EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 August 2018

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

Comments from:

Name of organisation or individual
The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment and commercialization of transformational treatments and cures for patients worldwide. By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory and public understanding of, and support for, this expanding field. ARM convenes all stakeholders with an interest in regenerative and advanced therapies to provide a unified voice for our 300+ member organizations, including companies – especially small- to medium-sized enterprises (SMEs); academic/research institutions; non-profit organizations; patients, and other members of the advanced therapies community. Our aim is to connect all parts of the innovation lifecycle to address the unmet needs of patients, particularly through supporting commercialization objectives via legislative and policy frameworks that enable next generation therapies to reach those who need them. To learn more about ARM, visit http://www.alliancerm.org. Transparency register number ID: 244710319190-73

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
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.	
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	

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	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 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	

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	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.	
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. • 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	

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	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.	
Need to involve HTA bodies and payers	• 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.	

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	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.	
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	

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	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 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.	
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	

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	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 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.	

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

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 50-51		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.	
Lines 87-88		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 be removed from the draft EBMT qualification opinion by EMA as this is not the primary purpose of the EMA qualification report.	

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Lines 89-101		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.	
Lines 104-107		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 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.	

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		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		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.	
Lines 121-122		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 in the guideline on registries that EMA could develop, as proposed above (see general comment about quality assurance and control mechanisms).	
Lines 128-144		Comment: ARM strongly supports the recommendations for enhancement provided on these lines, in particular harmonisation of	

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		requirements with CIBMTR. Besides, we recommend international collaboration through EUnetHTA WP5 and the US/EU collaboration (see general comment above).	
Lines 164-169		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.	
Lines 171-181		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 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	

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		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 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		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	

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		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 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	

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		identify the product, dose and date for multiple administrations. • 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 • Comment on Table 3, line "Early and later 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" • 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	

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		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 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	

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		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 • 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	

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		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. Proposed change: Add: Capture data on: - biomarker assessment – bone marrow/lymph node/other biopsy - biomarker assessment – whole blood sample	
Lines 189-198		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.	
Line 205-208		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	

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		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 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		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".	

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Lines 241-255		Comment: Please refer to the general comment above regarding the proposal to develop a guideline that could include guidance about the management of monitoring of centre's data.	
Lines 258-280		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.	

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Lines 288-301		Comment: 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		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".	
Lines 338-339		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 define requirements for the practical design, operational issues, and evaluation principles	

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		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		Comment: The capacity to add non-EBMT centres should be evaluated and encouraged.	
Lines 384-386		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).	
Lines 760-761		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. Proposed change:	

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		Access to patients' data should not be blocked, otherwise MAH cannot fulfil their long-term FU obligations.	
Lines 924-925		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.	
Lines 928-930		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.	

Please add more rows if needed.