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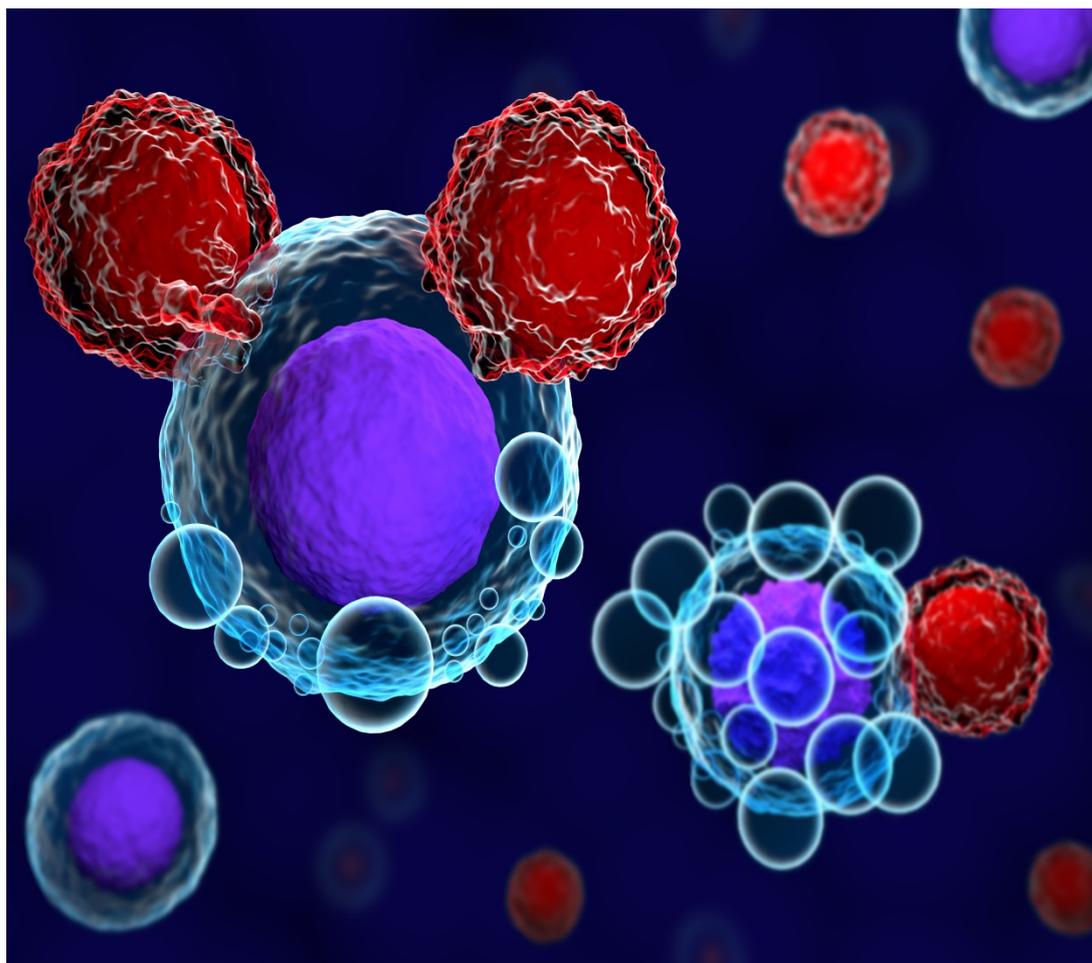
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Pharmacovigilance and Epidemiology Department
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Report on CAR T-cell therapy Registries

Workshop 9 February 2018

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1. Executive summary

The European Medicines Agency's [Initiative for Patient Registries](#) aims to optimise and facilitate the use of patient registries for benefit-risk evaluations of medicinal products.

Cell therapies pose particular challenges for regulators and healthcare providers, not least the need for long-term follow up of treated patients. In order to consider if registry data could contribute to evaluations of chimeric antigen receptor T-cell (CAR T-cell) therapies, the European Medicines Agency hosted a stakeholder workshop in February 2018. This explored in detail the opportunities and challenges of using existing registries to support CAR T-cell therapy benefit-risk evaluations and post-authorisation follow up. The expected outcome of the workshop was agreement by stakeholders on implementable recommendations that will advance CAR T-cell therapy evaluation and monitoring. The factors discussed included registry governance, patient consent, data sharing, data quality, registry interoperability, and core common data elements needed by stakeholders.

Workshop participants had clinical, regulatory, or development experience with CAR T-cell products and included representatives from two large registry holders, the European Society for Blood and Marrow Transplantation and the United States-based Centre for International Blood and Marrow Transplant Research, as well as marketing authorisation holders and applicants, health technology assessment representatives, a patient representative, and national competent authority and European Medicines Agency experts. Prior to the workshop, participants provided information on their experiences and requirements in relation to measures of efficacy and safety of CAR T-cell products and on registry quality assurance and governance matters. The information served as the basis for group-work undertaken during the workshop.

This report summarises observations made by the participants on the use of registry data to support regulatory benefit-risk evaluations of CAR T-cell therapies and, in particular, post-authorisation follow-up. It makes recommendations for actions that aim to facilitate and improve registry data use including the systematic collection of a set of core commonly-defined data elements (Appendix 1). Immediate priorities are to harmonise data element definitions across registries, to establish measures that ensure data are collected systematically with appropriate verification and quality assurance, to ensure arrangements are in place to permit data sharing, and to improve communications between registry holders, regulators and marketing authorisation holders and applicants. The workshop report is without prejudice to any EMA committee opinion on any products submitted or authorised in the European Union.

Table 1 summarises the main recommendations from the workshop.

Table 1: Summary of the main recommendations on utilisation of registry data in supporting regulatory benefit-risk evaluations of CAR T-cell therapies

Topic	Workshop Recommendations	Measures Agreed	Contributors
Governance	Regulators and MAHs/MAAs to be aware of the data elements that can feasibly be collected systematically by registries and to inform registries on their data needs	Improve registry, MAH/MAA and regulator collaboration so that registry holders understand the nature and quality of data needed for regulatory purposes and that MAHs/MAAs and regulators understand what information may feasibly be collected in registries	Registries Regulators MAHs/MAAs
	Communicate to patients and the public the benefits and uses of patient registry data	Raise patient and public awareness about the importance of registry data for benefit-risk evaluations and treatment follow-up	Registries; Patient representatives; Regulators
Informed consent, data protection and data sharing	Ensure centres confirm that registry patients have provided consent	Registry holders to ensure confirmation of consent is received from centres	Registries Regulators
	Review whether current patient consent is broad enough for 1) data sharing following European General Data Protection Regulation (GDPR), 2) data sharing between Europe- and US-based registries	Alert European centres to ensure consent is adequate for the necessary sharing of data following GDPR Registries to establish a centralised process for stakeholders to request and obtain data Determine if actions are needed to permit Europe-US registry data sharing	
Core Common Data elements	Agreement on core common data elements to be collected as a basis for regulatory evaluations	'Crucial' and 'should have' data elements to be included in registries	Registries; Regulators; MAHs/MAAs
	Harmonise data element definitions across registries	Provide data element definition information or source to stakeholders	Patient representatives
	Agree on PROs that could feasibly be collected systematically	All stakeholders to collaborate on defining PROs	HTA & payer representatives
Data Quality	Indicators on data consistency, accuracy and completeness (Section 4.7.) to be considered for implementation	Registries to publish at agreed intervals reports on data quality	Registries
		EBMT to act on regulatory recommendations made in association with the qualification procedure	Regulators

HTA = health technology assessment; MAH / MAA = marketing authorisation holder / applicant; PRO = patient reported outcome

Table 2 summarises the actions required from each of the stakeholder groups to achieve the objectives.

Table 2: Summary of actions for the main stakeholder groups

Group	Actions
Regulators	<ul style="list-style-type: none"> • Communicate to relevant stakeholders the potential value of data from patient registries for supporting regulatory decision making • Facilitate communications between Registries and MAHs/MAAs • Provide guidance on the EMA qualification procedure • Support registries in developing a policy on sharing aggregate (summary), pseudo-anonymised, and individual patient data and establishing a centralised process for requesting and obtaining data • Engage with relevant initiatives that are also exploring the potential of registry data for healthcare evaluations, e.g., the European Network for Health Technology Assessment (EUnetHTA) Joint Action 3
Registries	<ul style="list-style-type: none"> • Ensure that data elements prioritised as ‘crucial’ and ‘should have’ are available in the registries according to a harmonised definition of each element. • Collaborate across registries to ensure that harmonised processes for quality assurance of data, including source data verification, are applied systematically • EBMT to follow up on recommendations made in the regulatory qualification procedure • Develop a policy and a process for sharing aggregate (summary), pseudo-anonymised, and individual patient data and establish a centralised process for stakeholders to request and obtain data • Inform patients on the benefits and uses of registry data including appropriate data sharing with relevant stakeholders. • Inform MAHs/MAAs and regulators of the type and detail of data that may feasibly be collected by registries and shared within consent and governance parameters
MAHs / MAAs	<ul style="list-style-type: none"> • Commence planning for post-authorisation data collection early in product development • Understand the regulatory data requests that are likely to arise in the event of a successful marketing authorisation application, especially for post-authorisation surveillance • Develop a preliminary study protocol and explore with the registry holder/s and regulators if the registry could fulfil the data needs, for example, through a scientific advice procedure
Patient Representatives	<ul style="list-style-type: none"> • Engage with registries in order to understand and communicate to patients the potential uses and associated benefits and risks of sharing registry data to assist in medicines evaluations • Advise on appropriate quality of life and patient reported outcomes that might feasibly be collected and included in registries.
HTAs and Reimbursement Bodies	<ul style="list-style-type: none"> • Learn about the nature and purpose of the data collected and included in patient registries • Engage with Registries to adapt registry data collection where feasible to support information needs, including for quality of life measures and patient reported outcomes • Continue engagement with stakeholders through current initiatives, e.g., EUnetHTA Joint Action 3

It is recommended that, as a next step, an implementation plan should be developed by each of the stakeholder groups facilitated as needed by the EMA Registries Task Force.

2. Background

The European Medicines Agency (EMA) is exploring the use of real world data in supporting medicines authorisation and management on the market. EMA's [Initiative for Patient Registries](#), launched in September 2015, aims to optimise and facilitate the use of existing patient registries for the benefit-risk evaluation of medicinal products. Currently, regulators and marketing authorisation holders (MAHs), face multiple challenges in using registry information to support benefit-risk evaluations of new treatments, including post-authorisation follow up. These include poor coordination between ongoing initiatives at national and international level, absence of harmonised protocols, scientific methods and data structures for undertaking registry-based studies, limited transparency and capacity for data sharing and in some cases, doubtful sustainability of the registries.

At a Patient Registries Workshop in October 2016, stakeholders including registry holders, patient groups, MAHs, health technology assessment (HTA) representatives, reimbursement representatives and regulators made recommendations on optimising the use of registry data – [Report of the Registries Workshop](#). The EMA undertook to deliver on a number of the activities arising, including bringing together stakeholders in certain disease areas for in-depth discussions. The Cystic Fibrosis and Multiple Sclerosis Registries Workshops were the first of these and were held in June and July 2017 respectively. In both cases, workshop participants agreed on implementable recommendations to help assure the quality and interoperability of the respective registry data for supporting regulatory evaluations while ensuring also that appropriate governance arrangements are in place. The recommendations have been published ([Reports](#)) and have informed ongoing actions by registry groups in both areas.

Cell therapies pose particular challenges for regulators and healthcare providers, not least the need for post-treatment long-term follow up. In the context of pre-submission discussions of chimeric antigen receptor T-cell (CAR T-cell) products included in the [PRIME](#) scheme, it became clear that registries would play an essential role in risk-benefit evaluations, especially in post-authorisation data generation. In order to consider how registry data could contribute to the post-authorisation follow up needed for CAR T-cell) therapies, the EMA hosted a stakeholder workshop in February 2018.

3. Workshop objectives, participants and methods

3.1. Objectives

The primary objectives of the workshop were:

- To agree on implementable recommendations on core data elements to be collected, patient consent, governance, quality assurance and registry interoperability.
- To agree on recommendations to optimise collaboration among registry holders, marketing authorisation holders or applicants (MAHs/MAAs) and regulators in order to facilitate the long-term follow up of CAR T-cell products in a real world setting and enable the generation of meaningful efficacy and safety data using haemato-oncological registries.

3.2. Participants

Most workshop participants had experience with CAR T-cell products from a scientific, clinical or regulatory perspective. They included representatives from two large registry groups, the European Society for Blood and Marrow Transplantation (EBMT) and the United States-based Centre for International Blood and Marrow Transplant Research (CIBMTR), national competent authorities (NCAs), CAR T-cell product assessors, EMA experts, MAHs with CAR T-cell products approved in the United States and MAAs with CAR T-cell products in development, a patient representative and health technology assessment (HTA) agency representatives. Clinicians with experience using cellular therapies were included in several of the stakeholder groups. The workshop agenda and participant list are available in Appendix 2.

3.3. Methods

Prior to the workshop, three group work topics were identified that would assist in delivering the primary objectives:

Group 1: Common data elements that are needed by stakeholders on utilisation and measures of efficacy of CAR T-cell products; data verification and registry quality assurance processes needed to support regulatory decision-making;

Group 2: Common data elements that are needed by stakeholders for safety follow-up of CAR T-cell products; data verification and registry quality assurance processes needed to support regulatory-decision making;

Group 3: Informed consents and governance, data protection, common procedures and registry interoperability, quality assurance measures to support regulatory decision-making for CAR T-cell products.

Each work group included participants representing the EBMT and the CIBMTR registries, regulatory assessors, MAHs/MAAs and HTAs. Group 2 also included a patient representative. Five weeks before the workshop, the EMA Patient Registries Initiative team sent participants group-specific pre-work packages that sought their views, experiences, and needs in relation to their topic. The team collated the responses and provided these as background information for each group prior to the workshop. The intention was that participants had a good understanding of each other's perspectives in advance of the workshop in order to facilitate productive group work on the day.

The workshop commenced with an outline of the objectives, the regulatory perspective on the efficacy and safety issues relating to CAR T-cell therapies, an overview of the value of registries for certain regulatory activities, and descriptions by the EBMT and CIBMTR leads of their registries (Appendix 2, Workshop Agenda). During three hours of group work using the pre-work information and working together with two moderators, participants in each of the three groups discussed their specific topic and agreed on recommendations. Throughout the work group discussions, the moderators made notes of participants' observations in order to provide context for the final report and to explain factors that

facilitated or limited the scope of the recommendations. A group representative then presented the recommendations to all of the workshop participants for further discussion.

Following the workshop, the EMA Patient Registries Initiative team drafted the observations and recommendations made by each of the three groups and circulated these to the group members for review. In each case, the EBMT and CIBMTR registry participants clarified queries relating to their respective registries. Finally, the observations and recommendations were collated and grouped as seven topics in Section 4. Section 5 provides an outline of the actions arising.

4. Workshop observations and recommendations

In this section, participants' detailed observations and recommendations relating to the use of patient registry data to support CAR T-cell therapy evaluations are described.

4.1. Enablers and barriers to the use of patient (disease) registries for post- authorisation studies

Enablers

- Regulatory context: the regulatory guidelines and procedures for post-authorisation safety studies ([PASS](#)) and efficacy studies ([PAES](#)) provided by EMA enable a framework for dialogue between pharmaceutical companies, registry holders/academics and regulators on the design of such studies; parallel discussions with HTA and reimbursement agencies provide additional opportunities to collect data in the context of medicines authorisation and reimbursement.
- Standardisation of data elements (fields): harmonisation between EBMT and CIBMTR will support the standardisation of data elements collected in all treating centres (based on a single database for each registry), facilitate the mapping of data elements without the need for a common platform, and facilitate the conduct of studies based on both registries.
- Capacity to support and train new centres: through direct interactions with each participating treating centre, EBMT and CIBMTR have the capacity to integrate and support new centres and provide training when changes are needed (conditional to funding availability).
- Demonstration of quality standards (see Section 4.5. Factors affecting data quality): systems are already in place in the EBMT and CIBMTR registries and can be reinforced to assess whether quality standards are consistently applied in participating centres and may provide assurance on quality for data users; additional quality control measures may be implemented in the centres where CAR T-cell products will be used.
- Qualification process: the opportunity of [regulatory qualification](#) of the EBMT registry will foster in-depth regulatory understanding of the data while regulators' endorsement and/or recommendations concerning the proposed use of such data in regulatory decision making may provide reassurance on its suitability.
- Registry characteristics: the majority of the indications for which data will need to be collected imply a long-term patient follow-up and integration of a disease (patient) registry in clinical practice.

Barriers

- Quality standards of many registries may not fully meet the expectations of regulators, MAAs/MAHs and HTA bodies.
- Real time data compilation is rarely possible and timelines for routine data collection, pooling and analysis and for adverse event (AE) data collection and reporting may not meet the regulatory requirements. A distinction needs to be made between secondary use of registry data collected routinely, allowing aggregated analyses on the incidence of AEs, and primary collection of data for a specific study, e.g. analysis of AEs occurring in individuals.
- Quality standards: depending on the number of centres using CAR T-cell products, setting-up new procedures for data quality control may have large resource implications.
- Funding: CIBMTR is supported by US government grants but for EBMT, the sources of funding are membership, annual conferences and industry sponsorship. Besides funding that can be obtained for specific studies, EBMT would need structural funding to strengthen routine operations such as monitoring and auditing activities and maintenance of a quality system. This situation explains that quality assurance may be stronger for specific studies than for routine activities (e.g. data entry at centre level).
- Patient-reported outcomes (PROs), including quality of life, are not routinely collected by treating centres or by registries; certain PROs are of particular relevance for HTA and reimbursement bodies as well as for patients.

Recommendations

- Further progression of EBMT and CIBMTR harmonisation and agreement on standardisation of data fields in all centres will facilitate the mapping of data elements, and consequently the conduct of studies based on both registries.
- Sustainable funding is a prerequisite to support staff training and maintain adequate data and process standards; EBMT needs to pursue funding measures.
- Regulators and HTA bodies should provide guidance on the expected quality assurance approaches that support the use of registry data in benefit-risk evaluations.
- All stakeholders should collaborate to agree relevant PROs for regulatory, HTA and reimbursement evaluations that are feasible to be collected.

4.2. *Informed consents and data sharing*

Observations

- Patient consent is critical for the reporting and sharing of data. Under the general data protection regulation (GDPR) that will come into force in May 2018, patients own their personal data and can ask the centre to delete their data at any time (<http://www.eugdpr.org/>).
- An analysis by EBMT of its informed consent process in light of the GDPR has not identified any critical issues. In general terms, the EBMT approach is that it must comply with the strictest of the national regulations that apply.
- For EBMT, patients sign a consent form at the treating centre indicating their agreement to allow data to be sent to EBMT; the informed consent form includes a provision that the patient consents to data being forwarded to other (international) organisations for research purposes.

- In the event a patient is cared-for sequentially at centres in different countries, each centre must consent the patient. Future versions of the EBMT registry will permit patient data access to be limited to individual treating centres if necessary.
- For EBMT, the responsibility for managing consents lies with the centres; EBMT does not collect the consent forms but requests a confirmation from the centre that the consent has been signed; in case of requests for data sharing, EBMT can provide access to aggregated or anonymised individual patient data and needs to ensure that the patients have consented to share their personal data at the appropriate level.
- In the context of the implementation of GDPR, the EBMT plans to explain the main principles of the new legislation to patients and clinicians (e.g. explanations of why and which data are collected) via a communication on its website.
- For CIBMTR, centres are responsible for managing patient level consent. Allogeneic transplant data collection and reporting is mandated by the US federal legislation: data of patients who do not provide consent is still reported but is used only for specified federal reports and excluded from any other use. The same reporting obligation is being considered for cellular therapy data. CIBMTR confirms and tracks the consent status at each use of a patient's record to determine if the consent status has changed over time. CIBMTR plans to share data (summary data and patient-level data where required) with regulatory agencies. In case of a request for data in accordance with the CIBMTR Research Database Protocol in the context of observational studies ([CIBMTR request](#)), a standard process is in place with a review by an ethics committee. The CIBMTR audit includes review of the consenting process at individual centres including up to date institutional review board (ethics committee) approval document control.
- Depending on the nature of a study on CAR T-cell therapy, ethics approval may need to be sought by the concerned centres at a local level.

Recommendations

- EBMT should take a central role in harmonising patient consent forms aligned with the GDPR in each centre, allowing sharing of aggregated and anonymised patient-level data for research or regulatory purposes.
- Treating centres should remain accountable for ensuring patient consent; the EBMT and CIBMTR Study Offices should receive from each centre a confirmation that patients have consented to share their data. Regulatory agencies and HTA bodies should be able to receive from EBMT and CIBMTR aggregated data, fully anonymised or pseudo-anonymised patient data upon request, in line with governance procedures.
- Prior to commencing imposed studies, transparent arrangements should be in place for sharing and publishing data and results.

4.3. Governance and data collection procedures

Observations

- There is a single contact point for conducting studies based on EBMT registry data. The EBMT Study Office creates data entry manuals for every study and checks the data.
- The CIBMTR maintains a Registry Agreement with the EBMT for centres who have requested EBMT to forward their data to CIBMTR and a Data Transmission Agreement with centres who report data directly. An Agreement for cellular therapy is in progress currently.

- EBMT data are collected from over 500 transplant centres in Europe representing approximately 80% of European centres. CIBMTR data are collected from over 200 US centres reporting allotransplants, autotransplants and/or cellular therapy. Both registries anticipate collecting data from all of their affiliated centres that will provide cellular therapies.
- Scheduled follow-up visits to treating centres are at three months, six months, one year and then annually following treatment. Follow-up data are included in the registries for patients who attend for follow up.
- Many data element definitions are common across the EBMT and the CIBMTR registries and work is ongoing to harmonise cellular therapy definitions (Refer Section 4.6. Quality verification processes).
- Both EBMT and the CIBMTR have dedicated electronic cellular therapy forms onto which data may be entered directly by the treating centres. The forms include extensive detail about the malignancy, patient health status, prior treatments, the cell therapy information, and treatment response including complications and adverse events.
- By late 2018, EBMT anticipates moving to a new registry platform (MACRO) that will increase its capacity to perform PASS.
- For post-authorisation study protocols requiring data elements other than those already collected in the registry or collection at different time-points, both registries anticipate they could facilitate such needs with appropriate notice and planning.

Recommendations

- As a general principle, registry based studies should adhere to the recommendations of the [Good Pharmacovigilance Practice \(GVP\) Module VIII](#) (post-authorisation safety studies) and of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct ([ENCePP Code of Conduct](#)) for data management. While the patient owns her/ his data, the registry holder should be in charge of the control, use and sharing of the registry data. For specific studies fully or partially funded by MAHs/MAAs, the research contract and the study protocol should include the plans for the submission of progress reports and final reports to regulators, including milestones. The research contract should describe intellectual property rights arising from the study, access to study data and dissemination of results, allowing sharing of unpublished results with regulators and with MAHs/MAAs initiating the study.
- Data analysis should preferably be performed by the registry owner or by a third-party (e.g. academic centre, contract research organisation) rather than by MAHs/MAAs. If data analysis is conducted by the registry holder or a third party, results of product-specific data analysis should be shared with regulators and the concerned MAHs/MAAs in line with provisions of the study protocol.
- A three-way communication between MAHs/MAAs, EBMT/CIBMTR and regulators may be established before or at an early stage of product authorisation application with the following objectives:
 - To be aware of the data that are collected or can be collected by registries when information or studies are requested from MAHs/MAAs, and to agree on the data to be collected for a specific product.

- To support EBMT and CIBMTR centres' understanding of and compliance with regulatory requirements for MAHs/MAAs.
- To support harmonisation of datasets across registries to allow for pooled analysis by the registry, the MAHs/MAAs and /or the regulators.

Such communication should be initiated by MAHs/MAAs and supported by regulators at an early stage during the development process or authorisation procedure, using opportunities such as the EMA's business pipeline meetings, [PRIME](#)-related discussions, [scientific advice procedure](#), pre-submission meetings or interactions with Rapporteurs and Scientific Committees.

- Registries should communicate to the public the benefits for public health and the potential uses of the data arising from patient participation in registries.

4.4. Common data elements required for regulatory evaluations

The data elements suggested by the workshop participants in their pre-work as being necessary to support regulatory evaluations of CAR T-cell products for haematological malignancies were used to create a list of proposed core common data elements necessary for efficacy (Group 1) and safety (Group 2) evaluation at the time of treatment and in later follow-up.

At the workshop, participants in both groups evaluated the proposed elements, refining details as necessary, adding overlooked elements, and coming to agreement on whether, in a CAR T-cell therapy registry, each element proposed was 'crucial', 'should have', 'nice to have', or 'not needed'. The category definitions were as follows:

- **Crucial:** Participants agreed that this data element is core and must be included in the registry; if it is not currently available in the registry, then measures must be taken in the short term to include it in order to support regulatory decision-making.
- **Should have:** Participants agreed that this data element is very important and if it is not currently available in the registry, then measures should be taken in the short term to include it in order to support regulatory decision-making.
- **Nice to have:** Participants agreed that this data element is of interest and if already available in the registry, it may be useful for some stakeholders but they did not consider that measures should be taken to include it.
- **Not needed:** Participants agreed that this data element might be of interest for some stakeholders but did not consider inclusion in the registry necessary to support regulatory decision-making.

All workshop participants reviewed the recommendations. Following the workshop, the outline recommendations were collated by the EMA Patient Registries Initiative team and were reviewed by Group 1 and 2 participants. This step allowed for collection of missing information and clarifications where needed. Tables 3 and 4 (Appendix 1) set out the proposed core common data elements prioritised according to the workshop participants' recommendations.

4.5. Factors affecting data quality

Observations

- Factors affecting data quality include the systematic collection of core common data elements, common definitions, a common coding terminology, e.g. the Medical Dictionary for Regulatory Activities (MedDRA), a regular reporting process and the availability of an audit system allowing verification of the accuracy and completeness of the registry data.
- A harmonised dataset across different registries is desirable but multiple registry datasets could be used if data are mapped and standard queries are applied.
- The potential for data entry errors can be minimised by introducing automated checks in the data entry software (conditional on funding availability).
- Compliance of centres with accurate data entry and robust data management must be increased. This can be achieved by continuous training and feedback from the registries to the reporting centres (conditional on funding availability).
- Timelines for data entry: in the EBMT registry, data may be entered by treating centres directly to the registry using designated software. These data are immediately available to the registry. Alternatively, for a small number of centres, completed Cell Therapy [Med-A forms](#) are submitted to the national registries where the data are entered on their behalf. These data should be registered in the EBMT Registry database within 6 months post cell therapy or at time of death, whichever occurs first. In the CIBMTR registry, data are entered by treating centres in electronic forms that are immediately available to the registry.
- Timelines for reporting of AEs and suspected adverse drug reactions (ADRs) depend on the context (routine reporting versus reporting for specific studies and complexity of the report) and may be adapted if necessary, e.g. to be aligned with reporting timelines for PSURs periodic safety update reports (PSURs); EBMT can currently collect data at agreed intervals, e.g. every 6 months or every year, but the frequency of follow-up may differ depending on the centre or the country. EBMT cannot impose rules on when patients visit centres because this would constitute an intervention. In addition, high frequency of follow-up may lead to incomplete data collection. Amending the practices currently in place would require additional funding.

Recommendations

- Key components of data quality should include:
 - Uniformity: use of a minimum set of common core data elements, common definitions, a common coding system and common data entry procedures; as nomenclature systems evolve over time, a mechanism should be in place to take account of changes.
 - Completeness: registration of complete information on all eligible patients, absence of / minimal missing data.
 - Accuracy: data available in the registry are a correct representation of patient data, e.g. data available in medical charts / records.
 - Timeliness: there is timely recording and reporting of data based on the intended use of the data and an agreed procedure.

- The highest level of data quality should be pursued, and all quality assurance approaches justified given the anticipated use of the data.
- Timelines for data collection and reporting should be proposed in the study protocol by MAHs/MAAs (e.g. in the context of a scientific advice procedure or a risk management plan) or by registries (e.g. in the context of a scientific advice procedure) and agreed with regulators.
- EBMT or CIBMTR registry data are currently not suited for causality assessment of AEs in individual cases based on expedited reporting requirements, but a system should be in place in the registry to ensure that physicians are aware that suspected ADRs should be routinely reported according to the normal practice of the national pharmacovigilance system, even if they are also reported to the registry and even if an additional system for the reporting of AEs to the MAH has been established for a specific study. MAHs should be assured that any specific AE collection system put in place in the EBMT and CIBMTR registries meets the regulatory requirements of [GVP Module VI](#).
- The EBMT or CIBMTR registries are currently best suited for secondary data collection ([GVP Module VI C1.2.1.2](#)) and periodic reporting of aggregated or summarised data based on an agreed protocol; acceptable levels of data quality for regulatory evaluation purposes should be agreed between MAHs and regulators; funding mechanisms for reporting procedures should be agreed between MAHs and registries.

4.6. Quality verification processes

Observations

Both the EBMT and CIBMTR registries have measures to support and verify the quality of data in routine practice.

- **EBMT**
 - Standard operating procedures, work instructions, manuals and guidelines are in place and maintained by the Registry and Study Offices with version control.
 - Data elements are defined before their integration in data collection forms; harmonisation of definitions with CIBMTR has been in place for several years and is on-going in the context of cell therapy data collection.
 - Automated data quality checks are in place at data entry in the registry; Standard processes for additional data quality checks take place at data-file preparation;
 - Data quality control reports can be run by users (or by registry personnel) to check for missing or unusual or incorrect data.
 - Follow-up requests to treating centres on missing or incorrect data are issued by the Registry/Study Office and centres are aware of the need to report all consecutive patients.
 - Efficiency of data collection is improved through close interactions with participating centres.
 - Support systems on definitions and data management are available centrally at EBMT or through working parties (e.g. definitions group, topic-specific groups), or through other professional bodies (e.g. WHO disease classification).
 - Statistical analyses are performed to detect missing data and outliers, identify data that needs to be 'cleaned' by the treating centres, and adjust statistically for missing data.
 - Education and training sessions (face to face and on-line) are available for data managers.

- The Joint Accreditation Committee ISCT-EBMT (JACIE) offers accreditation to transplant programmes in order to encourage health institutions and facilities performing hematopoietic stem cell transplantation to establish and maintain quality management systems and to engage in continuous improvement. Application to JACIE accreditation is voluntary, although some countries require it for authorisation or reimbursement purposes, e.g. Belgium, the Netherlands and the United Kingdom. As of February 2018, 208 centres have a valid accreditation and 85 have a reaccreditation in progress in 29 European countries. Reaccreditation normally follows a four-year cycle. For treating centres, JACIE accreditation involves:
 - Comprehensive on-site peer-review by trained specialists;
 - Benchmarking the level of practice in comparison with agreed international standards of excellence;
 - Verification that the centre operates an effective quality management system, including for data entry;
 - Minimum requirements for data reporting to EBMT;
 - Audit of data submitted to EBMT against source documentation;
 - Follow-up of findings to verify that corrective measures have been implemented.
- Compliance with [FACT-JACIE standards](#) for haematopoietic cellular therapies is a pre-requisite for participation of centres in some MAH/MAA-initiated studies of cellular therapies.
- There is no external audit system of the EBMT registry and there are no known examples of regulatory inspections on the source data or the analytical datasets; however, data monitoring is undertaken when registries participate in clinical trials and can also be done in post-authorisation studies (PASS and PAES).
- EBMT would benefit from a structural source of funding to further develop its capability to implement quality control measures in its routine operations, including the monitoring of the completeness and quality of data through automated quality control systems (e.g. edit checks with alerts), to strengthen the follow-up of recommendations arising from the non-mandatory JACIE accreditation visits and to increase appropriate training and expertise.

CIBMTR

- The CIBMTR has established processes to increase efficiency of data quality assurance measures:
 - Automated data quality checks are in place at data entry;
 - Standard processes for additional data quality checks take place at data-file preparation;
 - Ongoing monitoring of reporting and compliance at submission of forms;
 - On site audit of source data occurs on a four-year cycle which serves as the data audit for FACT (Foundation for the Accreditation of Cellular Therapy) accreditation;
 - Efficiency of data collection is increased through close interactions with participating sites;
 - Interactions with manufacturers facilitates understanding of level of usage of different products across the sites;
 - Completeness of data can be improved with linkage between CIBMTR and electronic healthcare records.

Recommendations

- Established quality standards should be in place and adequate for all registry studies; a dedicated data control and follow-up system should be introduced only for very specific studies or where the existing system is not (yet) adequate.
- A critical aspect of quality control is the definition and implementation of key indicators measuring e.g. the extent of missing data, the timeliness of data entry or the fraction of data that undergoes source data verification, and their acceptance by regulators (see also Section 4.7.).
- Timelines for monitoring and periodic reporting of aggregated data should be defined between EBMT, regulators and MAHs/MAAs, as applicable, to allow data availability at important milestones, e.g. for PSURs.
- External (and/or internal) audits (routine or *ad-hoc*) may be agreed between EBMT and MAHs/MAAs or regulators to provide confidence in quality control systems, for example to verify that all eligible patients are registered; they could be performed in the context of specific studies based on joint industry collaborations but would be associated with additional costs; they may be easier to implement in the context of CAR T-cell products where it is expected that a limited number of centers will be involved. EBMT should support resolution/correction of findings from external audits.
- Software solutions for data entry, transfer and verification from electronic medical records should be pursued.
- European registry holders may submit an application for a [regulatory qualification](#) through a scientific advice procedure of the European Medicines Agency.
- In relation to harmonisation of EBMT and CIBMTR cellular therapy data elements:
 - The use of common definitions for data elements is critical to support comparative studies and /or studies potentially combining data from both registries and should be finalised as soon as possible.
 - The definitions in use by the EBMT and CIBMTR registries (or the system used, e.g. World Health Organisation [WHO definition](#)) should be available to stakeholders including regulators, MAHs/MAAs, and HTA and reimbursement bodies.

4.7. Data quality indicators recommended by workshop participants

During the workshop, participants of Group 1 considered three components of data quality - consistency, accuracy, and completeness of the data. The table below summarises potential indicators of quality proposed by participants and the registry systems or solutions that would be needed to facilitate these. The EBMT and CIBMTR registries indicated the operational feasibility in each case.

Table 5. Proposed indicators of data quality and feasibility of implementation for EBMT and CIBMTR registries

Data Quality Component	Definition	Proposed indicators of quality	Quality Solutions to facilitate data quality	EBMT & CIBMTR feasibility
Consistency	Uniformity of the data overtime (e.g. lab data routinely entered)	Number of fields changed over time	Manual checks at centres level, audits	Both: Feasible
		% of fields missing over time	Standard terminology, coding	Both: Feasible
		% of forms reported per scheduled follow-up	Standard operating procedures, user guides	Both: Feasible
			Campaigns, dashboards for clinicians	Both: Feasible
Accuracy	Accuracy of data entry: no errors, no contradictions or impossibilities in data, absence of duplicates	Change in value of data filed by x% creates alerts	Drop down menus, alerts, text prompts, flags	EBMT: Feasible CIBMTR: Simplify data collection to avoid redundancy
		Variability across fields	Validate against source data (eg, 10%), cross form validation	EBMT: Costly and only currently done for funded studies CIBMTR: Suggests 'crucial' elements be audited and 'acceptable' error rate defined (3% in CIBMTR)
			Staff training, software checks.	Both: Feasible
			Help screens/desks, training, newsletter	Both: Feasible
			Funding for data managers	EBMT: Requires new funding CIBMTR: Necessary to motivate data collection
Completeness	How much data is missing?	Agreed % of fields completed in audit procedures (e.g. >90%)	Audits	EBMT: Costly and only done for funded studies currently CIBMTR: May be reported directly from the registry
		Lost to follow up %	Mandatory fields	EBMT: Feasible CIBMTR: Feasible for 'crucial' and 'should have' elements
			Engagement with patients and/or health care providers (HCPs)	Both: high engagement with HCPs, less with patients CIBMTR: Implementing systems to collect patient reported outcomes
	Absence of core variables	Minimum agreed core common data elements reported	Agreed list of data elements and definitions	EBMT: Feasible CIBMTR: Feasible for 'crucial' and 'should have' elements
		All treated patients reported, not selected patients only	Cross check patient numbers with numbers of products used at treating centres during a defined period	Both: Feasible if there is access to orders/product supply information

5. Next steps and Actions

5.1. Role of the EMA Patient Registries Task Force in guiding implementation of recommendations

The EMA Patient Registries Task Force will work with stakeholders as needed to facilitate implementation of the workshop recommendations on the inclusion of cellular therapy data elements prioritised as ‘crucial’ and ‘should have’ in the EBMT registry (Appendix 1, Tables 3 and 4). Where possible, the Task Force will advise stakeholder groups in completing the actions outlined (Sections 5.2 – 5.6).

5.2. Actions for Regulators

Regulators need to support other stakeholders by:

- Facilitating communications between registries and MAHs/MAAs through existing EMA platforms;
- Encouraging registries in their efforts to harmonise cellular therapy data element definitions;
- Working with registries, MAHs/MAAs and others to ensure that where possible and appropriate, the data on relevant post-authorisation study outcomes are collected in the registries;
- Supporting registry efforts to optimise measures for assuring the quality of registry data;
- Providing guidance on the EMA qualification procedure with HTA/reimbursement body involvement;
- Collaborating with relevant initiatives that are also exploring the potential of registry data to contribute to healthcare evaluations, for example, the work of EUnetHTA in its Joint Action 3 ([Work Package 5B](#)) and the European Platform on [Rare Diseases](#) Registration.

5.3. Actions for Registries

Registries should ensure that data elements prioritised as ‘crucial’ and ‘should have’ are available according to a harmonised definition of each element. Element definitions (or the definition system used) need to be known by stakeholders.

Registries need to prioritise measures to assure the quality of registry data and its reliability by:

- Developing or reinforcing data quality control for routine operations in each registry.
- Ensuring that processes for quality assurance of registry data, including source data verification, are harmonised and applied systematically across registries.
- Considering opportunities such as a regulatory qualification of the EBMT registry that may provide reassurance on the suitability of the data to support regulatory decision making.

Registries should optimise communications with patients, MAHs/MAAs, HTA and reimbursement bodies and regulators by:

- Informing patients on the benefits and uses of patient registry data including appropriate sharing of patient data with relevant stakeholders in line with the [GDPR](#).
- Informing MAHs/MAAs and regulators of the type and detail of registry data that may feasibly be shared within consent and governance parameters.

5.4. Actions for MAHs/MAAs

MAAs for new cellular therapies need to:

- Understand the regulatory data requirements that are likely to arise during the application process especially in planning for post marketing surveillance given the prolonged duration of follow-up that is required for CAR T-cell products;
- Initiate discussions with registries and regulators before, or at an early stage of a marketing authorisation application on the relevance and adequacy of one or several existing disease registries for the long-term monitoring of their specific product;

Both MAHs and MAAs need to:

- Have an in-depth understanding of the extent and detail of data available in patient registries when planning registry-based post-authorisation studies;
- Develop a preliminary study protocol for post-authorisation studies of any new product and explore with the registry / registries and the regulator how the registry could fulfil the data needs, for example through the Scientific Advice procedure.

5.5. Actions for patient groups

Patient representatives are encouraged to engage pro-actively with registries in order to:

- Ensure they can communicate to patients the potential uses and associated benefits and risks of using patient registry data to assist in cellular therapy evaluations, especially in long-term follow up and including appropriate data sharing with relevant stakeholders;
- Provide insight for other stakeholders on patient reported outcomes that might feasibly be collected in registries.

5.6. Actions for HTAs and reimbursement bodies

HTAs and reimbursement bodies should develop their understanding of the possible roles for patient registries in supporting health technology assessments and informing reimbursement decisions by:

- Learning about the nature and purpose of the data collected in patient registries for cellular therapies;

- Engaging with registries to adapt or optimise data collection in order to support their information needs where feasible.

Ongoing work by the European Network for Health Technology Assessment in its Joint Action 3 ([Work Package 5B](#)) is highly relevant in this respect bringing together multiple groups to focus on registries in health technology assessment.

6. Conclusions

There is clear recognition by stakeholders of the opportunities and challenges of using existing registries to support CAR T-cell therapy benefit-risk evaluations and post-authorisation follow up, especially given the requirement for long-term follow up. Agreement on 'crucial' and 'should have' data elements to be collected, including harmonised definitions, along with systematic processes to verify source data and assure registry quality, will help ensure that data from as many patients as possible will be available to contribute to these activities. [Regulatory qualification](#) of the EBMT registry would help ensure regulators understand the data while regulators' endorsement and/or recommendations concerning the proposed use of such data would provide reassurance to users regarding its suitability.

An early priority is to improve communications between registry holders, regulators and MAHs/MAAs and to create a centralised process for requesting and obtaining data. The ultimate objective is that relevant data from patient registries will be incorporated in benefit-risk evaluations throughout medical product lifecycles.

7. Glossary

- Aggregate data: numerical or non-numerical information collected from multiple sources and/or on multiple measures, variables, or individuals and compiled into summary reports
- Anonymised Data: Data 'rendered anonymous in such a way that the data subject is not or no longer identifiable' (Recital 26, GDPR)
- CAR T-cell: Chimeric antigen receptor T-cell
- CIBMTR: Centre for International Blood and Marrow Transplant Research
- EBMT: European Society for Blood and Marrow Transplantation
- EUnetHTA: European Network for Health Technology Assessment
- FACT: Foundation for the Accreditation of Cellular Therapy
- GDPR: Generalised Data Protection Regulation <http://www.eugdpr.org/>
- GVP: good vigilance practice
- HTA: Health Technology Assessment

- Individual patient data - Data separately recorded for each participant in a clinical study
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf
- Informed consent: The process by which a patient learns about and understands the purpose, benefits, and potential risks of a medical or surgical intervention, including clinical trials, and then agrees to receive the treatment or participate in the trial (medicinenet.com)
- ISCT: International Society for Cellular Therapy
- JACIE: Joint Accreditation Committee ISCT-EBMT
- MAA: marketing authorisation applicant
- MAH: marketing authorisation holder
- NCA: national competent authority
- PAES: post authorisation efficacy study
- PAS: post authorisation study
- PASS: post authorisation safety study
- Patient Registry: An organised system that uses observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000658.jsp
- PRO: patient reported outcome
- Pseudo-anonymised Data: data processed 'in such a way that the data can no longer be attributed to a specific data subject without the use of additional information.' (Appendix 3; GDPR Article 4 (5))
- PSUR: periodic safety update report

8. Appendices

Appendix 1: [Proposed data elements relating to Efficacy \(Table 3\) and Safety \(Table 4\)](#), priority for collection in a registry, current capture in the EBMT and CIBMTR registries and workshop participant comments.

Appendix 2: [Workshop agenda and participant list](#).