21 February 2019
EMA/618737/2018
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Draft qualification opinion on Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry' (EMA/CHMP/SAWP/423488/2018)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Alliance for Regenerative Medicine (ARM)
2	Cell and Gene Therapy Catapult (CGT)
3	Dutch Society of Hematology
4	German Lymphoma Alliance (GLA)
5	Gilead Sciences International Ltd
6	Hannah Patrick, NICE UK
7	Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC)
8	Spanish Cell Therapy and Criobiology Group (GETCC) Spanish CAR Group (GECAR)
9	Spanish Group for Hematopoietic Progenitors Cells and Cellular Therapy (GETH)
10	Spanish Society of Hematology and Hemotherapy (SEHH)
11	Hematon
12	The Dental and Pharmaceutical Benefits Agency, TLV
13	Association for the fight against leukemia in the Valencian Community (ASLEUVAL)

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1. General comments – overview

[Add tables with general overview as received from interested party.]

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	*Welcoming the qualification process for the EBMT CAR-T initiatives* ARM welcomes and thanks the EMA for the qualification of the EBMT CAR-T registry initiative allowing a public consultation on CHMP responses and EBMT briefing. Many advanced therapies, including CAR-T products, seek to provide a transformative and long-lasting, potentially curative, effect with a single or few administrations, potentially enabling a shift from a focus on chronic treatment to possible cures. Real-life data generation and patient long-term follow-up will therefore be critically important for substantiating the medium- to long-term safety and efficacy profiles of these medicinal products. The EBMT registry is one of the first registries to be used in the context of real evidence data collection for a specific class of Advanced Therapy Medicinal Products (ATMPs). The answers provided in the consultation document therefore may set a precedent for the future use of other registries capturing data on ATMPs.	
1	*Questions & comments relating to the use of the registry for regulatory purposes* • As stated on lines 74-78, CHMP qualifies the EBMT registry for its use as a data source for regulatory purposes. As a consequence, EBMT, as registry holder, would become a platform for sponsored Marketing Authorisation Holder (MAH) studies (e.g. PAS studies) and for national registries.	

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	Does EMA intend to give further guidance on the concept of a single platform for all post-marketing data collection to guide national authorities' expectations? What expectations does EMA have for a MAH in terms of registry qualification as the platform for Post-Authorisation Safety (PAS) studies? MAH has certain quality assessment processes in place for CROs selection, but as EMA have pre-qualified EBMT, are MAHs able to accept this quality assessment? • We understand that the purpose of this qualification is also to allow long-term assessment which may raise the question of the sustainability of the platform as there is currently no public funding for the EBMT registry which will be the backbone to any subsequent PAS study. Industry would finance support specific PAS studies and their associated cost but not the overall registry structure. Transparency of funding and costs to be charged to industry should be ensured to avoid that, with the increased use of the registry as a source of data of marketed products, MAHs become the main source of funding for the whole EBMT registry infrastructure. ARM would welcome discussion with Member States and EU Commission to secure a sustainable system in line with the long-term regulatory requirements. • While EBMT's registry may be deemed adequate by the EMA for use in post-marketing setting, currently, there are limitations from the perspective of a MAH, including: it does not capture data from all countries where products may be administered; it does not capture data outside of transplant centres (this poses a substantial limitation, given current requirement to follow patients for 15 years, including for efficacy/effectiveness, and risk for	EMA has published a discussion paper (9 November 2018) on the use of patient disease registries for regulatory purposes (https://www.ema.europa.eu/documents/other/discussion-paper-use-patient-disease-registries-regulatory-purposes-methodological-operational_en.docx). MAH are required to discuss with registry holders the exact procedures and measures to ensure quality of the data. The prequalification process does not relieve the MAHs of this requirement. While it is agreed that sustainability is an important aspect for any registry there is currently no role for member states or the EU commission to develop a system for registries overall. The EBMT registry has been developed without industry participation and the possible contribution of industry will help to support specific studies but it is not expected that the registry overall will depend these contributions. No registry will capture all patients and the challenges to follow-up patients that change treatments centers and physicians are not specific to the EBMT registry. It is acknowledged that currently only transplant centers are members of EBMT but this does not seem an insurmountable hurdle as collaboration of physicians involved in follow-up could be facilitated with appropriate

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	patients to discontinue visits to the transplant centre after the first few years post-treatment); it does not capture patient-reported data. These aspects could be further developed by EBMT in the future. EBMT's plans regarding data-access are unclear. • ARM understands that EBMT intends to use the registry for CAR T-cell products with a marketing authorisation as well as other types of CAR T-cell products. For transparency reasons, and in order to ensure appropriate and thorough safety assessments, the manufacturer and batch number of the product should be systematically recorded, as well as the framework under which it is used, with appropriate authorisation reference number where relevant (e.g. hospital exemption). • In general, ARM supports the governance recommendations as outlined in the Report on CAR T-cell therapy Registries workshop held on 9 February 2018, in particular the adherence to the Good Pharmacovigilance Practice and the ENCePP Code of Conduct. It would be helpful if the EMA could refer to this in its response to EBMT questions. • ARM also questions whether the new Task Force established with the Heads of Medicines Agencies (HMA) and the EMA to explore how medicines regulators in the EEA can use big data to support research, innovation and robust medicines development has a role in providing an opinion on specific registries.	agreements. The addition of additional data fields is possible within studies and therefore PRO could in principle be added if required by the study. The possibilities for data access have to be discussed by the registry holder and the MAH of a specific study. This is not within the remit of regulators. It is agreed that the used product must be identifiable. Batch numbers may be dispensable for autologous products. If used pseudonymity of data must be ensured. The importance of adherence to the Good Pharmacovigilance Practice and the ENCePP Code of Conduct is acknowledged. However, as these aspects pertain to the conduct of the studies, essentially they should be considered and agreed by the MAH during the set up of the study protocol. Obviously there is some overlap in the different initiatives and the input is ensured by consultation of individual experts in the regulatory network knowledgeable in the topic. However, the "Big data task force" has no direct role in providing a qualification opinion which is a CHMP led procedure.
1	*European and international convergence of requirements* • In EU, in order to maximise its utility, it will be paramount to ensure the quality of data that is collected and captured in the registry in a consistent, harmonised way from all countries.	

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	• As the number of initiatives relating to registries multiply, ARM stresses the need for all organisations and networks to dialogue and align definitions, systems and requirements. In particular, it should be ensured that EUnetHTA (JA 3, Work Packages 5 and 7, and subsequent future JA) is involved. It is understood that the EMA/CHMP qualification procedure relates to the use of data for regulatory decision. In a similar way, qualification by EUnetHTA and HTA bodies should be encouraged as long-term product assessment is also of relevance to them. • Registries are also increasingly being developed and used outside Europe. Importantly, EMA/FDA collaboration and discussion on this harmonisation and on the recognition and the use of data from those registries would facilitate complex product development. ARM recommends that standards to develop and operationalise registries including definitions and methodologies for quality assurance should be part of the reinforced US/EU collaboration on medicines as announced by the EMA on 22 June 2018. The EBMT registry could be used as a pilot for such collaboration. • ARM welcomes and supports the effort of harmonisation and specifically with CIBMTR facilitating the use of data to support global development. Standardisation is essential to enable the use of several data sources. Work with organisations similar to EBMT such as CIBMTR to align practices and standard operating procedures is encouraged to allow data combination and more robust data.	It is welcomed that HTA bodies engage in the discussions and this spirit is reflected in the invitation of HTA bodies to the recent CAR-T cell registry workshop. It is expected that discussions will continue on the level of individual member states prompted by requests from MAHs. As EUnetHTA has no deciding role, this seems appropriate.
1	*Need to involve HTA bodies and payers*	

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	• As registries are often useful data source and requested by HTA bodies and/or payers (such as part of market entry agreements to address uncertainties that may exist at the time of marketing authorisation), it is important to also involve them and seek their opinion (see comment above re. European and international convergence of requirements). In practice this could be dealt with EUnetHTA through WP5 which involves 38 organisations from 22 countries. Parallel regulatory/HTA qualification of registries is encouraged (see above). Independent national HTA registry initiatives should be discouraged to avoid duplication of efforts and facilitate data access and scientific analysis.	See above, this should be addressed to EUnetHTA and not to regulators. While it is agreed that a common approach to the use of registries is the most meaningful approach, EMA has no role regarding national requirements and discussions.
1	*Quality assurance and control mechanisms* • As noted in the opinion the EBMT registry does not currently have an audit plan. While additional monitoring activities can be implemented per study protocol with additional funding from the MAH/sponsor, the registry owner should seek efficiencies in implementing these activities so as to make the best use of resources and avoid unnecessary duplication of work. • ARM recommends leveraging existing guidelines or possibly developing a new EMA guideline to provide guidance on design and use of patient registries in order to address the practical design and operational issues, evaluation principles, as well as quality indicators, source verification and control mechanisms. Previous work in this area (such as of the ISPOR-ISPE Task Force) and other existing international guidelines such as the AHRQ publication, "Registries for Evaluating Patient Outcomes: A User's Guide" could be reviewed and integrated in the guideline to be	EMA cannot require registry holders to conform to certain standards but make recommendations that would make it more likely that any given registry could be used for regulatory purposes. The interaction with the registry and the responsibility for implementation and agreement of additional activities relies, therefore with the MAH as defined in the study protocol agreed with regulators. Additional guidance may be developed depending on the need as judged by future qualification requests. As already mentioned, EMA has published a discussion paper (9 November 2018) on the use of patient disease registries for regulatory purposes (https://www.ema.europa.eu/documents/other/discussion-paper-use-patient-disease-registries-regulatory-purposes-

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	developed by the EMA so that registry holders and users are clearer about requirements and quality standards. • In order to realize the full potential of EBMT's registry in supporting the needs of MAH, EBMT must adopt a collaborative, transparent, and well-organized approach to industry engagement. Appropriate resources should be available at EBMT to support registry maintenance in compliance with industry and regulatory expectations.	methodological-operational_en.docx)..
1	*Terminology: clear distinction to be made between cells and ATMPs* • EBMT names the module of the registry dealing with CAR-T cell products the "Cellular therapy module". ARM believes that such terminology is misleading. CAR-T cell products clearly fall under the definition of medicinal products and need to comply with the requirements for medicinal products (as well as Genetically Modified Organisms), including pharmacovigilance requirements, which are significantly different from cells for transplantation/infusion. This is important as physicians or patients are not necessarily aware of the differences between cells and advanced therapy medicinal products based on cells. It is strongly recommended to review the terminology to avoid any possible confusion between medicinal products and cells for transplantation/infusion. A correct terminology should also be used in the data fields of the registry. • The EBMT form for data collection such as provided on the link provided on line 882-3 adds confusion on requirements for cells or ATMPs. On pages 5 & 6, the form includes description of	The "Cellular therapy module" was developed as a generic form prior to any qualification activities. It is not within the remit of EMA to ask the EBMT registry to implement certain changes but it has to be ensured via the specific protocols and agreements between MAHs and the EBMT registry. It is expected that appropriate measures are taken to ensure that the specific product that the patient receive is recorded otherwise the registry study would not be possible. Therefore, no confusion is anticipated. Other types of products or cellular preparations are not subject of the qualification opinion.

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	substantial and non-substantial manipulations carried out by the Cell Therapy Infusion Unit. Operations that constitute substantial manipulation fall under the scope of pharmaceutical manufacturing operations and therefore need to operate under GMP requirements, rather than the scope of an Infusion Unit which normally operates under Good Tissue Practice and/or JACIE accreditation. We understand that some MAHs for CAR T-cells are developing with EBMT specific forms to capture data about their product. Nevertheless, it is requested that forms used by EBMT for CAR T-cells or any other ATMPs that do not belong to a MAH (e.g. a product used under the hospital exemption framework) be reviewed to make clear distinction between cells for transplants and ATMPs.	
1	*Next steps and communication* • Anticipation of the evolution of the CAR T-cell therapies registry due to the inclusion of CAR T-cell data beyond haematology indications (oncology) or to other type of ATMPs such as gene therapy medicinal product consisting of genetically modified cells should be further discussed (impact assessment and core data collection). Some comments are offered in anticipation that a similar EMA opinion may be developed in the future. ARM would welcome the opportunity to collaborate further and contribute, with relevant stakeholders, to the development of a standardized form for other types of gene therapy medicinal products consisting of genetically modified cells. • ARM would welcome EBMT responses to the Qualification process	With publication of the qualification opinion, the current EBMT procedure is finalised and no further interaction is required. Based on regulatory approval of the respective study protocols it is the responsibility of MAH to ensure that the identified issues are addressed.

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	to clarify its plan to resolve gaps identified by EMA. A transparent communication on the resulting implementation plan would be welcome.	

2	The Cell and Gene Therapy Catapult welcomes the possibility to comment on 'Draft qualification opinion on Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry'.
	
	In addition to the ARM response, CGT would like to emphasise that the maximum utility of the registry is strongly encouraged:
	• It is recommended that the ability of the registry to interact /work in context with other international registries is regarded essential.
	• It is believed that ensuring the registry is able to capture data required for reimbursement purposes is key to maximising the utility of the registry and to facilitate this we recommend:
	  • A further workshop with companies, HTA, payers
	  • A further qualification of the registry after this.
	• We would suggest EBMT to work with CAR-T developers (SME and larger pharma) and industry stakeholders to develop the registry.
		While it is generally agreed that the EBMT registry could potentially serve other purposes than the regulatory requirements for follow-up and PASS, these comments are addressed at different stakeholders and outside the remit of a qualification opinion.

3	The Dutch Society of Hematology strongly supports the CAR T registry of EBMT as well as the draft qualified opinion of EMA, which will avoid duplication of data sets and allow capturing an excellent minimal data set. In particular, guidance on minimal data sets as well as quality measurements are very helpful for the community. This will not only allow assessing risks of individual CAR T but also in the	

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	long run comparing efficacy as well as cost effectiveness of individual assets.	
4	Generally, we would like to support this Qualification Opinion. Having worked in the field of cellular therapy and haematopoietic cell transplantation (HCT) for many years, we know the EBMT as a reliable, competent and most valuable partner in collecting outcome data of HCT procedures for benchmarking, quality assurance and scientific purposes. Together with its American partner organisation, the US-based Centre for International Blood and Marrow Transplant Research (CIBMTR), it is the global leader in this field. Whereas the majority of EBMT activities have been related to HCT, the collection of non-HCT cellular therapy data by the EBMT has gained increasing importance during recent years since these therapies are increasingly entering the clinical stage. Altogether, the EBMT seems to be well prepared to serve as a data source for regulatory and also scientific purposes in CAR-T cell therapies.	
6	The report suggests that good mechanisms are in place to enable appropriate quality control but each study will need to describe how those mechanisms were applied and action taken where inconsistencies were spotted. Coverage and Completeness will need to be reported. There is no mention of data linkage/triangulation to validate information. This is particularly important for mortality because if treatment is provided in specialist centres they will have difficulty gathering outcomes data for patients who live a long way from the	Data linkage could address important questions and improve data quality and completeness of follow-up. However this would require initiatives on a local/national level as there is no European system in place. It seems more important that

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	treatment centre. CHMP poses important questions – have they been addressed?	EBMT establishes mechanisms to ensure follow-up of patients that are treated outside of EBMT centres.
	It is implied but not clearly stated that studies should have a protocol with stated research questions and analysis plan at the outset – there is a temptation with registry data to add analyses as findings progress. It would be good if the EBMT made it clear that this would not be enabled. E.g. who owns the data at the end of a study? Will there be an opportunity for centres to request their data and collaborate on further analyses that were not originally planned? This should probably be allowed but the EBMT should perhaps maintain authority over use of data in order to ensure quality of subsequent analyses? Page 38 suggests that this is the case but not absolutely explicit.	The qualification opinion cannot pre-empt and mandate discussions between MAHs and the EBMT registry. This is particularly true for data ownership and data access. It is the understanding of CHMP that currently all EBMT members can initiate scientific studies based on the whole dataset once approved by the governing structure of the EBMT registry and the individual members.
	As a contributor to WP5 JA3, I would make one predictable comment: it would be much easier to assess whether the proposed registry meets requirements if an agreed tool were used. This would allow agreed criteria to be addressed and evidence presented in a repeatable form for all users to consider.	The comment is not completely understood. However, it is emphasized that the purpose of the current procedure is to qualify the registry as proposed by EBMT.
	Table 3 is relevant to interoperability of CIBMTR and the EBMT registry but only at a level of data set. The PARENT initiative refers to many more aspects of interoperability which could be considered unless CIBMTR is willing to forgo all data collection for patients covered by the EBMT? NB line 949 suggests that GDPR is being considered but there would still be more technical issues to deal with.	It is expected that European patients will be included in the EBMT registry and American patients will be included in the CIBMTR registry. For the anticipated Cell Therapy PASS studies, EBMT has drafted a PIL/ICF template that will be made PASS-specific

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	If treatment centres are responsible for consent, how will the EBMT ensure that their high governance standards are maintained by all centres? I think they need to have a copy of the consent form used by each centre and assure appropriateness for proposed uses (our experience is that this is necessary to avoid delays on sharing data). EBMT states that it does not have resource to check compliance on consent but it should have resource to check that it considers each centre's form to be adequate for the study purpose.	in collaboration with the MAH. This PASS ICF covers data collection and storage in the EBMT registry. This document will be part of the submission package to the CAs and ECs and will have to be signed by all participants in the PASS. However, at the present time, responsibility to ensure collection of consent from patients is left to the individual centres. EBMT has developed a consent template form and a patient privacy statement, all available on the EBMT website. These documents fulfil the current GDPR 2018 requirements. All centres will be required to sign a statement of conformity with their legal obligations under GDPR. Currently EBMT does not review the consent forms used by each centre. By implementation of the new MACRO software EBMT will consider the possibility to allow the centres to upload their consent template (the blank template, not ICF per patient) to the platform where the contents could be checked for completeness against the template. Availability of resources/budget to cover such aspects remains a critical issue.
	Do all centres use the same software to submit data? Our experience with registries that allow centres to use a variety of software for data submission is that this can cause delays and problems with interoperability. The submission is not clear on this point.	EBMT is implementing a common software for all centres. Currently, centres report via the online ProMISe tool and from 2019 will report data via the new MACRO online database.
7	Thank you for asking opinion regarding a registry dedicated to CAR-T	The internal organisation of the EBMT registry (e.g.

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	cells treatment. You pointed out a very important topic since it is of outstanding importance to have a registry, better at the European level. SFGM-TC do agree with a PROMISE approach since it is already working well and known by most actors of the cell therapy field. However, we should be very careful to three particular possible problems, which are 1) the resources, 2) the access to the data base and 3) the acceptance by non-transplant colleagues but expert of CAR-T cells. 1. Resources. I don't think we will have extra funds to run this registry. Our French authorities did not mention anything. Except the fact that it has to exist. It will thus be probably another task for centers except if EBMT redistribute compensation from company support since I believe EBMT will probably receive funds to run such registry. 2. Access to the data. It is for me of great importance that the producers of the data will in the end be able to take advantage of them easily. Data should thus not be published by people who have few clinical experience in it, at least at the beginning. And clear rules have to be written. 3. This last comment concerns in particular the non-transplant community. I can imagine their reaction about an EBMT registry. As well as all French physicians in copy, you know the discussion we already had in France, many times, about this. Very touchy and sensitive topic, which is fully understandable. The communication and collaboration with our non-transplant colleagues is for me fundamental and is the guarantee of success.	distribution of work and funding) cannot be commented on by CHMP. It is within the remit of EBMT how to structure the relationship of centres and the central organisation. As outlined above data ownership and access cannot be mandated by external stakeholders to the EBMT registry. The inclusion of non-transplant centres that are involved in the care of patients receiving CAR-T cells is sensible and important, however collection of data could also be achieved by other means. Only EBMT can define the process, start involving non-transplant centres and achieve agreement on who contributes to the registry in which way. Coverage and completeness are at the core of data collection and it is responsibility of EBMT to ensure this.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
8	From the Spanish Cell Therapy and Criobiology Group (GETCC) and its CAR Group (GECAR) we confirm our conviction that EBMT Registry is an excellent and suitable registry to record and follow-up information of patients treated with CAR-T cells. EBMT registry has been for several decades an important and trustable tool for development of hematopoietic stem cell transplantation (HSCT) in Europe. It has made possible the systematic and safe collection of quality scientific data and comparative studies between different treatment approaches for severe hematological and non-hematological diseases mainly genetic diseases, autoimmune diseases, and solid tumors. We confirm our disposition for a sustained strong partnership between GETCC, GECAR, the Spanish Group for Hematopoietic Progenitors Cells and Cellular Therapy (GETH), the Spanish Society of Hematology and Hemotherapy (SEHH) and the EBMT, in order to use EBMT Registry for that purpose and to improve points in which the EMA consider the EBMT Registry needs to expand to include data on important and specific CAR-T cells complications.	
9	From the Spanish Group for Hematopoietic Progenitor Cell Transplantation and Cellular Therapy (GETH) we confirm our conviction that EBMT Registry is an excellent and suitable registry to record and follow-up information of patients treated with CAR-T cells. EBMT registry has been for several decades an important and trustable tool for development of hematopoietic stem cell transplantation (HSCT) in Europe. It has made possible the systematic and safe collection of quality scientific data and	

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	comparative studies between different treatment approaches for severe hematological and non-hematological diseases mainly genetic diseases, autoimmune diseases, and solid tumors. In addition to the commitment to report data as EBMT members, the increasing number of JACIE accredited Spanish institutions includes a way to audit the reporting completeness and accuracy of data. Also, the GETH has recommended the Spanish Health authorities HSCT data be reported on a mandatory basis. We confirm our disposition for a sustained strong partnership between GETH, the Spanish Society of Hematology and Hemotherapy (SEHH) and the EBMT, in order to use EBMT Registry for that purpose and to improve points in which the EMA consider the EBMT Registry needs to expand to include data on important and specific CAR-T cells complications.	
10	From the Spanish Society of Hematology and Hemotherapy we confirm our conviction that EBMT Registry is an excellent and suitable registry to record and follow-up information of patients treated with CAR-T cells. EBMT registry has been for several decades an important and trustable tool for development of hematopoietic stem cell transplantation (HSCT) in Europe. It has made possible the systematic and safe collection of quality scientific data and comparative studies between different treatment approaches for severe hematological and non-hematological diseases mainly genetic diseases, autoimmune diseases, and solid tumors. In addition to the commitment to report data as EBMT members, the increasing number of JACIE accredited Spanish institutions includes a	

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	way to audit the reporting completeness and accuracy of data. Also, the SEHH joined to the GETH has recommended the Spanish Health authorities HSCT data be reported on a mandatory basis. We confirm our disposition for a sustained strong partnership between the SEHH, GETH and the EBMT, in order to use EBMT Registry for that purpose and to improve points in which the EMA consider the EBMT Registry needs to expand to include data on important and specific CAR-T cells complications.	
11	Hematon is the Dutch organisation which supports all patients who have lymphoma, blood cancer or underwent stem cell transplantation. Cellular / CAR T cell Therapy is a new therapy with many unknown factors and is associated with potentially serious side effects. Therefore patients need to be registered in a way it can enhance the safety of (future) patients. We are aware of the good reputation the European Society for Blood & Marrow Transplantation (EBMT) has in the haematological field concerning the registry of autologous and allogenic transplants in EU. EBMT registry has long lasting experience, a good data quality, a good reputation on clinical research data and the long term follow up is helpful for getting to know the long term effects of the Cellular Therapy. Because of the nature of Cellular Therapy we also feel that sufficient attention and care should be given to the registry of side effects as well as information on quality of life of patients treated. Hematon supports the request of EBMT that all the CAR T cell procedure will be documented in a registry in a way which EBMT is	

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	already doing for all stem cell transplantation procedures in Europe for many years.	
13	From ASLEUVAL, as an Association of patients, we are convinced that: the EBMT Registry (European Hematopoietic Transplant Group) is, by its trajectory, a necessary and adequate registry: ☐ to record the information of patients treated with CAR-T cells. ☐ to monitor and compare results in a safe way and with adequate data protection for patients	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 50-51	1	Comment: We understand that the involvement of HTA bodies and payers goes beyond the scope of the qualification of the EBTM registry by the EMA but, as explained above, ARM encourages additional consideration to be given to requirements from HTA bodies and payers as they also share similar interest in Post-Launch Evidence Generation and long-term value assessment.	Accepted. As mentioned by the stakeholder, it's outside the scope of CHMP qualification.
Lines 87-88	1	Comments: The EMA draft qualification opinion reports the use of EBMT Registry as a source of external control data that could be used for comparative purposes in the context of non-randomized clinical trials, when this would be the only reasonable option. The EMA qualification purpose is primarily intended for post-marketing monitoring of a CAR T medicinal product. The use of EBMT registry data as external control needs to be evaluated in the context of each specific study, with the potential bias or data limitations being appropriately identified and addressed (for instance by match paired analysis when the variables captured in the registry are sufficiently complete to allow this). The registry use as a source of external control data should	Not accepted. This appears to be based on a misunderstanding: the extent of the qualification opinion is determined by the applicant that has asked for qualification and not by the current discussion among different stakeholders. CHMP has addressed this question with appropriate caveats.

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		be removed from the draft EBMT qualification opinion by EMA as this is not the primary purpose of the EMA qualification report.	
Lines 89-101	1	Comment: While this may be a good system for collection of safety information, considerations on access to data to MAH for routine pharmacovigilance activities are missing. ARM understands that these aspects will be part of the agreement between MAHs and EBMT. EMA recommendation on the need to have access to data would be welcome.	Accepted; no change is considered necessary. Access to data cannot be mandated by CHMP, this entirely up to discussion and contractual agreement between MAHs and the EBMT registry.
Lines 104-107	1	Comment: It is unclear whether the approval referenced in this sentence relates to regulatory endorsement of a study design or regulatory authorisation to conduct a study. These are separate activities and not every study requires to go through both procedures: - regarding the regulatory authorisation to conduct a study: non-interventional trials do not need regulatory approvals in most EU countries. - regarding regulatory endorsement of a study design: even though it may be preferable to have an agreement with regulatory authorities on the study protocol, only certain studies need to have their design endorsed by regulatory authorities (e.g. PAS study design endorsed by PRAC). As per the report on the CAR T-cells therapies	Accepted; explanation added ("within a centralised procedure"). The term "regulatory approval" is applicable only for PASS and PAES requested by regulators within a centralised procedure.

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		registries workshop, the MAH is expected to develop a preliminary protocol and discuss with registry holder(s) and EMA the CAR-T registry protocol proposal. It is recommended to adopt the same wording in this qualification opinion. In addition, it is recommended that HTA bodies should be encouraged to take part in the early discussions on individual study considerations.	
Lines 112-119	1	Comment: ARM agrees that source-document verification should be conducted. Given the importance of post-infusion follow-up, we recommend that, rather verifying full records for 10% of patients, instead 10% of data elements, reflecting the most critical data elements in the registry, are verified for every patient. Clarifications on who would be the responsible entity for this verification (MAH or EBMT or third party) is welcome.	Partly accepted. The elements of the individual studies are discussed between the MAHs and regulators, based on a protocol developed by the MAHs. A second discussion has to occur between MAHs and the EBMT registry. From the perspective of the regulator, the responsibility lies with the MAHs.
Lines 121-122	1	Comment: Individual study considerations report that "procedures to assure sequential inclusion of all patients treated with the individual centres, to identify and collect missing data as well as to minimise patient lost to follow-up should be detailed". ARM questions the interpretation of such a study consideration in the post-marketing setting. These aspects should be dealt with	Not accepted. The primary responsibility for study conduct lies with the MAHs who remain to be the partner for interacting with regulators and cannot be dealt in a general fashion but only within a specific protocol and a specific product.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		in the guideline on registries that EMA could develop, as proposed above (see general comment about quality assurance and control mechanisms).	
Lines 128-144	1	Comment: ARM strongly supports the recommendations for enhancement provided on these lines, in particular harmonisation of requirements with CIBMTR. Besides, we recommend international collaboration through EUnetHTA WP5 and the US/EU collaboration (see general comment above).	Accepted; no change is considered necessary.
Lines 164-169	1	Comment: JACIE qualification is not mandatory in all EU Member States. Please provide additional clarity regarding the position for non-JACIE accredited centres. The sentence on lines 164-167 is also not very clear. Proposed change: Delete "for authorisation and/or reimbursement purposes" on lines 166-167.	Not accepted. JACIE accreditation is not required, this is only a supportive line of argumentation taking into account the views of independent stakeholders. The statement on reimbursement purposes should be understood in a similar fashion.
Lines 171-181	1	Comment: • In general, we share CHMP concerns regarding the lack of certification and audit system of the EBMT registry when the data serve as a basis for assessing and reviewing the marketing authorisation and/or funding of medicinal products. In light of the tripartite collaboration	Accepted; no change is considered necessary as the comments go beyond the scope of the qualification opinion.

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		recommended by the EMA, the CAR T study sponsors/MAH expect to get updates on the outstanding EBMT actions flagged in the draft EMA opinion as they may influence the use of EBMT Registry as data source by MAH. E.g. Standardisation (e.g. AE grading) between EBMT and CIBMTR. Also, key indicators measuring the extent of missing data are not defined and implemented, there is no definition of the timelines for data entry and there is no collection of information regarding the fraction of data that undergoes source verification. • ARM believes that a guideline on the use of registries to evaluate patient outcomes, including recommendations on the quality certification mechanisms, should be developed, taking into account the work already carried out by other groups and jurisdictions in this area (see above, under general comments). Clarification regarding the type of accreditation and/or data collection standards that would be required for databases used for post-launch evidence generation (PLEG) purposes is welcome and could be addressed in the guideline. • In the meanwhile, it is requested that marketing authorisation holders and/or regulatory authorities have a right to audit the EBMT registry and assess the quality – accuracy, consistency, and	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		completeness - of the data before these are used in the context of drug efficacy/effectiveness or safety evaluation. It is suggested that pharmacovigilance inspectors could inspect the registry prior to its use for PLEG.	
Lines 185-198	1	Comment: It is unclear which EBMT's Cellular Therapy form is referred to in this question. ARM presumes that it relates to the EBMT's "Cell Therapy Med-A - registration to month 6" form, as provided on lines 882-883. However, ARM understands that other forms relating to specific CAR T-cell products are being revised between EBMT and some MAHs. As stated above under 'General comments', the current form 'Cell Therapy MED-A' does not make a clear distinction between cells for transplant/infusion and ATMPs. CHMP answer refers to discussions during the Workshop held by EMA on the 9th February 2018. However, it is noted that the information provided on variables collected in this form lacks the granularity associated with Appendix 1 of the report on the CAR T-cell Therapy Workshop (EMA/299528/2018). ARM takes this opportunity to comment on the variables provided in Appendix 1 "Proposed data elements relating to Efficacy (Table 3) and Safety (Table 4)" of the Report on CAR T-cells therapies Registries: • Comment on Table 3, line "Prior therapy for	Acknowledged.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the malignancy": The information to be provided need to be sufficiently specific to identify patients studied as part of a post-authorization study and exclude others. Proposed change: Add: Record licensed indication of CAR T-cell administration that best fits the characteristic of the patient.	
		• Comment on Table 3, line "CAR T-cell administration": The data capture looks like it may not allow for the capture of more than 1 dose of CAR T-cells. Proposed change: Ensure that the form includes sufficient fields to identify the product, dose and date for multiple administrations.	Acknowledged.
		• Comment on Table 3, line "CAR T-cell Early Response: Efficacy measures & assessment": Collecting the date of MRD negativity (if applicable) would be of significant value to measure response for patients with multiple myeloma. Proposed change: Add date of MDR negativity in patients with multiple myeloma	Not accepted. There is currently no approved CAR T-cell product for multiple myeloma. Relevant changes can be considered in the future.
		• Comment on Table 3, line "Early and later	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		responses: Efficacy measures": Collecting data from either the EQ5D or SF-36 generic quality of life questionnaire will enable utility derivation to inform quality-adjusted survival calculations. These data will inform the long-term quality of life outcomes form CAR T therapies. Note that the EQ5D 5L is a shorter PRO and hence may be easier to capture from patients but the SF-36 PRO may generate more useful insights on health status. Proposed change: Add "Capture of data on either the EDQ5D or SF-36"	Not accepted. There is no regulatory requirement; it is up to other stakeholders to reach agreement.
		• Comment on Table 3, line " Follow-up: efficacy -Subsequent anti-cancer treatments given [Name/s, start/end date, response evaluation for each therapy]": From an HTA perspective, it is important to capture data on subsequent anti-cancer treatment to support value-based pricing agreements where data on subsequent treatments can help inform interpretation of the benefits obtained from the CAR T therapy as well as generate data to better understand the treatment pathway by country for patients receiving CAR T therapies. Capture of response evaluation for each therapy would enable research questions around whether the receipt	Not accepted. There is no regulatory requirement; it is up to other stakeholders to reach agreement.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of CAR T therapies achieves (1) a deeper and prolonged response to subsequent therapies (i.e. a preferential response) compared to non-CAR-T patients (2) a similar response to subsequent therapies as experienced by non-CAR-T patients (3) an inferior response to subsequent anti-cancer therapies as experienced by non-CAR-T patients. Proposed change: Add: Information on all subsequent products should be captured to include product name(s) and dose(s) and start/end date. Capture of data on ORRs to subsequent therapies would enable the above research questions to be addressed. • Comment on Table 3, line "Early Response: Efficacy Measures – Minimal residual disease (MRD)": Collecting the date of MRD negativity (if applicable) would be of significant value for patients with multiple myeloma particularly if MRD negativity at a given time point was deemed an appropriate measure of treatment benefit to inform value-based pricing agreements. Proposed change: Add: Capture date of MRD negativity in patients with multiple myeloma	Not accepted. There is currently no approved CAR T-cell product for multiple myeloma. Relevant changes can be considered in the future.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• Comment on Table 3, line "Follow-up: Quality of life (EQ-5D, HRQoL) / Performance status" on page 10: Proposed change: Add: Include the EQ-5D 5L questionnaire at baseline and a 6-month interval time intervals post-initiation of CAR T treatment. • Comment on Table 3, line "CAR T-cell administration: product and dose": CAR T-cell therapy may be preceded by a chemotherapy conditioning regimen, or given with concomitant treatment as substantial part of the therapy Proposed change: Add: capture data on: - conditioning regimen (listed as *Nice to have*) - Concomitant treatment (not listed yet) • Comment on Table 3, line "CAR T-cell Early Response: Efficacy measures & assessment": Immunophenotyping to evaluate expression of biomarkers on cancer cells, immune cell populations, cytokines and other circulating serum proteins following chemotherapy conditioning (t=0) as well as following infusion of CAR-T cells (t=1/2/..) may reveal (early) predictive value for response/resistance in due time based on trial data, hence application in clinical practice should be anticipated.	Not accepted. There is no requlatory requirement. Acknowledged. Not accepted. Exploratory research questions are not within the remit of this exercise.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Add: Capture data on: - biomarker assessment – bone marrow/lymph node/other biopsy - biomarker assessment – whole blood sample	
Lines 189-198	1	Comment: In general, ARM believes that the data required depend on the study objectives. It is therefore difficult to determine whether the form captures data suitable for any type of study. Similarly, the frequency of data reporting may not be adequate to identify short- to medium term effects. A case-by-case evaluation should be carried out to evaluate the adequacy of the form and the frequency of data report. ARM suggests a statement along those lines to be added.	Agreed; no change is considered necessary. Study protocols will determine what data have to be collected at what intervals. Short term effects are reasonably well covered by clinical trials and by the more frequent collecting that is recommended initially.
Line 205-208	1	Comment: The capture of data on appropriate measures of treatment benefit to support long-term benefit/risk and value assessment is essential. ARM strongly recommends collaborating with EUnetHTA to validate the frequency of data reporting. ARM believes that the capture of information on response status at 3 months, 6 months and so on for the first 3-5 years and then annually (rather than doing so annually from 6 months) is a frequency more adapted to meet the	Not accepted. While there are no objections to more frequent data collection, there can be no regulatory requirements for the needs of other stakeholders. The proposed intervals seems well suited for regulatory purposes and do not put an untoward burden on the treating centres.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		needs of all stakeholders. The speed of data availability at specific data point is equally important to ensure timely assessment and meet regulatory requirements.	
Lines 216-234	1	Comment: ARM believes that having a final agreed protocol is a pre-requisite before the study can start and should not be made optional as CHMP response suggests. Similarly, study amendments should be documented and agreed upon in writing with the same parties as involved in the initial study protocol development prior to the amendments being implemented. Protocol deviations should be documented and reported. We support the answer provided by the CHMP on lines 223-234 and suggest the words "by the MAH" to be inserted after "will be submitted". Proposed change: "For Registry studies performed on request by regulatory authorities (e.g. CAT/PRAC), the (draft) protocol including rationale, design, objectives, research question, methodology and time lines for enrolment and reporting will be submitted **by the MAH** to the PRAC/CAT for agreement prior to study start".	Accepted; explanation added ("by the MAH").
Lines 241-255	1	Comment: Please refer to the general comment above regarding the proposal to develop a guideline that could include	Accepted; no change is considered necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		guidance about the management of monitoring of centre's data.	
Lines 258-280	1	Comment: • Question 6, as well as the Applicant's position on that question (lines 617-655) relates to the use of the registry for a comparator arm. Creation of a control arm from the existing database may not be most appropriate due to the biased patient population included in the EBMT registry, which may only include transplant eligible patients. This qualification opinion should be focused on the registry itself and not the design of studies that would be discussed between EMA and MAH. As stated above (comment on lines 87-88), the registry use as a source of external control data should be removed from the draft EBMT qualification opinion by EMA as this is not the primary purpose of the EMA qualification report. • If the EBMT Registry is considered as a source of data for CAR T-cell product comparative studies, ARM recommends that a multipartite interaction with all stakeholders involved be organised prior to the initiation of such studies. • ARM agrees with CHMP considerations regarding the suitability of data for comparative analyses.	Not accepted; see above.
Lines 288-	1	Comment:	Agreed; no change is considered necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
301		ARM strongly supports the standardization of data elements/fields collected in all treatment centres and harmonisation with other registries (e.g. CIBMTR). The handling of proprietary data regarding the manufacturing of the product or other aspects, proposed to be stored in a restricted area of the registry, should be discussed and agreed upon with the marketing authorisation holder(s), as mentioned above.	
Lines 309-320	1	Comment: The sentence on line 309-312 is pointing the primary collection vs the secondary use with regards to the AE reporting obligations. The sentence reads unclear and would be clarified and linked to the next paragraph. Proposed change: Line 314: Replace "in the first case" by "In the primary data collection" Line 317: Replace "In the second case" by "In the secondary use".	Not accepted. The two sentences have been clarified (i.e., replacement of the text "in the first/second case" with text specifically mentioning "secondary/primary"). Moreover, a paragraph has been added to clarify that, in agreement with GVP Module VI, non-interventional post-authorisation safety studies (PASS) that allow long term follow up of CAR-T cellular therapy products pertain to primary data collection and therefore solicited reporting of ICSRs applies.
Lines 338-339	1	Comment: It is recommended that the requirements for the process and information on the consent form are addressed in a guideline to be developed which would	Not accepted. This is outside of the scope of a qualification opinion. Specific recommendations are given in the opinion.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		define requirements for the practical design, operational issues, and evaluation principles of registries, as well as quality indicators, source verification and control mechanisms (see above general comment about 'Quality assurance and control mechanisms'). A consent template for use in all Member States would also be very helpful.	
Line 365	1	Comment: The capacity to add non-EBMT centres should be evaluated and encouraged.	Not accepted. Regulators cannot mandate how EBMT works overall. The importance of completeness and coverage are emphasised.
Lines 384-386	1	Comment: We support CHMP answer provided to question 11 and share their concerns regarding the quality controls applied. We suggest leveraging existing guidelines or developing a new one to include guidance on quality assurance and control aspects, as well as audits, inspections or external qualifications to address these concerns (see under general comments above).	Accepted; no change is considered necessary.
Lines 760-761	1	Comment: As the purpose of the registry is the long-term follow-up, it should be recommended that a patient moving to a clinical trial should not be lost from the long FU analysis. The registry should be obliged to ensure certain data elements are still collected to ensure long-term outcome can still be assessed.	Accepted. It is understood that long term follow-up is maintained once patients are included in the registry, whatever the further therapy may be.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Access to patients' data should not be blocked, otherwise MAH cannot fulfil their long-term FU obligations.	
Lines 924-925	1	Comment: National registries can access data directly which could jeopardise the analysis of the PAS study, so governance about data access should be put in place for a specific PAS study (different from routine registry patients). Proposed change: Put in place agreements about how third parties (such as national registries) can directly access and analyse a national part of the MAH PAS study.	Not accepted. Any agreement between other stakeholders and the EBMT registry are outside the remit of the CHMP qualification opinion and cannot be mandated in any way.
Lines 928-930	1	Comment: Data ownership remains with EBMT but MAH needs to be able to analyse appropriately anonymised data from their PAS study to allow them to fulfil their PSUR and other reporting requirements. Proposed change: Remove the restriction that pharmaceutical companies cannot access data for their PAS study directly.	Not accepted. While it is agreed that access of different stakeholders to parts of the database that is relevant to them should be enabled it cannot be mandated but is subject to agreement between the stakeholders and EBMT.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 50-51	2	Comment: CGT would encourage additional consideration to gather and collect data for reimbursement purposes.	Not accepted; not within the CHMP remit.
Line 104-120	2	Comment: CGT would recommend including HTA in the early discussion, approval for individual study considerations.	Not accepted; not within the CHMP remit.
Line 144	2	Comment: CGT receives positively the CHMP recommendation on "Efforts for the collection of Quality of Life data are encouraged". This is necessary for full utility of the registry	Accepted; no change is considered necessary.
Line 182	2	Comment: In terms of EBMT data quality, CGT would recommend an inspection of the registry by the Pharmacovigilance inspectors of the Member States before rollout.	Partly accepted; no change is considered necessary. The quality of data collection is considered a crucial point. Regarding the proposed inspection, this should be performed in the study centres from national competent authorities, according to their requirements (routinely or in case specific triggers emerge in relation to a study). The Pharmacovigilance inspectors will assess suitability of contractual agreements describing the roles/responsibilities of each party and associated data collection/reporting (see lines 317-320).
Line 338-339	2	Comment: CGT would advise EBMT to produce a consent template that can be suitable for use in all Member States.	Accepted; no change is considered necessary (see above). EBMT has developed a consent template form and a patient privacy statement, all available on the EBMT website. These documents fulfil the current GDPR 2018 requirements. All centres will be required to sign a statement of conformity with their legal obligations under GDPR. Currently EBMT does not review the consent forms used by each centre.
Line 365	2	Comment: The capacity to add non-EBMT centres	Agreed but cannot be mandated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should be encouraged	The inclusion of non-transplant centres that are involved in the care of patients receiving CAR-T cells is sensible and important, however collection of data could also be achieved by other means. Only EBMT can define the process, start involving non-transplant centres and achieve agreement on who contributes to the registry in which way. Coverage and completeness are at the core of data collection and it is responsibility of EBMT to ensure this.
82-96 (Drug efficacy studies and Drug safety evaluation)	4	Comment: In addition to the points mentioned in the document, CAR-T cell data collected in the EBMT registry could be compared with outcome data of competing cellular therapies routinely collected by the EBMT, such as autologous and allogeneic HCT, in order to better characterize the added value provided by CAR-T cells in comparison to established treatments in the approved indications.	Not accepted. This is outside the scope of the present qualification procedure.
103 ff (Individual study considerations)	4	Comment: It should be explicitly stated which of these considerations (if any) are also meant for pure retrospective registry studies with data collected on CAR-T therapies by the EBMT registry	Not accepted. Comments are made for studies initiated for regulatory purposes that are made on prospectively collected data.
153 - 181	5	Comment: EBMT should be responsible for maintaining data quality mechanisms. However these have to be agreed with the Industry partners and in the first couple of years, there should be more intensive training and personnel dedicated to maintaining data quality.	Agreed; no change is considered necessary.

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		Industry partners should agree on harmonized data quality checks since the data collection forms are standardized. It's unlikely that a site will be able to enter correctly data for drug A but not for drug B on the same form and so no need for different data quality monitoring. We would also recommend a standardization of data coding (e.g., MedDRA, WHO DD, ICD, etc.) with similar approach in up-versioning strategies, across all studies. Enhanced quality may also be achieved by establishing a centralized definition of variables (e.g., prolonged cytopenias).	
188 - 198	5	Comment: Information on the treatment of Cytokine Release Syndrome (CRS) and neurotoxicity (NE) should be collected including the agent used, dose, what triggered the use of the agent (Severity or lack of response to another agent). Treatment for CRS is not yet harmonized and this will add some evidence as to whether the recently approved tocilizumab use is being optimized as well as understand the patient or CRS characteristics leading to use of tocilizumab or other alternate immunosuppressants e.g. steroids or siltuximab. The same applies for neurologic events as the scales for grading severity, defining what is a neurologic event and treatment of neurologic events is not	Agreed; no change is considered necessary. EBMT is in the process to use common scales for CRS and neurological events. Recommendation has been made to record treatment of these specific observed AE.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		standardized. Wherever possible the PASS sponsors should establish a single harmonized method of assessing the severity of adverse events (e.g., Lee, Penn, etc., for CRS).	
204 - 208	5	Comment: Events like secondary malignancy, or those with fatal outcome, should be reported to the EBMT as soon as possible rather than wait for the 3 months. That will allow EBMT to follow up on any sample testing that would have been performed.	Not accepted. Requirements for AE reporting and collection of AE within the registry can follow distinct reporting pathways and do not necessarily have to be harmonised. It is responsibility of MAH to establish clear and transparent procedures.
215 - 234	5	Comment: Cellular therapy is a new novel therapy and it's inevitable that new safety signals will be detected that may require further studying using registry data. The first approach would be for an MAH to discuss with the EMA on whether the new safety signal can be studied within the on-going PASS study, meaning the protocol has to be updated. If that is not feasible or the EMA does not agree, mechanisms should be in place for the MAH to be able to conduct their own study as long as the results will be shared by the Agencies . The expectation is that the safety profile of the CAR-T therapy will be further refined and better understood during the conduct of the 15-year long-term follow-up PASS, which may result in an amendment to the protocol as appropriate. Establishing flexibility to make	Accepted; no change is considered necessary.

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		such changes to the protocols, as appropriate and within reason is recommended.	
240 - 255	5	Comment: The monitoring of centres data should be agreed between the MAH and EBMT. However it's essential that EBMT be responsible for the monitoring for all PASS so that the process which the sites have to abide by is similar to prevent undue burden on resources if different MAHs conduct their own monitoring. It is highly unlikely that the same site will be able to maintain good quality data for one cellular product but not another given that the data collection forms are similar for most of the PASS activities. Aiming to monitor data quality for 10% of patients in any PASS would work. However if a site has already been monitored for another PASS, either a different site can be chosen or a more limited quality check can be conducted to avoid duplication. MAHs should provide funding for the monitoring of their studies and hopefully MAHs will agree on a harmonized monitoring scheme.	Accepted; no change is considered necessary. The requirements for individual studies are primarily agreed between regulators and MAH and then the EBMT registry. EBMT has to develop a process that assures that good quality data are generated and establish monitoring and auditing.
261 - 280	5	Comment: This will depend on how thorough the data collection has been and how inclusive the registry is in terms of patients consenting to be enrolled. This question should be re assessed once the initial data elements	Accepted; no change is considered necessary. Although the issue is acknowledged, a follow-up assessment after 1 year is outside the scope of the present qualification procedure.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		have been analysed for completeness e.g. a year after the registry has started collecting data for both Kymriah™ and Yescarta™.	
287 - 301	5	Comment: A robust and dynamic database, such as the ones used by EBMT and Center for International Blood and Marrow Transplant Research (CIBMTR), will most likely be able to support the collection and processing of multiple variables in addition to the minimal core elements. EBMT and CIBMTR have aligned on vast majority of the core data elements. An opportunity to capture all data elements in a single database globally would be highly beneficial from both analytical and operational perspectives.	Accepted; no change is considered necessary.
308 – 320	5	Comment: For real time reporting of SAEs, the sponsors should rely on the Spontaneous AE/SAE reporting system of which a robust system should be in place as a part of their routine pharmacovigilance plan.	Accepted; no change is considered necessary.
328 – 352	5	Comment: We agree with the general position of the EMA. However if the registry starts collecting Patient Reported Outcomes (PROs), then additional consenting will be required as PRO data collection is not part of standard medical practice	Not accepted. Collecting data on PRO is not necessarily regarded as interventional and could well be regarded as compatible with good medical practise. Consenting is required in any case.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
359 – 364	5	Comment: The EU network of EBMT centres is adequate for the initial CAR-T products which have been approved for hematological cancers and will mainly be used by transplant centres. However EBMT needs to build up a network of centres for the second wave of genetic or cellular therapies, e.g. the ones for Sickle Cell disease etc. that may not be administered by transplant centres.	Accepted; no change is considered necessary. Coverage and completeness are of importance. This opinion is only for CAR-T cells products and here no immediate concerns are foreseen. For other disease, this may pose a bigger challenge but is outside of this procedure.
371 - 386	5	Comment: We agree with the EMA that EBMT can be considered fit to serve as Post-Launch Evidence Generation (PLEG) resource. However this has to be reviewed after the initial data elements have been collected, e.g. a year from the date when the data was first collected to see if these conditions are still being met.	Not accepted. A follow-up assessment after 1 year is outside the scope of the present qualification procedure.
178-181	12	*Moreover, key indicators measuring the extent of missing data are not defined and implemented, there is no definition of the timelines for data entry and there is no collection of information regarding the fraction of data that undergoes source verification. EBMT should collect such data and publish at pre-specified intervals reports on data quality.* Comment: In order to ensure high quality in the EBMT registry, it is proposed that the data should be entered within one month after interaction with the health care provider.	Agreed; no change is considered necessary. It is expected that specifics are laid down in the study protocols that have to be agreed with regulators.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
189-198	12	*The minimum requirements for collection of safety data regarding CAR-T cell therapies have been discussed during the related Workshop held by EMA on the 9th of February 2018. Overall, the proposed Cellular Therapy Form appears appropriate to capture adequately details regarding demographics, malignancy, patient health status and medical history, prior treatments, cell therapy information, and treatment response including complications and adverse events.* *However, crucial information regarding the implemented treatment for side effects (e.g. cytokine release syndrome and neurotoxicity) as well as information on quality of life of patients treated is not collected by the form.* Comment: For the purposes of health technology assessment (HTA) and health economy analysis, precise estimates of overall survival, relapse-free/progression-free survival and duration of response, together with quality of life, are issues of major importance. In the TLV's view, information on dates for response, progression/relapse and death is therefore essential. In addition, all anti-neoplastic treatment received before and after CAR-T is of high relevance. It is not clear to TLV if all these elements will be collected according to the current form. Their availability will define the usefulness of the EBMT	Accepted; no change is considered necessary. This qualification advice can address requirements by regulators. Input from other stakeholders is welcome but cannot be mandated. HTA requirements should be communicated to MAHs that can then incorporate these issues in discussions with the registry holders.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		register for HTA purposes. TLV proposes that the following variables are included in order to increase the precision and reduce the uncertainties: - Duration of response - Quality of life (This data has been captured in the ZUMA-1 registry study of Axicabtagene Ciloleucel) - A specification of treatment received after CAR-T - A specification of treatment received before CAR-T. Currently only the number of treatment lines appears to be collected - The date of death in the annual follow up form needs to be separated from date of last follow up. We propose that there are separate entries for last follow up and death date. Proposed change (if any):	
269-271	12	*Other critical issues are related to completeness of data capture, the actual coverage (what proportion of patients overall is estimated to be included), data quality and consistency over time.* Comment: The coverage of the data is of great importance for the quality of the health economic analyses. Therefore, it is critical that the coverage is high enough in order to be able to draw any conclusions from the data.	Accepted; no change is considered necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
295-301	12	*In principle, the proposal that (proprietary) data regarding the manufacturing of the product can be stored in a restricted access area of the Registry in a form that would not be available to unauthorized third parties (e.g. treating physicians or centres) if required, is considered acceptable. However, EBMT is recommended to collaborate with other registries as well as regulatory authorities and stakeholders in order to facilitate the development of a policy on sharing aggregate (summary), pseudo-anonymised, and individual patient data and establish a centralized process for requesting and obtaining data.* Comment: In TLV's experience, collaboration with other registries is often of great importance in order to avoid duplication of registration. If the data is combined with other registries, it could facilitate collection of variables not collected in the EBMT registry such as duration of response, overall survival, quality of life and treatment received after CAR-T, if any of these are not captured directly in the EBMT register. Proposed change (if any):	Accepted; no change is considered necessary.
350-352	12	*EBMT should be able to provide to regulatory agencies and HTA bodies aggregated data, fully anonymised or pseudo-anonymised patient data upon request, in line with governance procedures.* Comment: In order for HTA bodies to be able to make necessary analyses, it is of great importance that data	Accepted; no change is considered necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		is provided upon request, so we agree with that answer. TLV has experienced that receiving data from registries often could take so long time that the data could not be used in the assessment. We would therefore like to emphasize the need to implement a procedure to share data that is smooth and not time consuming. Our recommendation is that it should take no more than two months to receive the requested data. Furthermore, since EBMT is a treatment-based registry, full potential will only be obtained if there are possibilities to create "data lakes" with other sources, e.g. with national or international diagnose-based registries or registries over genomic sequencing. Only aggregated data is mentioned above. In order to make high quality health economic analyses, TLV would also be interested in taking part of individual data (fully anonymized). The possibility of combining data from different countries is of great importance for the usefulness of our analyses.	