or time spent in progression free state/responding to treatment.

With respect to ide-cel, the incremental cost-effectiveness ratios were approximately $319,000 per QALY gained, $250,000 per LY gained, $280,000 per evLYG gained, and $35,000 per additional progression-free survival month gained.20 With respect to cilta-cel, incremental cost-effectiveness ratios for were updated with newly released 18-month trial data and found approximately $253,000 per QALY gained, $207,000 per LY gained, and $228,000 per evLYG gained.20 Ide-cel and cilta-cel would lead to additional $35,000 and $17,000 for every progression-free survival month gained, respectively. Model findings across all interventions were sensitive to quality of life (QoL) related to progression-free survival (on and off treatment), and overall health care costs for multiple myeloma patients. However, widespread adoption would substantially increase multiple myeloma health care costs, while these analyses can only approximate measures from published trial results, and QALYs are currently not part of primary objectives in most trials.21 Furthermore, analyses depend on single-arm trials illustrating the inherent uncertainty in evaluating treatments not compared using randomization, particularly when the comparator is an historical cohort.22 For instance, a superficial examination of the results reported above would lead to a premature conclusion that ide-cel has inferior economic value compared with cilta-cel. Of note, calculated measures presuppose a willingness-to-pay which may differ significantly across countries and healthcare systems.

We furthermore aim to highlight that affordability and value issues of CAR-T cell therapy for multiple myeloma may entail differing relevance in comparison to other diseases. Multiple myeloma has seen remarkable progress in drug development, constantly improving progression-free and overall survival for patients. Therefore, although overall survival at current indication for CAR-T (after at least 3 lines of treatment) is dismal, outcomes with respect to overall outcomes over years or even decades of the disease course need to be taken into account. Patients may have lived several years and reached >70 years of age receiving various treatments including autologous or even allogeneic haematopoietic cell transplantation. For those, end points of CAR-T treatment should be selected carefully and offer significant benefit to really increase the value of undergoing this complex and time-consuming treatment. For example, we suggest that CAR-T trials need to show overall survival benefit and include quality of life as primary end point.23

With current approvals of ide-cel and cilta-cel for patients with at least three prior lines of therapy, cumulative financial burden and toxicity must be considered as holistic measure,24,25 especially in multiple myeloma which has seen remarkable number of new therapies in the last recent years. With the introduction of daratumumab-containing regimens as first line treatment, an improvement of 0.52 QALYs and 0.66 discounted life-years compared with second line daratumumab was achieved. However, an incremental cost of $322,836 for first line daratumumab led to an incremental cost-effectiveness ratio of $618,018 per QALY. Therefore, only a decreased cost of daratumumab by 67% for first-line treatment would be cost-effective at a willingness-to-pay threshold of $150,000 per QALY. Access to generics such as to lenalidomide from this year may provide some relief.26 However, other patents on the widely used monoclonal antibody daratumumab will not expire before 2029 for intravenous and 2036 for subcutaneous application.27

Though drug costs may be high across countries, their effect will differ depending on a country’s wealth and model of healthcare, shifting the balance from patient-centered to budget-centered care.28,29 National healthcare systems may be able to afford limited short-term use of a potent new therapeutic class, though may still be financially overwhelmed when a critical mass of patients has been reached.30 Structural inequalities can potentially be worsened in the context of international political instability such as the COVID-19 pandemic, regional wars, and rising inflation.31-33 We propose that pharmaceutical companies consider significant price reductions or response-based payment models, which would improve cost effectiveness, increase access, and be more resilient in times of financial uncertainty, even with modest long-term outcomes.

**Access**

Improving access to CAR-T in multiple myeloma is a multidimensional problem, including the following: timely cell collection, manufacturing, and delivery;34 density of qualified centers;17 adequate training of a multidisciplinary team (MDT);35 increasing access to clinical trials;9 and continuous patient involvement.36

*Manufacturing and delivery*

CAR-T cell manufacturing consists of several steps: (1) collection via leukapheresis and shipment to the manufacturing center; (2) complex procedures under Good Manufacturing Practice conditions to activate, expand and engineer the T cells; (3) quality control; and (4) shipment of the final product to the hospital for re-infusion.37 The complete manufacturing process can take several weeks. This delay is problematic for many patients who may have aggressive disease. For instance, nine percent of all patients who received leukapheresis did not proceed to ide-cel infusion due to several reasons (including death, progression, or physician decision).6 Efficient selection and planning of patients for CAR-T, together with well-organized bureaucracy algorithms may help to reduce the timespan from decision for CAR-T and actual infusion. As CAR-T cell therapy will potentially be applied in earlier lines of myeloma treatment, bridging therapy may play a significant and increasing role to prevent rapid progression of the disease during the manufacturing period,17 and should therefore be taken into account when screening patients for CAR-T. For instance, in lymphoma, reducing wait times significantly increased the number of eligible patients receiving CAR-T by ten percent.38 For patients already receiving CAR-T, a reduction in wait times resulted in a three percent increase in survival gains per patient, highlighting the inherent risks and inequalities in the procedure itself. However, if reduced wait times are not compensated by higher production rates, this may lead to pre-selection of patients for various reasons, including patients with certain insurance accelerating reimbursement process or patients living closer to the CAR-T centre.

Due to its complexity, CAR-T production may be particularly susceptible to supply chain constraints in the context of growing demand, political instability, and international crises. For instance, Bristol-Myers Squibb admitted early following drug approval that demand for ide-cel was outstripping supply capacity, resulting in delays in product delivery.39 Another problem can be a shortage of viral vectors, which are used to deliver the cell therapy. Limited viral vector supply adversely affected other cell therapies globally during the COVID-19 pandemic.40 Despite their huge and welcome effort to maximize production for as many patients as possible, companies’ ability to meet growing demands are finite.

These challenges associated with production have driven research into finding an improved manufacturing method itself. One approach may be closed and automatic manufacturing to reduce workload, including time needed to produce CAR-T cells. So-called closed-loop production maintains the sequential application of activation, transduction, and expansion ex vivo and may result in a theoretical lower bound of six to eight days.

Another highly attractive alternative are allogeneic ‘off-the-shelf’ CAR-T cells depleted of T cell receptor expression, currently under investigation.41 Allogeneic CAR-T cells may overcome several inequalities in access for patients worldwide. Here, however, additional engineering is required to prevent life-threatening graft-versus-host disease;41 and with respect to efficacy, allogeneic CAR-T cells showed lower persistence *in vivo*, which is mainly due to alloreactivity resulting in elimination of these cells by the host’s own immune system, with subsequent risk of insufficient response or relapse.21,41-43 For myeloma, preliminary results of ALLO-715, a genetically modified CAR-T against B cell maturation antigen showed high measurable residual disease negativity without requiring leukapheresis or bridging therapy.42

Furthermore, fully in vivo CAR-T generation is currently under investigation, administering systemic CAR-encoding nanocarriers with viral constructs.44 In vivo generation of CAR-T cells eliminates extensive ex vivo culture, requiring several days.45 Another most recent approach suggested subcutaneously implantable multifunctional alginate scaffold for T cell engineering and release,46 streamlining in vivo CAR-T cell manufacturing and thereby reducing the whole process to a single day. Early phase results suggested even greater persistence than conventional CAR-T cells, promising to transform CAR-T cell therapy by fast-tracking manufacture and less resources due to simpler design.

Currently approved CAR-T cell therapies for multiple myeloma are centrally improved and leukapheresis products need to be shipped to the United States if the patient lives in Europe. This is one key driver for long turnaround time. Although companies aim to build production facilities in Europe to partly overcome this issue, the whole process would still be centralized within Europe. Moreover, raw material and consumable costs seem to be one of the greatest drivers for cost, and costs associated with genetic modification may account for approximately one third of raw material and consumable costs.47 Simulation studies comparing centralized versus decentralized systems showed that although centralized manufacturing offers better economies of scale,48 a decentralized system may spread facility costs across a greater number of treatments and be more efficient in resource utilization at high demand levels. Turnaround time per treatment for the decentralized scheme is shown to be consistently lower, although time savings may be influenced by the density of a geographical setting and quality/quantity of transportation networks.49 However, decentralized business model may further facilitate academic CAR-T programmes, which would further hold the control within the local medical, regulatory, and patient frameworks.49,50

*Qualified centres, adequate training, and communication*

Many problems in CAR-T could be mitigated by the education of the whole multidisciplinary team (MDT) including trainees, patients and families, physicians, nurses, and by transparent reporting of all stakeholders, including medical societies and companies. The main challenge in education is inequal access to hands-on practice. There is a significant difference in current numbers of CAR-T procedures between high-income countries and lower- and upper-middle-income countries, and even within high-income countries (for instance between Europe and United States).9,51,52 This may create imbalance in evidence findings, given the impact of different healthcare settings with regard to complex therapies. Furthermore, significant improvement in accessibility needs to be achieved by minimizing geographic disparities and travel burden, as many in-person visits before actual CAR-T infusion are rather used for regulatory purposes to establish indication, eligibility, and safety of the procedure.

In Europe, FACT-JACIE accreditation was established to ensure that stem cell transplants centres adhered to well defined quality standards,53 and, in many countries, both health authorities and pharmaceutical companies mandate that those wishing to provide commercial CAR-T cell therapy are accredited. The standards cover all the steps in which the centre is involved, including patient evaluation, cell collection and receipt, storage and infusion. The revised standards also include special safety monitoring systems in view of the unique toxicity profile of CAR-T cell therapies. It is our belief that all centres providing CAR-T therapy should have to achieve FACT-JACIE accreditation for immune effector cell therapies, thereby harmonising care internationally and ensuring that patients receive well benchmarked care pathways.54

The ability to freely access and critically evaluate the literature is one of the most important skills in clinical care; this should be emphasized in medical societies, training programs and continuous education worldwide. Exchange programs and fellowships, supported by medical societies and other parties, are necessary to allow people with all backgrounds to learn CAR-T procedures and follow-up. Importantly, education resources and clinical practice guidelines need to be open-access for everyone and inclusive addressing needs of trainees, physicians, nurses, patients and others alike. Trainees should be equipped with basic skills in critical appraisal that would allow them to ask tough questions and view evidence and consensus with the appropriate scientific skepticism.

Furthermore, better knowledge will result in more clinically meaningful scientific reports, which then influence how patients perceive these treatments. If patients receive unrealistically positive information on the efficacy of treatment, we risk disappointment and loss of hope for patients.55,56 We may even excerbate pre-existing psychiatric conditions such as reactive depression resulting from their cancer diagnosis. For instance, a recent study estimated the risk of self-harm after the diagnosis of a psychiatric disorder in patients with cancer and found that the cumulative burden per 100 individuals with depression for multiple myeloma was 8.5 for patients at age 60 years and as high as 25 for patients at age 75 years.57

Patients should be better informed and should be given unbiased educational materials that clearly explain inclusion criteria of trials that led to approval, their actual magnitude of benefit, toxicity, and cost.58 Specific for CAR-T, patients should receive transparent explanation about the duration between screening and infusion. Social media is a major platform for oncology education of patients and others, but we highlight that the content often is driven by spin and bias itself. Independent patient-advocacy groups such as the EBMT-PAC have an important role in producing educational materials, while several other advocacy groups are funded by the pharmaceutical industry, which may be a conflict of interest. Furthermore, scientific medical journals, the gatekeepers of research, traditionally focus on outcome research rather than access or other more soft and individual outcomes and variables.

As multiple myeloma is mainly treated by community oncologists, close communication between the CAR-T center and the referring oncologist is paramount for successful access and outcomes. Centers should build active, participative local networks with referring oncologists to build collaborative education platforms and to reduce waiting times for potential screening and, in the end, to ensure timely referral. For example, the timing and optimal immediate therapy prior to T cell collection as well as type of bridging therapy, which are often delivered by referring oncologists, will become more important as CAR-T cell therapies will possibly be applied in earlier treatment sequences.59

*Clinical trials*

Contemporary oncology clinical trials largely measure surrogate end points such as progression-free survival, and most trials keep being funded by pharmaceutical companies.60 In relapsed or refractory multiple myeloma, for which more than 300 different treatment regimens comprising more than 40 different compounds are currently used, new and expensive treatments such as CAR-T may complicate to which extent study end points and target effect size provide real and meaningful benefit to patients.61 Furthermore, because direct comparisons are currently lacking, indirect comparisons with historical controls or other trial arms are undergone, which provides questionable evidence because of inherent selection and attrition bias.62

Rather, investigations prioritizing the needs of the patient at all stages, including design, activation, enrollment, data collection, completion and outcome reporting are needed.63 In patient-centric trials, hypotheses that are important to patients can be outlined in close collaboration with patient advocacy groups, study designs focusing on burden reduction to patients can be developed, and measures that ensure holistic improvement to standard of care.

Unfortunately, still, many patients lack understanding of clinical trials, while not all patients are systematically informed about possible participation, resulting in reduced diversity of clinical trial populations.64 In addition, restrictive selection criteria further limit participation and the translation of trial data to real-practice conditions. How to broaden patient eligibility remains a major challenge. In a survey from the American Society of Clinical Oncology, half of the respondents agreed that some criteria are too stringent and harm translation of the trial, while no agreement could be achieved on which changes would improve generalizability.65 Specifically, recent CAR-T trials were controversially discussed to focus on patients with certain backgrounds, skewing the real effects of these treatments and limiting overall access.66 Amongst multiple myeloma patients, only one percent of CAR-T recipients had African American and 5% Hispanic background, and the majority of recipients living >2 hours from the next CAR-T centre belonged to a higher socioeconomic strata.67 More importantly, clinical trials in multiple myeloma showed the lowest participation to prevalence ratio of 0.2.68 New data-driven methodologies may help to design more-inclusive trials while maintaining safeguards for patient safety.69

Furthermore, many multiple myeloma patients are treated in the outpatient setting, which leaves screening for trial availability to the local area, remaining a major barrier as many trials are limited to academic medical centers with existing CAR-T programs. A recent study found that no trials were offered in about one-third of practices.70 This gap is particularly significant in lower- and upper-middle-income countries.9

*Patient involvement*

Little is known about patient priorities and needs before, during, and after CAR-T cell therapy. Patients and their advocacy groups need to be actively included in trial design, data evaluation of real practice and long-term survivorship programs. The current literature underscores the importance of appropriate information, most patients felt not well prepared for most aspects surrounding CAR-T therapy nor were they directly prepared for the nature and intensity of potential toxicities. Importantly, family members, friends, and connected primary caregivers need to be included in education and communication to assure the overall care and eventually well-being of the patient.71

Patient involvement becomes crucial in the assessment of outcomes that matter the most within a clinical trial and beyond,72 a dimension that has yet to be significantly improved.73 In our perspective, this is even more important in treatments that are associated with unique toxicity profile as well as individual and societal financial toxicity such as CAR-T cell therapy. Patient-reported outcome (PRO) evaluation in large groups of patients with extended longitudinal follow-up is particularly important to identify predictors of quality of life, specifically of mental health and cognitive function (as shown above, most patients develop depressive episode during the disease course). For instance, the Patient-Reported Outcomes Tools: Engaged Users and Stakeholders Consortium developed a website to promote tools and resources to optimise the rigorous assessment of PROs in cancer clinical trials and facilitate the use of those outcomes by patients, clinicians, and decisions makers.74 Longitudinal depictions and incorporation of data from the PRO version of the Common Toxicity Criteria for Adverse Events (PRO-CTCAE)75 are not usually documented in current large registries or clinical trials but should be implemented. Several additional novel analytical approaches such as the Event Burden Score with a single metric for the frequency and severity of multiple adverse events or the Toxicity Index accounting for the burden of multiple cumulative toxicities may more accurately reflect patients’ experience with specific treatments.76,77

*Regulation and real-practice data*

Inconsistencies between national and even international regulatory agencies present a significant barrier to equal access to new treatments.78 Differing requirements and varying delays in the times needed for regulatory approval may limit effective international cooperation. For instance, EMA approval is often granted several months after FDA approval. In addition, EMA regulatory approval does not necessarily translate into immediate access across all European countries, as European national healthcare systems generally operate different systems for the financial as opposed to the regulatory approval of new drugs. The need for separate submissions to multiple national agencies results in redundant workflow and increased workload and cost. However, the confidential pricing arrangements insisted upon by pharmaceutical companies can also be an obstacle to transparent agreement on the budgetary impact of these expensive novel therapies. Furthermore, in the post-COVID era, legal and regulatory policy to guide telemedicine and remote monitoring are lacking internationally. Finally, patient frustration at their lack of access to CAR-T programs operating in neighbouring countries can be an understandable source of stress.

The European Union Clinical Trials Regulation79 was recently introduced to allow for unified trial submissions in a single application instead of requiring applications to each individual European Union member state. Such international collaboration has the potential to accelerate trial development and to increase participation, thereby making innovative medicines accessible to more patients.

In Europe, clinical data from patients treated with gene and cellular therapies are reported to many different registries, each built for a specific purpose, with different governance rules and often with bespoke software tools managing the data. This results in siloed data, inefficiencies, and duplication of efforts.80 In 2019, EBMT received regulatory approval from the EMA for the use of its patient registry to collect data on novel CAR-T cell therapies, thereby allowing for the collection of consistent European clinical data. The streamlined reporting of this high-quality data stream can inform real time clinical practice and will undoubtedly contribute to the collaborative development of new therapies.

The widespread adoption of collaborative, agreed Health Technology Assessment (HTA) processes would be another important step towards ensuring more equal access.81 HTA is a multidisciplinary field that addresses the health impacts of new technologies, considering its specific healthcare context as well as available alternatives. The unique approach of HTA focuses on the contextual factors of a certain technology, including include economic, organizational, social, and ethical impacts.

**Conclusion**

Many countries worldwide, including some in Central and Eastern Europe, have not yet developed adequate processes for the assessment and appraisal of CAR-T cell therapy for multiple myeloma. High prices and the complexity of manufacturing and delivery are serious impediments to the general uptake of this treatment and the sustainability of health systems. They are by no means the only factors influencing accessibility, and it is important to stress that we do not regard the reduction of high medicine prices as an end in itself.

This position paper by the EBMT (list of statements in Table 1 and 2) aims to be call to action for all clinical trial leaders, multiple myeloma practitioners, patient advocacy groups, international regulatory agencies, insurance companies, and leaders both in industry and academia - those represented in our authorship and those beyond - to spearhead changes needed to bring CAR-T cell therapy to all patients battling multiple myeloma. Significant improvement in practice harmonization and in the prospective collection of PRO and QoL measures, identifying novel ways to capture efficacy and access through real-world data, designing representative clinical trials, accurate and equal training of an MDT, free access to knowledge resources for medical personnel and patients alike (Table 3), remain essential. The statements should encourage and guide all stakeholders to improve affordability and access to CAR-T cell therapy in multiple myeloma.

**Declaration of interests:** N.G. received support for attending meetings/travel from Janssen.J.M. received honoraria from Kite/Gilead and Janssen.D.ML. received honoraria from Novartis. L.G. received consulting fees from Janssen and BMS/Celgene. H.S. and K.M. have received funding from Novartis, BMS/Celgene, Janssen, and Gilead. The other authors declare no conflict of interest.

**References**

1 Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2021; **32:** 309–22.

2 Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia* 2019; **33:** 2266–75.

3 Moreau P, Kumar SK, San Miguel J, et al. Treatment of relapsed and refractory multiple myeloma: recommendations from the International Myeloma Working Group. *Lancet Oncol* 2021; **22:** e105-e118.

4 Bruno B, Wäsch R, Engelhardt M, et al. European Myeloma Network perspective on CAR T-Cell therapies for multiple myeloma. *Haematologica* 2021; **106:** 2054–65.

5 Gagelmann N, Ayuk F, Atanackovic D, Kröger N. B cell maturation antigen-specific chimeric antigen receptor T cells for relapsed or refractory multiple myeloma: A meta-analysis. *Eur J Haematol* 2020; **104:** 318–27.

6 Munshi NC, Anderson LD, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *N Engl J Med* 2021; **384:** 705–16.

7 Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet* 2021; **398:** 314–24.

8 Ludwig H, Novis Durie S, Meckl A, Hinke A, Durie B. Multiple Myeloma Incidence and Mortality Around the Globe; Interrelations Between Health Access and Quality, Economic Resources, and Patient Empowerment. *Oncologist* 2020; **25:** e1406-e1413. https://doi.org/10.1634/theoncologist.2020-0141.

9 Horgan C, Serroukh Y, Gjærde LK, Gagelmann N, EBMT Trainee Committee. Recognising inequalities in haematopoietic stem-cell transplantation and cellular therapy training. *Lancet Haematol* 2022;9(5):e323-e324.

10 Buradagunta CS, Garacci Z, D’Souza A, et al. Socioeconomic disadvantage contributes to ethnic disparities in multiple myeloma survival: a matched cohort study. *Blood Cancer J* 2022;**12**:82. doi: 10.1038/s41408-022-00681-x

11 Goodman AM, Kim MS, Prasad V. Persistent challenges with treating multiple myeloma early. *Blood* 2021;**137**:456-458.

12 Ouchveridze E, Banerjee R, Desai A, et al. Financial toxicity in hematological malignancies: a systematic review. *Blood Cancer J* 2022;**12**:74. doi: 10.1038/s41408-022-00671-z

13 Efficace F, Cottone F, Sparano F, Caocci G, Vignetti M, Chakraborty R.

Patient-Reported Outcomes in Randomized Controlled Trials of Patients with Multiple Myeloma: A Systematic Literature Review of Studies Published Between 2014 and 2021. *Clin Lymphoma Myeloma Leuk* 2022:S2152-2650(22)00014-3. doi: 10.1016/j.clml.2022.01.009

14 Gajra A, Jeune-Smith Y, Kish J, Yeh TC, Hime S, Feinberg B. Perceptions of community hematologists/oncologists on barriers to chimeric antigen receptor T-cell therapy for the treatment of diffuse large B-cell lymphoma. *Immunotherapy* 2020;**12**:725-732.

15 Hagenbeek A, Gribben J, Jäger U, et al. Fair Pricing of Innovative Medicines: An EHA Position Paper. *Hemasphere* 2020; **4:** e488. https://doi.org/10.1097/HS9.0000000000000488.

16 Dhakal B, Shah N, Kansagra A, et al. ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Multiple Myeloma. *Transplant Cell Ther*. 2022;**28**:284-293.

17 Kröger N, Gribben JG, Chabannon C, Yakoub-Agha I, Einsele H, eds. The EBMT/EHA CAR-T Cell Handbook. Springer, 2022.

18 Green T, Bron D, Chomienne C, et al. Costs of haematological disease high and rising. *Lancet Haematol* 2016; **3:** e353-e354. https://doi.org/10.1016/S2352-3026(16)30074-6.

19 Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. *Br Med Bull* 2010; **96:** 5–21.

20 Beinfeld M, Lee S, McQueen B, Fluetsch N, Pearson SD, Ollendorf DA. Anti B-cell maturation antigen CAR T-cell and antibody drug conjugate therapy for heavily pretreated relapsed and refractory multiple myeloma. *J Manag Care Spec Pharm* 2021; **27:** 1315–20.

21 Gagelmann N, Riecken K, Wolschke C, et al. Development of CAR-T cell therapies for multiple myeloma. *Leukemia* 2020; **34:** 2317–32.

22 Lin JK, Muffly LS, Spinner MA, Barnes JI, Owens DK, Goldhaber-Fiebert JD. Cost Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Multiply Relapsed or Refractory Adult Large B-Cell Lymphoma. *J Clin Oncol* 2019; **37:** 2105–19.

23 Schuster SJ, Tam CS, Borchmann P, 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. *Lancet Oncol* 2021;**22**:1403-1415.

24 Huntington SF, Weiss BM, Vogl DT, et al. Financial toxicity in insured patients with multiple myeloma: a cross-sectional pilot study. *Lancet Haematol* 2015; **2:** e408-16. https://doi.org/10.1016/S2352-3026(15)00151-9.

25 Jensen C. The high cost burden of third- to fifth-line treatments for multiple myeloma: unsustainable and unaffordable. *J Manag Care Spec Pharm* 2021; **27:** 1321–24.

26 https://www.ema.europa.eu/en/medicines/human/EPAR/lenalidomide-mylan. Accessed, 23 April 2022.

27 https://www.ipdanalytics.com/. Accessed, 23 April 2022.

28 Chabannon C, Kuball J, McGrath E, et al. CAR-T cells: the narrow path between hope and bankruptcy? *Bone Marrow Transplant* 2017; **52:** 1588–89.

29 Kamusheva M, Turcu-Stiolica A, Gierczyński J, Subtirelu M-S, Czech M, Petrova G. Do Advanced Therapies Have a Future in the Low- and Middle-Income Countries - The Case of Bulgaria, Romania, and Poland. *Front Public Health* 2021; **9:** 729847. https://doi.org/10.3389/fpubh.2021.729847.

30 Keating SJ, Gu T, Jun MP, McBride A. Health Care Resource Utilization and Total Costs of Care Among Patients With Diffuse Large B-Cell Lymphoma Treated With Chimeric Antigen Receptor T-Cell Therapies in the United States. *Transplant Cell Ther* 2022. https://doi.org/10.1016/j.jtct.2022.03.021.

31 Mackenbach JP, Stirbu I, Roskam A-JR, et al. Socioeconomic inequalities in health in 22 European countries. *N Engl J Med* 2008; **358:** 2468–81.

32 Zaliska O, Oleshchuk O, Forman R, Mossialos E. Health impacts of the Russian invasion in Ukraine: need for global health action. *Lancet* 2022; **399:** 1450–52.

33 Miller IF, Becker AD, Grenfell BT, Metcalf CJE. Disease and healthcare burden of COVID-19 in the United States. *Nat Med* 2020; **26:** 1212–17.

34 Harrison RP, Ruck S, Medcalf N, Rafiq QA. Decentralized manufacturing of cell and gene therapies: Overcoming challenges and identifying opportunities. *Cytotherapy* 2017; **19:** 1140–51.

35 Hayden PJ, Roddie C, Bader P, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). *Ann Oncol* 2022; **33:** 259–75.

36 Chakraborty R, Sidana S, Shah GL, Scordo M, Hamilton BK, Majhail NS. Patient-Reported Outcomes with Chimeric Antigen Receptor T Cell Therapy: Challenges and Opportunities. *Biol Blood Marrow Transplant* 2019; **25:** e155-e162. https://doi.org/10.1016/j.bbmt.2018.11.025.

37 June CH, Sadelain M. Chimeric Antigen Receptor Therapy. *N Engl J Med* 2018; **379:** 64–73.

38 Chen AJ, Zhang J, Agarwal A, Lakdawalla DN. Value of Reducing Wait Times for Chimeric Antigen Receptor T-Cell Treatment: Evidence From Randomized Controlled Trial Data on Tisagenlecleucel for Diffuse Large B-Cell Lymphoma. *Value Health* 2022. https://doi.org/10.1016/j.jval.2022.02.007.

39 https://www.fiercepharma.com/manufacturing/bristol-myers-hits-car-t-manufacturing-bottleneck-as-abecma-demand-outstrips-supply. Accessed, 19 April 2022.

40 https://www.pharmaceutical-technology.com/features/a-perfect-storm-covid-19-viral-vector-manufacturing-adds-further-burden-to-car-t-development/. Accessed, 19 April 2022.

41 Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. 'Off-the-shelf' allogeneic CAR T cells: development and challenges. *Nat Rev Drug Discov* 2020; **19:** 185–99.

42 Mailankody S, Liedtke M, Sidana S, et al. Universal Updated Phase 1 Data Validates the Feasibility of Allogeneic Anti-BCMA ALLO-715 Therapy for Relapsed/Refractory Multiple Myeloma. *Blood* 2021;**138**:651. https://doi.org/10.1182/blood-2021-145572

43 Brudno JN, Somerville RPT, Shi V, et al. Allogeneic T Cells That Express an Anti-CD19 Chimeric Antigen Receptor Induce Remissions of B-Cell Malignancies That Progress After Allogeneic Hematopoietic Stem-Cell Transplantation Without Causing Graft-Versus-Host Disease. *J Clin Oncol* 2016; **34:** 1112–21.

44 Smith TT, Stephan SB, Moffett HF, et al. In situ programming of leukaemia-specific T cells using synthetic DNA nanocarriers. *Nat Nanotechnol* 2017; **12:** 813–20.

45 Agarwal S, Weidner T, Thalheimer FB, Buchholz CJ. In vivo generated human CAR T cells eradicate tumor cells. *Oncoimmunology* 2019; **8:** e1671761. https://doi.org/10.1080/2162402X.2019.1671761.

46 Agarwalla P, Ogunnaike EA, Ahn S, et al. Bioinstructive implantable scaffolds for rapid in vivo manufacture and release of CAR-T cells. *Nat Biotechnol* 2022. https://doi.org/10.1038/s41587-022-01245-x.

47 Harrison RP, Zylberberg E, Ellison S, Levine BL. Chimeric antigen receptor-T cell therapy manufacturing: modelling the effect of offshore production on aggregate cost of goods. *Cytotherapy* 2019; **21:** 224–33.

48 Lam C, Meinert E, Yang A, Cui Z. Comparison between centralized and decentralized supply chains of autologous chimeric antigen receptor T-cell therapies: a UK case study based on discrete event simulation. *Cytotherapy* 2021; **23:** 433–51.

49 Maschan M, Caimi PF, Reese-Koc J, et al. Multiple site place-of-care manufactured anti-CD19 CAR-T cells induce high remission rates in B-cell malignancy patients. *Nat Commun* 2021; **12:** 7200. https://doi.org/10.1038/s41467-021-27312-6.

50 Ortíz-Maldonado V, Rives S, Castellà M, et al. CART19-BE-01: A Multicenter Trial of ARI-0001 Cell Therapy in Patients with CD19+ Relapsed/Refractory Malignancies. *Mol Ther* 2021; **29:** 636–44.

51 Passweg JR, Baldomero H, Chabannon C, et al. The EBMT activity survey on hematopoietic-cell transplantation and cellular therapy 2018: CAR-T's come into focus. *Bone Marrow Transplant* 2020; **55:** 1604–13.

52 https://www.cibmtr.org/About/AdminReports/Pages/index.aspx. Accessed, 20 April 2022.

53 Snowden JA, McGrath E, Duarte RF, et al. JACIE accreditation for blood and marrow transplantation: past, present and future directions of an international model for healthcare quality improvement. *Bone Marrow Transplant* 2017; **52:** 1367–71.

54 Snowden JA, Saccardi R, Orchard K, et al. Benchmarking of survival outcomes following haematopoietic stem cell transplantation: A review of existing processes and the introduction of an international system from the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). *Bone Marrow Transplant* 2020; **55:** 681–94.

55 Hoffmann TC, Del Mar C. Clinicians' Expectations of the Benefits and Harms of Treatments, Screening, and Tests: A Systematic Review. *JAMA Intern Med* 2017; **177:** 407–19-

56 Abola MV, Prasad V. The Use of Superlatives in Cancer Research. *JAMA Oncol* 2016; **2:** 139–41.

57 Chang WH, Lai AG. Cumulative burden of psychiatric disorders and self-harm across 26 adult cancers. *Nat Med* 2022. https://doi.org/10.1038/s41591-022-01740-3.

58 Gyawali B, Booth CM. Cancer treatments should benefit patients: a common-sense revolution in oncology. *Nat Med* 2022; **28:** 617–20.

59 Manjunath SH, Cohen AD, Lacey SF, et al. The Safety of Bridging Radiation with Anti-BCMA CAR T-Cell Therapy for Multiple Myeloma. *Clin Cancer Res* 2021;**27**:6580-6590.

60 Del Paggio JC, Berry JS, Hopman WM, et al. Evolution of the Randomized Clinical Trial in the Era of Precision Oncology. *JAMA Oncol* 2021; **7:** 728–34.

61 Mateos M-V, Weisel K, Stefano V de, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. *Leukemia* 2022. https://doi.org/10.1038/s41375-022-01531-2.

62 Dhakal B, Hari PN, Usmani SZ, Hamadani M. Chimeric antigen receptor T cell therapy in multiple myeloma: promise and challenges. *Bone Marrow Transplant* 2021; **56:** 9–19.

63 Li BT, Daly B, Gospodarowicz M, et al. Reimagining patient-centric cancer clinical trials: a multi-stakeholder international coalition. *Nat Med* 2022; **28:** 620–26.

64 Getz KA. Examining and Enabling the Role of Health Care Providers as Patient Engagement Facilitators in Clinical Trials. *Clin Ther* 2017; **39:** 2203–13.

65 Kim ES, Bernstein D, Hilsenbeck SG, et al. Modernizing Eligibility Criteria for Molecularly Driven Trials. *J Clin Oncol* 2015; **33:** 2815–20.

66 Gangat N. Reliving #ASH21: The Historic 63rd ASH Annual Meeting. *The Hematologist* 2022; **19**.https://doi.org/10.1182/hem.V19.1.2022114.

67 Ahmed N, Shahzad M, Shippey E, et al. Socioeconomic and Racial Disparity in Chimeric antigen receptor T cell (CAR T) Therapy Access. *Transplant Cell Ther* 2022. https://doi.org/10.1016/j.jtct.2022.04.008.

68 Al Hadidi S, Schinke C, Thanendrarajan S, Zangari M, van Rhee F. Enrollment of Black Participants in Pivotal Clinical Trials Supporting US Food and Drug Administration Approval of Chimeric Antigen Receptor-T Cell Therapy for Hematological Malignant Neoplasms. *JAMA Netw Open* 2022; **5:** e228161. https://doi.org/10.1001/jamanetworkopen.2022.8161.

69 Liu R, Rizzo S, Whipple S, et al. Evaluating eligibility criteria of oncology trials using real-world data and AI. *Nature* 2021; **592:** 629–33.

70 Lee SJC, Murphy CC, Geiger AM, et al. Conceptual Model for Accrual to Cancer Clinical Trials. *J Clin Oncol* 2019; **37:** 1993–96.

71 Foster M, Fergusson DA, Hawrysh T, et al. Partnering with patients to get better outcomes with chimeric antigen receptor T-cell therapy: towards engagement of patients in early phase trials. *Res Involv Engagem* 2020; **6:** 61. https://doi.org/10.1186/s40900-020-00230-5.

72 Terpos E, Mikhael J, Hajek R, et al. Management of patients with multiple myeloma beyond the clinical-trial setting: understanding the balance between efficacy, safety and tolerability, and quality of life. *Blood Cancer J* 2021; **11:** 40. https://doi.org/10.1038/s41408-021-00432-4.

73 Thanarajasingam G, Minasian LM, Bhatnagar V, et al. Reaching beyond maximum grade: progress and future directions for modernising the assessment and reporting of adverse events in haematological malignancies. *Lancet Haematol* 2022; **9:** e374-e384. https://doi.org/10.1016/S2352-3026(22)00045-X.

74 https://more.bham.ac.uk/proteus. Accessed, 23 April 2022.

75 Dueck AC, Mendoza TR, Mitchell SA, et al. Validity and Reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *JAMA Oncol* 2015; **1:** 1051–59.

76 Le-Rademacher JG, Hillman S, Storrick E, et al. Adverse Event Burden Score-A Versatile Summary Measure for Cancer Clinical Trials. *Cancers* 2020; **12.** https://doi.org**/**10.3390/cancers12113251.

77 Gresham G, Diniz MA, Razaee ZS, et al. Evaluating Treatment Tolerability in Cancer Clinical Trials Using the Toxicity Index. *J Natl Cancer Inst* 2020; **112:** 1266–74.

78 https://www.forbes.com/sites/forbeschina/2021/09/16/expanding-international-clinical-trials-for-cancer-saves-lives-why-not-act-faster-now/?sh=179e53744bed. Accessed, 20 April 2022.

79 https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-regulation. Accessed, 20 April 2022.

80 Raphael MJ, Gyawali B, Booth CM. Real-world evidence and regulatory drug approval. *Nat Rev Clin Oncol* 2020; **17:** 271–72.

81 Health technology assessment of medical devices. Geneva, Switzerland: World Health Organization, 2011.

**Figure legends**

**Figure 1. Dimensions of access to and affordability of chimeric antigen receptor T cell therapy.**