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Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion on Cellular therapy module of the European Society for Blood & Marrow Transplantation (EBMT) Registry

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The European Society for Blood & Marrow Transplantation (EBMT) Registry holds data on patients given a haematopoietic stem cell transplantation (HSCT) procedure. EBMT has developed the Minimal Essential Data form for Cellular Therapy, including chimeric antigen receptor (CAR)-T cell therapy. EBMT requested qualification of the cellular therapy module of the EBMT Registry as suitable for performing pharmacoepidemiological studies for regulatory purposes, concerning CAR-T cell therapy for haematological malignancies.

Eleven questions were posed by EBMT to SAWP in their request together with supporting documentation:

1. The Agency is asked if the data quality control mechanisms proposed by EBMT are adequate for Post Launch Evidence Generation (PLEG) purposes for CAR-T cell products.
2. The Agency is asked if EBMT's Cellular Therapy form is adequate for capturing safety/outcome data.
3. The Agency is asked if EBMT's ability to adjust the frequency of data reporting is adequate.
4. The Agency is asked if EBMT's management of request for changes or amendments to study design is adequate.
5. The Agency is asked if how EBMT manages monitoring of centres' data is sufficient.
6. The Agency is asked whether the EBMT Registry can be used as a source of data for CAR-T cell product comparative studies.
7. Does the Agency agree with the approach of EBMT in capturing additional variables, requested by the MAH, to avoid duplication of reporting?
8. Does the Agency agree with EBMT's proposal on Severe Adverse Events (SAE) reporting for CAR-T cell products?
9. Does the Agency consider that EBMT's current consent form and consenting procedure are adequate for EBMT-based CAR-T cell product studies for regulatory purposes including data access by regulators?
10. The Agency is asked whether the current EU network of EBMT centres is considered adequate in covering the potential centres that will be used for administering CAR-T cell products.
11. The Agency is asked if the Registry can be considered fit to serve as a Post-Launch Evidence Generation (PLEG) resource.

Interactions with Regulators
A multi-disciplinary qualification team of regulators was constituted with representatives from SAWP, CAT, and PRAC. Patient representatives and Health Care professionals were invited.

Specific issues were raised by SAWP for discussion within the qualification procedure and discussed with EBMT on 07 February 2018.

A public workshop with representatives from EBMT and the Center for International Blood and Marrow Transplant Research (CIBMTR), regulatory participants, Health Technology Assessment (HTA) bodies and other stakeholders also took place at the EMA premises on 09 February 2018.

Content of report
This report provides a final agreed draft Context of Use (p 3-4) for public consultation describing where the cellular therapy module of the EBMT registry is deemed by CHMP as an appropriate data source for post-authorisation studies to support regulatory decision making concerning CAR-T cell therapy for haematological malignancies, together with CHMP's response to the questions posed by EBMT (p4-8).

Qualification opinion

Study aims

On the basis of the initial briefing document and additional information submitted during the procedure, CHMP considers that the current status of the cellular therapy module of the EBMT registry (coverage, core dataset, governance, quality assurance approaches, and completeness of core variables), may allow its use as a data source for regulatory purposes in the context of the following studies concerning CAR-T cell therapies authorised for haematological malignancies:

- Drug utilisation studies for total recorded population and by subgroup such as age, gender, centre, etc.
- Drug efficacy/effectiveness studies
  Data from the cellular therapy module of the EBMT registry could be used:
  - To measure efficacy/effectiveness of CAR-T cell therapies in the post-authorisation setting, i.e. early and late response (objective response rate, duration of response, relapse free survival, event free survival) as well as follow up to document overall survival;
  - 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.
- Drug safety evaluation
  The cellular therapy module of the EBMT registry could be used as a tool to collect CAR-T cell therapy safety data with a particular focus on early and late stage a) adverse events of special interest (i.e. neurological events (incl. cerebral oedema), cytokine release syndrome (CRS) / macrophage activation syndrome (MAS), hematopoietic cytopaenias, tumour lysis syndrome (TLS), certain infections, depletion of normal B-cells / a-/hypo-gammaglobulinemia, new malignancies), b) drug-related (grade 3-4) adverse events (skin; respiratory, cardiovascular, hepatic, renal, gastrointestinal, other system events).

  In this context, in addition to assessment of cumulative annual incidence of adverse events, it may be possible to conduct comparative assessment of newly solicited safety data (adverse events of special interest), provided an appropriate control cohort can be constructed, i.e. if patients not exposed to the drug of interest are also monitored for the AE of interest.

Individual study considerations

- Individual studies for regulatory purposes within a centralised procedure, using the cellular therapy module of the EBMT registry, should be conducted under a study protocol that is agreed with regulatory authorities, before study start. Appropriate methods for observational studies to control for bias, chance and confounding factors should be considered.
- Early tripartite interaction - preferably at the stage of clinical development - with EBMT, regulators and Applicants is encouraged to discuss the design/methodology and feasibility of post authorisation studies using the cellular therapy module of the EBMT registry as a source of data, based on the foreseen study objectives.
- In order to ensure acceptable data quality for individual studies conducted for regulatory purposes, source data verification and periodic auditing on a reasonable amount of data should be conducted on a risk analysis-based approach and following a step strategy dependent on the scope of the study. As a general rule, data source verification for a minimum of 10% of registered patients in individual study centres would be required, however the level of data verification will have to be agreed upfront between EBMT and MAA/MAH in the context of the study performed. Appropriate measures in case relevant findings are observed should be specified. Quality of short and long term data should be assured. Agreements on relevant logistical aspects should be made between EBMT and MAA/MAHs in advance of study start.
- Procedures to assure sequential inclusion of all the patients treated by the individual centres, to identify and collect missing data as well as to minimise patient lost to follow up should be detailed.
- In certain cases, modifications to the current cellular therapy module may be implemented for additional data collection, e.g. to address a particular research question. In such a case, relevant modifications to the consent form may be needed for prospective data collection or patients may need to re-consent for retrospective data analysis.

Further recommendations for enhancement

- Harmonization and agreement on standardization of data elements/fields in all centres and between EBMT and other registries (i.e., CIBMTR) is recommended in order to facilitate harmonization of data set across registries to allow data sharing and pooled analysis. In view of this it is recommended to:

  - Use of MedDRA coding for unbiased collection of adverse events;
  - Implement standardized and harmonized (between centres and registries) criteria for grading severity of adverse events;
  - Use of ICD coding for diagnosis of solid malignancy is recommended.
- Collaboration 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. This would allow generation of a data platform encompassing different CAR-T cell therapies in the long term.
- Data on the treatments administered for toxicities (e.g. cytokine release syndrome) related to CAR-T cells therapies should be collected.
- Efforts for the collection of Quality of Life data are encouraged.

Based on the coordinators' reports, the CHMP gave the following answers:

Question 1
The Agency is asked if the data quality control mechanisms proposed by EBMT are adequate for Post Launch Evidence Generation (PLEG) purposes for CAR-T cell products.

CHMP answer
According to the data provided by the Applicant in the briefing document and within the qualification procedure (discussion meeting, CAR-T cell therapy Registries workshop hosted by EMA), the EBMT presents internal quality control measures to support and verify data quality in routine practice. Actually, the data are entered in the system by the center by compilation of standardized forms. Continuous support to the data managers as well as regular training (face to face and on-line) is given by the registry office. Automated data quality checks are in place at data entry in the registry: over 4,000 control triggers are in use to prevent the introduction of inconsistent data. Data quality reports can be run by users (or by registry personnel) at any time to check for missing or unusual or incorrect data. Follow-up requests to treating centres on missing or incorrect data are issued by the EBMT on a regular basis. Statistical analyses are performed to detect missing data and outliers, identify data that need to be “cleaned” by the treating centres, and adjust statistically for missing data. Moreover, completeness and reliability of the dataset are indirectly assured by the requirement in several EU countries (e.g. NL, UK and BE) for the centres administering CAR-T cell therapies to achieve Joint Accreditation Committee ISCT-EBMT (JACIE) accreditation for authorisation and/or reimbursement purposes. Data reporting to EBMT is strongly recommended for JACIE (re-)accreditation and an audit of data collected in EBMT data forms against source documentation is currently performed during JACIE (re-)accreditation procedures.

However, there is no external audit system of the EBMT registry and there are no known examples of regulatory inspections on the source of data or the analytical dataset in order to provide confidence/reassurance in the quality control mechanisms proposed by EBMT. At this time, due to the lack of a structural source of funding to support monitoring the high volume of patients entered into the registry each year, quality control via an external audit control system cannot be guaranteed for the entire EBMT database. However, data monitoring is undertaken in presence of specific funding, for instance in clinical trials and can be done in postauthorisation studies by visiting the participating centres. 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.

Question 2
The Agency is asked if EBMT’s Cellular Therapy form is adequate for capturing safety/outcome data.

CHMP answer
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.

Question 3
The Agency is asked if EBMT's ability to adjust the frequency of data reporting is adequate.

CHMP answer
In general, a data capture at 6 months with retrospective review of response status at 3 months in case of disease progression at 6 months, with yearly update afterwards, is considered sufficient. Therefore, the proposed standard data capture is agreed, particularly as some flexibility has been built in.

Question 4
The Agency is asked if EBMT's management of request for changes or amendments to study design is adequate.

CHMP answer
It is agreed that it is highly preferable to have a final agreed protocol prior to the start and that significant protocol changes after start of the study should be avoided.

EBMT has built in a system to manage additional requests, showing that it might be flexible upon request. It is understandable that additional funding is required for changes to protocol and data collection.

For Registry studies performed on request by regulatory authorities (e.g. CAT/PRAC), the (draft) study 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. In addition, in order to support transparency on non-interventional PASS conducted voluntarily or pursuant with an obligation and to facilitate exchange of pharmacovigilance information between the Agency, member states and marketing authorisation holders, the marketing authorisation holder should make study information (including studies conducted outside the EU) available in the EU electronic register of post-authorisation studies (EU PAS Register) maintained by the Agency and accessible through the European medicines web-portal. The study protocol should be entered in the register before the start of data collection. Updates of the study protocol in case of substantial amendments, progress reports where applicable, and the final study report should be entered in the register (preferably within two weeks after their finalisation).

Question 5
The Agency is asked if how EBMT manages monitoring of centres' data is sufficient.

CHMP answer
The proposed risk based method for monitoring of centre data quality and completeness is acceptable. However, while it is noted that EBMT does not monitor centres systematically, monitoring is possible on request of study MAA/MAHs, i.e. the details of monitoring have to be negotiated on a case by case basis. By default, the MAA/MAHs conducting a registry study within the EBMT should be requested to do the monitoring or provide funding for that. Details are expected to be described in the registry study protocol. Data should be collected regarding the fraction of data that undergo source verification. In order to ensure acceptable data quality for individual studies conducted for regulatory purposes, source data verification and periodic auditing on a reasonable amount of data should be conducted using a risk-based approach and following a step strategy dependent on the scope of the study. As a general rule, data source verification for a minimum of 10% of registered patients in individual study centres would be required, however the level of data verification will have to be agreed upfront between EBMT and MAA/MAH in the context of the study performed. In case relevant findings are observed, appropriate measures should be specified. Quality on short and long term data should be

assured. Agreements on relevant logistical aspects should be made between EBMT and MAA/MAHs in advance of study start.

Question 6
The Agency is asked whether the EBMT Registry can be used as a source of data for CAR-T cell product comparative studies.

CHMP answer
CHMP is of the opinion that randomised, controlled trials remain the standard for comparative evaluations. Registry based evaluations can extend and add to the findings from randomised trials or be useful in situations where randomised trials are not feasible, e.g. rare adverse reactions or long term safety evaluation.

It is recognised that the EBMT collects data that might be suitable for comparative analyses. Whether or not these data can be used as source of comparative data for CAR-T-cell studies will depend on the particular research question and/or the specific treatment studied. 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. Moreover, it is important to consider that the potential set of variables required for a matched pairs (or similar) approach may vary among studies, and will need to be available for both the treatment and control groups. Furthermore, a critical assumption for most matching methods is that all key prognostic factors/confounders have been adequately measured and included as part of the matching process. In effect, well-known limitations associated with the use of registry data for comparative analyses are related to the potential introduction of bias that are not controlled by randomisation. Also, the systematic collection of treatment effects (efficacy and safety) is more limited compared to a trial. These limitations affect the acceptability of the data. It is expected that all these considerations will be reflected in the study-specific protocol and related statistical analysis plan.

Question 7
Does the Agency agree with the approach of EBMT in capturing additional variables, requested by the MAH, to avoid duplication of reporting?

CHMP answer
The approach taken and proposed by EBMT seems sensible and is likely to increase adherence to data collection in the individual treating centres. The CHMP endorses a unified collection structure. Standardization of data elements/fields collected in all treating centres (based on a single database for each registry) and harmonization between EBMT and other registries (e.g. CIBMTR) is recommended, in order to facilitate harmonization of data set across registries to allow data sharing and pooled analysis.

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. 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.

Question 8
Does the Agency agree with EBMT's proposal on Severe Adverse Events (SAE) reporting for CAR-T cell products?

CHMP answer
CHMP is of the opinion that a distinction needs to be made between secondary use of registry data collected routinely (i.e. where the events of interest have already occurred and have been collected for another purpose allowing aggregated analyses on the incidence of adverse events (AEs)), and primary collection of data for a specific study (i.e. where the events of interest are collected as they occur specifically for the study with AE reporting obligations).

In the case of secondary use of registry data, it is agreed that AEs reporting to regulatory authorities/Eudravigilance is the responsibility of the treating centre, physician, or Sponsor/MAH, not EBMT.

In the case of primary collection of data, contractual agreements with the MAH should be in place to clearly define the roles and responsibilities of each party for implementing requirements for individual case safety report submissions. There should be provisions described in the study protocol concerning Individual Case Safety Report (ICSR) requirements to be compliant with the EU legislation.

The use of registry data in non-interventional post-authorisation safety studies (PASS) can constitute primary or secondary use of data, depending on the study protocol. It is considered in line with the provisions of GVP Module VI.C.1.2.1 that the non-interventional PASS, with the objective of long term follow up of patients treated with CAR-T cellular therapy products, pertains to primary data collection as the design relies on data collection directly from healthcare professionals and the events of interest are collected as they occur specifically for the study. As a consequence, in line with the recommendations of chapter VI.C.1.2.1.1 of GVP Module VI ("Non-interventional post-authorisation studies with a design based on primary data collection"), solicited reporting of ICSRs is required.

Question 9
Does the Agency consider that EBMT's current consent form and consenting procedure are adequate for EBMT-based CAR-T cell product studies for regulatory purposes including data access by regulators?

CHMP answer
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/)

In general terms, the EBMT approach is that patient consent must comply with the strictest of the national regulations applying. 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 treated/monitored 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. 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 individual patient data and needs to ensure that the patients have consented to share their personal data at the appropriate level. The current consent form and consenting procedure is considered acceptable.

In the context of the implementation of GDPR, 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 and/or regulatory purposes. Treating centres should remain accountable for ensuring patient consent; the EBMT Study Offices should receive from each centre a confirmation that patients have consented to share their data. 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.

Question 10
The Agency is asked whether the current EU network of EBMT centres is considered adequate in covering the potential centres that will be used for administering CAR-T cell products.

CHMP answer
Currently, the EBMT has an acceptable, wide network when considering the centres performing autologous and allogenic transplants in EU. As it is expected that CAR-T cell therapies will be administered essentially in centres performing transplants, a considerable overlap is likely between centres that administer CAR-T cells therapies and those that already collaborate within EBMT. Therefore, the current EU network of EBMT centres is considered adequate.

Question 11
The Agency is asked if the Registry can be considered fit to serve as a Post-Launch Evidence Generation (PLEG) resource.

CHMP answer
EBMT is a well-recognised and respected entity in the field of bone marrow transplantation, especially for the treatment of malignant disease. The set-up of registry and the current use of the data support the view that the EBMT registry is a valuable resource and functioning organisation. Also, the possibility to include protocols that are developed with external sponsors supports the relevance of this registry. For haematological malignancies, whether the Cellular Therapy module of the EBMT registry is fit for regulatory purposes will heavily rely on the collection of pertinent and good quality data. Dependence of the registry on the input of data of the collaborating treating physicians is one of its strengths, but may also pose a threat for its success. The applicant's initiatives to facilitate or simplify the actual data entry process are strongly encouraged. However, the term post licence evidence generation is regarded as very broad and many different uses of registry data are possible. The Cellular Therapy module of the EBMT registry enables retrospective data analyses as well as prospectively planned data collections and analyses which have to be evaluated differently and where the capabilities of EBMT may be different from case to case. It is recognised that the registry collects data that might be suitable as source for Post Launch Evidence Generation but concerns are raised at this time on the quality controls applied on the data collected, potentially challenging reliability of the data (refer to answer to question 1 and 5).

Background information as submitted by the Applicant

1. Introduction

Medicinal products made from human living cells or tissues are likely to exert positive effects but also trigger side-effects over prolonged periods of time if not for the entire remaining lifespan of treated individuals. Possible temporal changes in the characteristics of the living material in advanced therapy medicinal products (ATMP) may affect efficacy. The time required for new tissue to be fully functional may be several years (use of surrogate end-points needed for marketing authorisation, but confirmation with clinical end-points needed in post-authorisation phase). Some ATMP may be a once-in-a-lifetime treatment and long-term follow-up is needed to demonstrate the sustainability of efficacy. Efficacy may be highly dependent on the quality of the administration procedure (e.g. patient conditioning, surgery). This may differ between clinical trial and normal health-care settings. Cell therapy products with a limited lifetime may require an efficacy follow-up system that monitors the dynamics of efficacy.[1]

Chimeric antigen receptor T-cell (CAR-T) immunotherapies are one of such products. While clinical results of CAR-T cell products so far have been impressive, the treatment can also have substantial adverse effects e.g. cytokine release syndrome (CRS) leading to severe complications in patients including death. Therefore expedited market access for manufacturers is being accompanied by broader post-market checks as evidenced by the substantial long-term follow-up requirements for the first CAR-T products recently authorised by U.S. regulatories.[2]

While manufacturers have demonstrated their ability to organize short-term clinical and biological follow-up of limited numbers of patients included in clinical trials, long-term follow-up of large cohorts of patients in the post-marketing phase is expected to be more challenging. The difficulty will be even higher considering that a single individual is likely to sequentially receive several types and categories of cellular therapies in combination with other categories of treatments. This is where registries established by professional associations such as the European Society for Blood and Marrow Transplantation (EBMT) or the Center for International Blood and Marrow Transplant Research (CIBMTR[**]) will potentially prove of crucial importance. An EU report from 2015 observed that these data will allow authorities to not only monitor and ensure safety, quality and functionality of novel therapies but also to justify public investments to ensure availability of tissue and cell therapies.[3]

It is recognised that their successful use will depend on their ability to capture sufficient data in a timely fashion on the nature of cellular therapies. Importantly however, there are precedents for clinical data provided by such registries being used in successful post-marketing evaluation surveys of chemical drugs.

These expedited market access schemes e.g. PRIority MEdicines (PRIME) (European Medicines Agency), Breakthrough designation (US Food and Drug Administration) will increasingly depend on the use of Real World Data (RWD) to monitor safety and efficacy of these novel therapies. Real-world data are key to determining whether benefits observed in clinical trials are also seen in unselected patient populations in real-world settings and to understanding the impact of a given innovation on patient outcomes, particularly in the case of rare adult and paediatric cancers. They are also a key component of 'coverage with evidence' schemes increasingly being used for new anti-cancer medicines, particularly 'breakthrough innovations' that are approved on the basis of early-stage trial data through accelerated approval schemes.[4]

Closer collaboration between registries and regulators to improve quality and usefulness of registry data could benefit both regulatory utility and value for health care providers.[5] This is of particular importance for medicinal products that fall within the concept of personalized medicine and as a consequence are associated with price tags that far exceeds the price of most other commercialized therapeutics.

2. Registry history

EBMT is a Dutch-registered international not-for-profit organization founded in 1974 with approximately 50 staff working in data management, study coordination, clinical trials, registry management, accreditation, event organisation and general management. See 5.2 for additional information.

[**] https://www.cibmtr.org

Among EBMT's first initiatives after its foundation was to establish a registry of bone marrow transplants. Forty years later the registry is now the principle source of data in the field for clinical research for retrospective clinical studies, epidemiological trends and feasibility studies for prospective clinical trials. The registry holds data on more than 500,000 transplants and receives data from approximately 80% of European transplant centres. It also holds data on rare diseases such as germ cell tumours, systemic sclerosis and mantle cell lymphoma. In addition, the Registry is collecting donor follow-up information and data on cell therapies such as mesenchymal cells among others. The clinical content is curated by clinicians specialised in transplant and particular diagnoses, who are knowledgeable in new indications, drugs and techniques and who strongly contribute to standardisation by establishing and enforcing definitions across countries and diagnoses.

EBMT is leading the transplant field within Europe and has close collaborations with other societies like CIBMTR, EORTC and LeukemiaNet. Every year, EBMT publishes more than 50 new scientific manuscripts in high impact peer reviewed journals, of which many are based on Registry data.

In more recent years, the registry is also being used regulatory purposes such as by the Pharmacovigilance Risk Assessment Committee (PRAC) for Plerixafor and Defibrotide. For Plerixafor, the EBMT-run CALM project[††] has collected more than 600 plerixafor patients and 7000 control cases for Multiple Myeloma and Lymphoma. For Defibrotide, the VOD Project, a multi-centre, multinational, prospective observational registry study, is under way to collect safety and outcome data in patients diagnosed with severe hepatic VOD following hematopoietic stem cell transplantation (HSCT) and treated with Defitelio®.[‡‡] Increasingly manufacturers of novel therapies are approaching EBMT to understand more about the registry, partly through EMA support for these interactions. For instance, in the EMA Assessment report for Strimvelis dated 01/04/2016, the applicant was strongly encouraged to contact the EBMT registry about support for a long-term prospective, non-interventional follow-up study.[§§]

The registry is also being used to support an annual survey of practice changes in the field of HCT[6] as well as to analyse global factors that affect those practices, including country of origin, gross national income[7], impact of quality management and JACIE accreditation[8],[9] in addition to patient or disease related factors.

Finally, in 2017 EBMT announced the start of work on moving from the current ProMISe database to the MACRO platform with full implementation expected to conclude in November 2018. The MACRO project requires a sizeable investment by EBMT but which is expected to lead to significant Improvements for investigators and users and ultimately for EBMT's scientific capacity.[***]

EBMT publications can be accessed at https://www.ebmt.org/research/publications

EBMT current research can be accessed at https://www.ebmt.org/research/studies.

3. Specific questions for EMA review and EBMT positions

3.1. **The Agency is asked if the data quality control mechanisms proposed by EBMT are adequate for PLEG purposes for CAR-T cell products.**

Applicant's position

Data originates with the centres who in most cases enter the data directly (see also 4.7). Each centre typically has one or more designated staff to enter data. Bigger hospitals may have professional data management teams working on reporting. However it is more common that the profile of persons entering data varies and can include physicians, data managers and research

[††] https://www.ebmt.org/research/studies/calm-collaboration-collect-autologous-transplant-outcomes-lymphoma-and-myeloma

[‡‡] https://www.ebmt.org/research/studies/multi-centre-multinational-prospective-observational-registry-collect-safety-and

[§§] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003854/WC500208201.pdf. Accessed 09/11/2017

[***] Press release - "The European Society for Blood and Marrow Transplantation (EBMT) implements Elsevier's MACRO platform to upgrade patient registry" http://tinyurl.com/ybyb8sqq

nurses among others. However, regardless of the profile, data is entered in the same way via the data forms (see 5.1 below) with the important proviso that staff can 'translate' the data from the patients file into the correct fields in Promise.

Variability will depend on the experience of the person entering data and their knowledge of the data. To countermand this variability, for general data reporting the Registry incorporates several data quality control measures, including:

- regular training provision for data managers
- 4000+ database control 'triggers' preventing the introduction of inconsistent data
- a clinical data definitions group accessible during working hours [†††]
- continuous support to data managers by Registry Office through the helpdesk
- a set of reports looking at possible errors that data managers can run themselves to check their data
- annual reports to centres to tell them how they are doing
- annual requests for follow-up
- regular communications through the Data Management News on new features, issues, changes, etc.

For data required for sponsored studies, additional data quality controls are applied by the Studies Offices with dedicated registry personnel. These specialists are recruited specifically to support studies and their costs are charged to the sponsor. Given that novel therapies are likely to require follow-up periods of 10 years or more, sponsors will need to take into account these charges.

EBMT Study Offices create data entry manuals for every study to ensure that data is correctly entered into the data base. Where a location error is found, it will be the same error for every patient. This is to prevent open interpretation of where to enter data where several persons are working on the same study.

The Study Offices checks the entered data with one data manager entering the data while a second person checks for accuracy.

After downloading the data for analyses, there are also system checks in SPSS to identify inconsistencies in the data. These inconsistencies are communicated back to the centres. Data is corrected directly by the centre or by EBMT based on centre feedback. Finally the date is downloaded again for final analyses. Data that includes uncorrected inconsistencies (not all centres reply to requests) and which could influence the analyses will be excluded.

The Registry also collects data on therapy-related complications within and without studies. See 3.8 below.

There are geographical and resource-related differences in transplantation volume and efficacy between centres which have been identified in publications.[7,10] These differences could affect treatment and eventual outcome although there is no evidence showing qualitative differences in the data reported to the Registry.

Although the Registry does not do data source verification due to its enormous cost (30,000 registrations a year from more than 500 centres), data source verification can be included in any protocol as long as adequate funding is provided.

See also 4.7, 4.13 and 5.1 below.

3.2. **The Agency is asked if EBMT's Cellular Therapy form is adequate for capturing safety/outcome data.**

Applicant's position

EBMT has developed a specific Cellular Therapy form for reporting data on these novel therapies.

As with other EBMT data-sets, the content is curated by clinicians specialised in the treatments and particular diagnoses covered, who are knowledgeable in new indications, drugs and

[†††] https://www.ebmt.org/registry-structure

techniques and who strongly contribute to standardisation by establishing and enforcing definitions across countries and diagnoses.

The full set of items is laid out in 4.4 below.

The form is accompanied by a detailed guide called the "CELL THERAPY FORM MANUAL. A Guide to the completion of the EBMT Cell Therapy Med-A Form".

Note that the existing data set is not exhaustive. It was meant to set the standard for reporting this type of treatments with the expectation that more specialised modules will be built for targeted treatments.

See also 4.4 below.

Examples

The ZALMOXIS study as an example of comparing standard of care against a novel ATMP. This study supported the manufacturer's request for EMA approval.[‡‡‡]

See 3.6 for more details on the Zalmoxis study.

The CALM study is an example of an EBMT-run safety study. The study is being performed on behalf of Genzyme / Sanofi regarding the safety of plerixafor in mobilisation in autologous transplants in Multiple Myeloma and Lymphoma, based on data collected in the standard MED B forms for MM and Lymphoma. An additional page of questions (MED C) was created by EBMT and Genzyme / Sanofi to meet the specific needs for this product.

EBMT collected data on more than 7800 transplants of which 7450 were suitable to be used for analyses. The remainder were excluded from analyses due to missing data. Sanofi used the propensity scoring methodology to analyse the final data set.

During the study EBMT decided, together with Genzyme / Sanofi, to focus on collecting a list of core items needed to be able to perform the analyses. An MS Excel file was created including several worksheets (treatments, drugs, MED C etc.) highlighting the items that were missing data from the centres.

The Studies Office repeatedly sent these overviews to the centres, updating them as centres completed their data. Gradually more and more data was collected during the data collection and data quality period. This procedure was also used for the follow-up of patients whereby multiple lines per patients whereby items were classified as follows into *Mandatory*, *Major* and *Nice-To-Have*. Each of these classifications were colour-coded to facilitate the centres' task. While completing the data for all their patients represented a large workload for centres, most of them managed to complete the *Mandatory* and *Major* items while a smaller proportion of centres also completed the *Nice-To-Have* items indicating the centres' own interest in building complete patient datasets.

Finally the Study Office created an overview to count the numbers of follow-ups received from the centre per patient to check that it was performed annually. Where a patient died, that patient was marked that follow-up had stopped. Where follow-up was missing, this was marked in the overview and centres could read at patient's level which follow-ups had to be done.

Throughout the study, regular teleconferences were held with Genzyme / Sanofi on progress.

See 5.1 and 5.2 below.

3.3. **The Agency is asked if EBMT's ability to adjust the frequency of data reporting is adequate**.

Applicant's position

Standard data capture is typically performed at Day 0, 100 and 1 year following infusion for transplant, and at 6 months and 1 year for cell therapy. However a higher or lower frequency can be established depending on the study requirements and can be established in the study design.

‡‡‡

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002801/smops/Positive/human_smop_001000.jsp&mid=WC0b01ac058001d127

3.4. **The Agency is asked if EBMT's management of request for changes or amendments to study design is adequate**.

Applicant's position

EBMT experience has shown that when companies are not clear on what they want or need at the study inception, this can produce unexpected changes to requirements later on which potentially adds substantial overheads even to establish a feasibility study. EBMT firmly believes that early discussions on study design and including all stakeholders and sharing experience from other projects is critical to meeting expectations and needs of all stakeholders.

Where changes are requested after a study has commenced, these are evaluated for their complexity and impact and managed accordingly. The time required to implement changes depends on their complexity and impact.

The study investigator instructs the Registry on the fields to be used. The Registry advises which are new and which are not. The new fields are defined by the clinicians and then implemented in the database. Forms are published, centres are informed and trained, manuals are written, etc.

The main participants in this process are the researchers, the registry and the definitions group while the EBMT Scientific Council gives final approval.

Where manufacturers turn to EBMT to provide the registry infrastructure to pursue their aims, funding will be assigned to recruit additional personnel to be dedicated to the study and data. Registry staff will train personnel recruited for these studies in building the necessary datasets as required by sponsors into the registry.

3.5. **The Agency is asked if how EBMT manages monitoring of centres' data is sufficient.**

Applicant's position

EBMT experience shows that studies that provide sufficient resources and/or incentives to centres have higher levels of data quality and completeness. Additionally, practitioners are known to report more assiduously when data collected is of clinical interest and utility.

See also 3.7 and 4.13 below.

Sponsors who require monitoring will be charged by EBMT. EBMT utilizes different models that can be adopted depending on the needs of the study:

- Initiation visit: to check the centre on several point before you include the first patients.
- Visit: during study inclusion to check if patients data is correctly registered
- Close out visit: at end of the study

Within the protocol a company has to decide what percentage of patients or centres will be monitored. EBMT can also decide to perform "risk based monitoring", meaning that EBMT defines, together with the Client, which fields have the most impact on the data and/or on patient safety and perform monitoring on those fields particularly or with extra attention for those parts.

Monitoring can also be done on the electronic data fields during and at the end of the study to ensure data quality.

The percentage of the total numbers of patients included will depend on the numbers of participating countries and sites within that country.

For instance, a sponsor may want to monitor 10% of the enrolled patients based on inclusion of 2000 patients in total. The sponsor could undertake the initiation visit themselves, selecting these centres with the capacity to deliver a novel therapy.

EBMT itself does not monitor centres.

The EBMT already has experience of working with a German provider that has a pool of monitors all over Europe with the advantage that they read and speak the local language so can read patients files and check the data.

3.6. **The Agency is asked whether the EBMT Registry can be used as a source of data for CAR-T cell product comparative studies.**

Applicant's position

Patient registries like the EBMT's allow comparisons between patients with different treatments based on similar sets of data and on similar data collection methods which is not possible in a dedicated product registry.[11] The EBMT registry contains historical data on patients treated including data on disease, age, status of disease at transplant and availability of donor. Autologous transplantation are captured for a series of indications, including Multiple myeloma, Lymphoma's and Solid Tumours. Autologous transplantations with genetic modification are also captured.

EBMT can facilitate comparative groups of patients in studies once both treatments are stored in the Registry. The Registry has already been used for the purpose of tracking the impact of drug development on stem cell transplantation.[12]

As a general observation, EBMT is unlikely to have data on cell therapy that is given in departments that are not at least haematology if not transplantation. On the other hand, if one of the treatments is not regularly stored in the Registry, there are no impediments to storing data for patients that have received neither a transplant nor a cell therapy treatment, therefore technically speaking the Registry can accommodate this. The challenge may arise from working with centres that are not familiar with the EBMT Registry but provision can be made for training and education of teams at these sites.

There may also be particular complications associated with comparing a non-transplant with a transplant cohort that need to be taken into account.[13]

In more recent years, the registry is also being used for regulatory purposes for therapies involving Plerixafor and Defibrotide. For Plerixafor, the EBMT-run CALM project[§§§] has collected more than 600 plerixafor patients and 7000 control cases for Multiple Myeloma and Lymphoma. For Defibrotide, the VOD Project, a multi-centre, multinational, prospective observational registry study, is under way to collect safety and outcome data in patients diagnosed with severe hepatic VOD following hematopoietic stem cell transplantation (HSCT) and treated with Defitelio®.[****] In the EMA Assessment report for Strimvelis dated 01/04/2016, the applicant was strongly encouraged to contact the EBMT registry to support a long term prospective, non-interventional follow-up study.[††††]

Furthermore the Registry was used in the evaluation of Zalmoxis, the first immunogene therapy for the treatment of adult patients with high-risk haematological malignancies, granted conditional authorization by EMA in 2016.[14] The EBMT registry allowed for a matched pair analysis comparing the outcome of patients who received Zalmoxis versus those being treated as standard of care. This comparison was presented as an oral session during the American Society of Hematology annual meeting in 2016.[15]

Additionally, Zalmoxis was used as an example of using RWD in an EMA presentation at the Industry Stakeholder Platform on Research and Development Support on 25 April 2017. Post-authorisation, a non-interventional safety and efficacy study will investigate effectiveness in real clinical practice by collecting data about the disease status and outcome of all patients treated with Zalmoxis using the EBMT registry. [‡‡‡‡]

EBMT is able to use these historical cases including their long term follow-up as controls for other more novel therapies such as cell therapy. Comparison can be made by match pair analyses, or other statistical methods.

3.7. **Does the Agency agree with the approach of EBMT in capturing additional variables, requested by the MAH, to avoid duplication of reporting?**

Applicant's position

[§§§] https://www.ebmt.org/research/studies/calm-collaboration-collect-autologous-transplant-outcomes-lymphoma-and-myeloma

[****] https://www.ebmt.org/research/studies/multi-centre-multinational-prospective-observational-registry-collect-safety-and

[††††] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003854/WC500208201.pdf. Accessed 09/11/2017

[‡‡‡‡] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2017/05/WC500227703.pdf. Accessed 09/11/2017

Storing data in different databases makes data management very complex and very vulnerable. Subjects need to be matched in order to merge the data and matching is an extremely time consuming operation. Identifiers need to be kept in all databases posing unnecessary risk to confidentiality.

An agreed set of core data requires its own set of resources. Communication must be perfect, all groups involved must ensure that they never change anything until everybody has agreed and, regular and effective meetings need to take place. A good coordinator is vital to lead the group as each researcher will have his/her own opinion on how to collect each item of data. The likelihood that this approach would delay a project is very high as consensus is needed at almost every step, sometimes even when correcting of bugs and typos.

For the above reasons, EBMT's approach to this problem is to establish a single reporting platform. The Registry should essentially act as the companies' registry so if the manufacturer wishes to have additional items, EBMT can build them into a module in the Registry to be completed by the participating physicians. Note that any additional work or maintenance beyond the core dataset would have to be underwritten by the manufacturer.

EBMT sets out to ensure that every question, regardless of whether it comes from EBMT or the manufacturer will exist only once in the Registry. EBMT will retain an overview of all of the questions and can identify duplicates early. Of course an existing question can be reused and asked at a different time point e.g. at diagnosis, at CT infusion or at follow-up.

Data regarding the manufacturing of the product can be stored in the Registry in a form that is not available to the treating physicians if required.

The manufacturer should create their questionnaire already knowing the content of the EBMT CT registry. This again highlights the need for early dialogue as referred to in 3.2 above. However, later requests for additional items or alterations to existing ones can always be incorporated subject to an assessment of the complexity of the change. Note that the time required to incorporate changes will vary depending on the complexity of the change.

The reader should bear in mind that "form" is a word that is used in different ways. CT paper forms should not be seen as a block. The paper forms are themselves made up of a series of electronic forms know as e-forms.

Admittedly while in ProMISe getting these "forms" to mix is very complicated and prone to errors due to the navigation that lies behind, in MACRO the e-forms are quasi-independent modules that can be added or removed as necessary with much reduced difficulty. Therefore EBMT will be able to add any type of MACRO form to the CT forms: haematological measurements, biochemistry, comorbidities, pre CT therapy, etc.

For instance, in the new registry platform, centres participating in a Novartis-sponsored study will answer the questions already in the CT registry and any questions added by Novartis. As far as the centre is concerned, the items follow each other seamlessly so a centre has only one list to complete thus avoiding duplication. However, for the purposes of access, different access rights can be provided for different sets of questions depending on the needs of the study.

In terms of avoiding questions being asked by multiple persons within EBMT, a dedicated EBMT team and dedicated data managers will work on the CAR-T-cell studies. There will be a data management plan indicating how often data is asked, who is responsible for asking and answering, how data will be entered, checked etc. If centres do not answer, EBMT will keep on asking as long as it takes to get the data (described in the plan) or finally exclude the patient if data is inconsistent or contains excessive missing items. A Statistical Analyses Plan (SAP) is also prepared which includes how to deal with missing data.

In conclusion, if manufacturers use EBMT as their registry, centres will only have to enter data into a single source.

3.8. **Does the Agency agree with EBMT's proposal on Severe Adverse Events (SAE) reporting for CAR-T cell products?**

Applicant's position

EBMT considers that management of SAE is the responsibility of sponsors of studies and centres are used to reporting SAE directly to the sponsor / pharma.

Variables are add to the database and are then available to be used on any product thereafter. The list of variables can be made available at the study design discussions and any existing variables can be incorporated. Whether a field will be used for one product or for all products only depends on its clinical suitability for that product and that indication.

EBMT understands that according to the *Guideline on good pharmacovigilance practices (GVP) Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1)*[§§§§], the use of the registry for non-interventional post-authorisation studies constitutes secondary use of data and therefore the reporting of suspected adverse reactions in the form of individual case safety reports (ICSRs) is not required. Reports of complications can be collected retrospectively and summarised as part of any interim safety analysis and in the final study report unless the protocol provides for different reporting.

The Registry is used to collect two types of adverse events:

- events associated with the disease itself (mostly for autoimmune and inherited disorders)
- events associated with the treatment.

This is part of the 100-day report for HSCT and the 6-month report for cell therapy with the possibility to change the frequency of reports as already stated, and of the regular follow-up for all patients.

Currently, EBMT collects the following information:

For non-infectious complications

- incidence
- date started /date of resolution / ongoing
- grade
- whether associated to the cell therapy

For infectious complications

- type of infection
- pathogen involved
- location
- date started / date of resolution / ongoing
- blood isolation method

For these purposes, SAE data stored in the registry could be used to generate aggregate reports for third parties such as regulators and MAHs but as written above, these would constitute summaries of incidence and character but not be spontaneous reports.

At this early stage in clinical development and commercialization, CAR-T cell products are used to treat rare subsets of haematological diseases. A single reporting resource will avoid fragmentation of small data sets and achieve a meaningful body of pooled data. As patient numbers increase, rare events could start to be observed that simply did not occur in the smaller patient populations treated in the studies phases.[16]

3.9. **Does the Agency consider that EBMT's current consent form and consenting procedure are adequate for EBMT-based CAR-T cell product studies for regulatory purposes including data access by regulators?**

Applicant's position

Following the EU Data Protection directive, and to ensure the maximum accordance with the law of all EU/EEA nations, all individuals residing in EU member countries must give informed consent for their personal data to be entered into EBMT-type registries.

Current EBMT practice is that the patient signs a consent form at their treating centre indicating their agreement to allow data to be sent to EBMT. EBMT understands that most centres incorporate this in the

§§§§

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf. Access 16/11/2017

transplant consent form signed before treatment proceeds. EBMT asks centres to include provision for data forwarding to other organisations for research purposes within this consent process.

Regarding requests for data sharing, a sentence is included stating that the centre is responsible for ensuring that the request agrees with the patients' wishes. Bear in mind that the patient can say 'yes' to treatment and 'no' to data forwarding.

If a patient who is already in the Registry passes to a clinical trial, that patient's data is not lost but access can be blocked on request from the centre. This is already performed for non-consented patients.

In the unlikely event that a subject withdraws consent after their data has been submitted, EBMT will remove from the database all semi-anonymous identifiers, including UPN, date of birth and initials, and the date of diagnosis will be reverted to "unknown". The log entries relating to the storage of these items will be deleted.

EBMT has members which do not belong to the EU/EEA countries and may submit data –for research purposes- to groups or individuals outside the EU/EEA. To cover these issues and ensure the legality of all procedures relating to the flow of research data, all centres inside and outside the EU must obtain informed consent from their patients and/or donors before the data can be submitted to EBMT. This informed consent must explicitly state that the data is to be kept in an "international" database and can be exported to a non-EU/EEA country. This is to avoid misunderstandings pertaining to the data being kept in a national database or even in an EU database. It is the legal responsibility of the member institution to ensure this is the case for all data submitted to EBMT.

With the MACRO platform, this process will be easier and more nuanced. For instance, we will be able to block access to a patient's cellular therapy form while allowing other data to be seen so that a user could see the total number of cell therapies given but without specifying which cell therapies. (This is just an example and exactly what is done will depend on the protocol.)

EBMT requires registry users (centres) to confirm that they will abide by data protection regulations and considers that the legal obligation lies with the centres for all data protection aspects. Note that EBMT does not have the capacity nor competency to check compliance.

Similarly, for CAR-T cell studies, responsibility for managing consent lies with the centres and/or the sponsor and EBMT does not collect consent forms.

During study monitoring patient consent can be checked to be present and signed. Should EBMT be required to note if the consent is given and stored by centres, a field could be added to the form for centres to confirm this.

Regulators' access to data

Data can be provided as summary, pseudo-anonymised, and individual patient data. Access can be facilitated at all three levels to regulators. For example, the Agence de la Biomedecine, a French competent authority, is directly accessing selected patient-level data of French patients.

Requests for access by regulators can be made to EBMT detailing the information required. EBMT will evaluate all requests taking into account its obligations under data protection regulations.

See also 4.7 and 4.9 below.

As the Registry Office is located in London, the database is registered with the Information Commissioner's Office in the United Kingdom.

3.10. **The Agency is asked whether the current EU network of EBMT centres is considered adequate in covering the potential centres that will be used for administering CAR-T cell products.**

Applicant's position

EBMT has over 550 member centres across more than 50 countries with the largest concentrations in European Union member states, most of which are reporting data to the Registry.

EBMT is aware that there are transplanting centres that are not reporting data to the Registry. Although almost by definition it is difficult to know why they do not report since they are outside our network, EBMT considers that they tend to be smaller autologous units or BMT units in non-EU countries e.g. Russia. In the most recent EBMT Activity Survey[6], a 'snapshot' questionnaire updated annually, approximately 16% of the responding centres were not EBMT members and therefore not reporting data to the Registry. This group of centres is calculated to represent approximately 10% of all autologous and 2% of all allogeneic transplants reported in that Survey.

It is reasonable to expect that only centres functioning at a high level will be selected to administer these novel therapies and the expectation is that these will be concentrated in high-income countries, at least in the early phases of roll-out.

It is expected that where manufacturers identify a centre that is not an EBMT member, this would be notified to the study coordinator who could then make contact with the centre and assign a Centre Identification Code (CIC) to facilitate reporting.

Finally, there are countries such as Germany whereby reporting of data to the national registry is obligatory so even if the centre is not an EBMT member, their data is entered in the Registry either by themselves or through the national organisation.

In terms of risk assessment, this document is based on the assumption that CAR-T Cells will be administered in transplant programs only, given the high risk of the intervention and its close relation to other stem cell transplantation activities in terms of toxicity and clinical management. However, some non-transplant healthcare professionals e.g. haematologists challenge this view and consider that CAR-T cells could be administered in haematology wards outside of the transplant context. Looking even farther towards the horizon, the question arises of how will care be organized and monitored when CAR-T cells are used in targeting solid tumours in the field of oncology. For these reasons, EBMT strongly considers that BMT units are best placed in terms of experience of working with cellular therapy products to administer CAR-T cell products, particularly in terms of handling the products (receipt, storage, and infusion) and management of therapy-related reactions and events in addition to data reporting. Bone marrow transplant teams already work as multi-disciplinary teams (MDT) with colleagues from other services and specialities assuring essential support for delivering complex therapeutic products. We have not seen a full list of the specific sites in Europe participating in recent CAR-T cell studies but anecdotally we are aware that several of these sites are EBMT bone marrow

transplantation (BMT) centres specifically because of their know-how, experience and supportive care structure.

The JACIE Accreditation scheme, run by EBMT in collaboration with the International Society for Cellular Therapy (ISCT) now includes standards for administration of immune effector cells including CAR-T cells. Accreditation by JACIE is cited in regulations by several European states including Belgium, Croatia, France, Switzerland, The Netherlands and United Kingdom as part of authorisation and/or reimbursement requirements.[*****] Accreditation by JACIE shows that a centre is working in line with international professional standards and this should be considered among selection criteria for centres to deliver these therapies.[16] We are already aware that manufacturers of these products include JACIE accreditation among their criteria for centres being evaluated as sites.

More information on JACIE including accredited centres can be found at http://www.jacie.org.

3.11. **The Agency is asked if the Registry can be considered fit to serve as a Post-Launch Evidence Generation (PLEG) resource**.

The Context of Use

The main function of the Registry is to collect pertinent and good quality clinical data. The context of use of the Registry is to collect clinical data on patients who have received CAR-T cell products as part of their treatment. This data is of high interest for the treating physicians, investigators, manufacturers and regulatory authorities in relation to these novel therapies.

At this early stage in clinical development and commercialization, CAR-T cell products are used to treat rare subsets of haematological diseases. A single reporting resource will avoid fragmentation of small data sets and achieve a meaningful body of pooled data. As patient numbers increase, rare events could start to be observed that simply did not occur in the smaller patient populations treated in the earlier phases.[16]

EBMT's history and expertise with the Registry, its dedicated Cellular Therapy module and its extensive network of experts should be considered as unique resources to support PLEG needs for CAR-T cell products. The Registry can respond positively to issues identified by the Agency's *Initiative for Patient Registries* such as lack of harmonised protocols, scientific methods and data structures, data sharing and transparency and sustainability.[17]

4. Technical and Operative Information

4.1. Frequency of submission of data

- Day 0 of transplant
- Day 100 post-transplant
- 6 month post cell therapy
- Annual follow-up
- These are the standard frequency periods but can be modified as needed depending on the type of cell product, type of study or other variables.

4.2. Base population

- Patients who receive a hematological transplant
- Donors that donate hematological products
- Patients receiving immunosuppression
- Patients receiving cell or gene therapy

[*****] https://www.ebmt.org/regulations-guidelines

4.3. Core data sets / variables for drug safety/effectiveness

- Subject description and general health
- Disease-specific clinical evaluation
- Pre-treatment including drugs
- Complications related to the treatment or diseases
- GvHD (acute and chronic)
- Outcome
    - Including relapse
    - Secondary malignancies

4.4. EBMT Data Collection Forms:

All forms available at https://www.ebmt.org/registry/data-collection

4.4.1. MED-C for Cellular Therapy https://www.ebmt.org/sites/default/files/migration_legacy_files/document/25%20Cellular%20Therapy%20MED-A.pdf

4.4.2. Cellular Therapy Manual https://www.ebmt.org/sites/default/files/migration_legacy_files/document/Cellular%20Therapy%20Manual.pdf

See also 5.1 below.

Table 1 Summary of EBMT Registry Cell Therapy subsets

Section	Items
Patient	43
Diagnosis	45
Assessment(1)	41
Treatment	41
Drugs_(Chemo_MoAB_etc)	4
Cell therapy infusion unit	112
Donor	11
Treat Compl	7
Cell therapy infusion episode	49
Total	**353**

Table 2 EBMT Registry Cell Therapy subset

MEDAORB	Form about to be entered	Patient
INDICAT	Main indication for therapy	**Patient**
MEDANUMB	To which registered transplant number are you adding data?	**Patient**
NEWTRAN	For subsequent treatment: same diagnosis?	**Patient**
NEWTRAN1	For subsequent treatment: same centre?	**Patient**
NEWTRAN2	For subsequent treatment: same unit or team?	**Patient**

MEDAORB	Form about to be entered	Patient
CENTRNR	Centre	**Patient**
UNIT	Unit or team	**Patient**
TEAMTYPE	Unit or team type	**Patient**
MEDNAME	Contact person	**Patient**
VADMIN10	Area code	**Patient**
DAT1STRE	Date of the 1st report	**Patient**
DATLSTRE	Date of the last report	**Patient**
UPN	UPN	**Patient**
VDOSSIER	Dossier number	**Patient**
GIVNAME	1st initials	**Patient**
FAMNAME	2nd initials	**Patient**
DATPATBD	Date of birth	**Patient**
PATSEX	Sex	**Patient**
COMMENT1	Comments 1	**Patient**
COMMENT2	Comments 2	**Patient**
COMMENT3	Comments 3	**Patient**
SURVSTA	Status	**Patient**
DLASTSE	Last seen	**Patient**
VCAUSDTH	Main cause of death	**Patient**
VCSDTGVH	Cause of death: GvHD	**Patient**
VCSDTINP	Cause of death: interstitial pneumonitis	**Patient**
VCSDTPTX	Cause of death: pulmonary toxicity	**Patient**
VCSDTINF	Cause of death: Infection	**Patient**
VCSDTBAC	Cause of death: bacterial infection	**Patient**
VCSDTVIR	Cause of death: viral infection	**Patient**
VCSDTFUN	Cause of death: fungal infection	**Patient**
VCSDTPAR	Cause of death: parasitic infection	**Patient**
VCSDTVOD	Cause of death: VOD	**Patient**
VCSDTHMR	Cause of death: haemorrhage	**Patient**
VCSDTCTX	Cause of death: cardiac toxicity	**Patient**
VCSDTCNS	Cause of death: CNS toxicity	**Patient**
VCSDTGIT	Cause of death: GI toxicity	**Patient**
VCSDTSKI	Cause of death: skin toxicity	**Patient**
VCSDTREN	Cause of death: renal failure	**Patient**
VCSDTMOF	Cause of death: multiple organ failure	**Patient**
DEACSBMR	Other transplant / cell therapy related cause of death	**Patient**
DEACSBMU	Cell therapy independent cause of death	**Patient**

MEDAORB	Form about to be entered	Patient
DISMCLFD	Diagnosis	**Diagnosis**
VACLEUK	Acute leukaemia diagnosis	**Diagnosis**
VAML	AML: FAB classification	**Diagnosis**
AML	AML WHO classification	**Diagnosis**
ALLL	Precursor lymphoid neoplasms (PLN): WHO classification	**Diagnosis**
VCHRLEUK	Chronic Leukaemia classification	**Diagnosis**
WHOLYCLS	Lymphoma WHO subclassification	**Diagnosis**
VREALCLS	Lymphoma WHO subclassification (archived)	**Diagnosis**
HODGKIN	Hodgkins type	**Diagnosis**
VPLCEDS1	M myeloma / Plasma cell disorders	**Diagnosis**
VPLCEDS3	Type of Multiple myeloma	**Diagnosis**
VPLCEDS2	IG type	**Diagnosis**
VPLCEDS4	Light chain type	**Diagnosis**
VSOLTUMO	Solid tumour classification	**Diagnosis**
VMDSMPS	MDS and Myeloproliferative neoplasias subclassifications	**Diagnosis**
MDSAMPS	Myelodysplastic/Myeloproliferative neoplasms	**Diagnosis**
BMFTYPE	Bone marrow (BM) failure type	**Diagnosis**
BMFSACQ	Acquired BM failure syndrome	**Diagnosis**
ACQBMFE	Acquired BM failure etiology	**Diagnosis**
VOTHSAAE	Other etiology for aplastic anaemia: specify	**Diagnosis**
BMFSGEN	Genetic BM failure syndrome	**Diagnosis**
INHDIS	Inherited disorders	**Diagnosis**
IMMDEF	Primary immune deficiencies	**Diagnosis**
VINBERR2	Inherited disorders of metabolism	**Diagnosis**
VINBERR3	Other inherited disorders	**Diagnosis**
HISTIOCY	Histiocytic disorders	**Diagnosis**
VAUTOIM1	Autoimmune disease classification	**Diagnosis**
VAUTOIM2	Autoimmune: Connective tissue	**Diagnosis**
VAUTOIM3	Autoimmune: Vasculitis	**Diagnosis**
VAUTOIM4	Autoimmune: Arthritis	**Diagnosis**
PRAONSET	Polyarticular rheumatoid arthritis: type of onset	**Diagnosis**
VAUTOIM5	Autoimmune: Other neurological disorders	**Diagnosis**
VAUTOIM6	Autoimmune: Haematological	**Diagnosis**
VAUTOIM7	Autoimmune: Inflammatory bowel disorders	**Diagnosis**
VAUTOIM8	Autoimmune: Other	**Diagnosis**
VHEMOGLO	Haemoglobinopathy	**Diagnosis**

MEDAORB	Form about to be entered	Patient
THALTYPE	Thalassaemia type	**Diagnosis**
NEURODIS	Neurologic disorders	**Diagnosis**
CARDIODIS	Cardiovascular disease	**Diagnosis**
MUSCSKDIS	Muscoskeletal disorders	**Diagnosis**
INFTRTAIM	Aim of the infection related treatment	**Diagnosis**
INFTRTPATH	Pathogen involved	**Diagnosis**
INFTRTPATOTH	Other pathogen, specify	**Diagnosis**
VDIAGTX	Indicate other diagnosis	**Diagnosis**
VSECORIG	Disease of secondary origin or transformed	**Diagnosis**
PERFSYST	Performance system used	**Assessment(1)**
KARNOFSK	Karnofsky or Lansky status	**Assessment(1)**
ECOG	ECOG status	**Assessment(1)**
CENTRE	Centre Tx	**Treatment**
VCENLAND	Country	**Treatment**
CENTR	Unit Tx	**Treatment**
TEAMTYPF	Unit type	**Treatment**
UPN2	UPN Tx	**Treatment**
AACOD2T	Diagnosis Tx	**Treatment**
VCHEMOTH	Drugs or chemotherapy	**Treatment**
REASDRUG	Reason for this drug	**Drugs_(Chemo_MoAB_etc)**
OTHECHEM	Other drug or chemo: specify if not coded	**Drugs_(Chemo_MoAB_etc)**
DOSE	Dose of drug	**Drugs_(Chemo_MoAB_etc)**
DOSEUNIT	Units of measurement	**Drugs_(Chemo_MoAB_etc)**
VRADIOTH	Radiotherapy (not TBI)	**Treatment**
VGRWFACT	Growth factor treatment	**Treatment**
VOTHERT	Other treatment	**Treatment**
VOTHERTS	Other treatment: specify	**Treatment**
CELLTHNR	Chronological number of cell therapy treatment for this patient	**Treatment**
SAMEPACKG	Cell infusion unit same as for previous cell therapy treatment	**Treatment**
DATPREVCINF	Date previous cell therapy treatment	**Treatment**
PASTCINFTYP	Type of previous cell therapy treatment	**Treatment**
SAMECIDNR	Same donor used for a prior treatment	**Treatment**
DIFFCTINST	Was last cell therapy treatment at a different institution?	**Treatment**
DIFFCTCNTR	CIC of the other institution, if known	**Treatment**
DINSTNAME	Name of the other institution if CIC unknown	**Treatment**

MEDAORB	Form about to be entered	Patient
DCTINSTCTY	City of the other institution if CIC unknown	**Treatment**
REASPRIMCT	Primary aim of the cell therapy treatment	**Treatment**
OTHTREASPC	Other reason for treatment, specify	**Treatment**
GVHDRELTRMT	Treatment related to GvHD?	**Treatment**
GVHDRELFXN	Treatment related to graft function?	**Treatment**
GVHDIMMRCNST	Treatment related to immune reconstitution	**Treatment**
CTCLNSETTN	Clinical setting	**Assessment(1)**
CTCLNPHASE	Clinical setting phase	**Assessment(1)**
CTCLNBLIND	Blind trial?	**Assessment(1)**
CTCLNRAND	Randomised trial?	**Assessment(1)**
CTEUDRANUM	Eudract number	**Assessment(1)**
CTUSANUMB	USA CT number	**Assessment(1)**
CTJAPANUMB	UMIN CT number (Japan)	**Assessment(1)**
HIDEREG	Do you want this registration hidden temporarily from the EBMT?	**Assessment(1)**
DATHIDEREG	Date by which registration can be made available for research	**Assessment(1)**
CETHORIG	Cell origin	**Treatment**
COMMANFPRD	Product manufactured from	**Treatment**
MNYINFUSED	Were there more than 1 CIU administered during this treatment	**Treatment**
NUMCINFUNIT	Number of cell infusion units	**Treatment**
NAMCTIMNF	Manufacturing facility	**Cell therapy infusion unit**
NAMCTIPKG	Name of the (CIU) package	**Cell therapy infusion unit**
CTIPKGBAT	Batch number	**Cell therapy infusion unit**
CTIUCID	Identification of CIU given by the centre	**Cell therapy infusion unit**
DONRL	HLA match	**Donor**
IONDR	ION of the Donor Registry or Cord Blood Bank	**Donor**
WMDAID	WMDA / BMDW code for the Donor Registry	**Donor**
DONREGID	Name of the Donor registry	**Donor**
DONORID	Identification of donor or CBU given by donor registry	**Donor**
TRTDONOR	Manipulation in the donor	**Donor**
VCYTOKDN	Growth factors administered to donor	**Donor**
VCYTOSD	Growth factors administered to donor: specify	**Donor**
GWFCTDO	Other growth factor given to donor: specify	**Donor**
DONMANO	Other in vivo manipulation in the donor	**Donor**
DONMANOS	Other in vivo manipulation in the donor, specify	**Donor**

MEDAORB	Form about to be entered	Patient
CIUBMRRW	Bone marrow (BM)	**Cell therapy infusion unit**
CIUPFRBLD	Peripheral blood (PB)	**Cell therapy infusion unit**
CIUUMBCBLD	Umbilical cord blood	**Cell therapy infusion unit**
CIUUMBCTIS	Umbilical cord tissue	**Cell therapy infusion unit**
CIUADPTISS	Adipose tissue	**Cell therapy infusion unit**
CIUPLCNT	Placenta	**Cell therapy infusion unit**
CIUAMNTFL	Amniotic fluid	**Cell therapy infusion unit**
CIUCARDTIS	Cardiac tissue	**Cell therapy infusion unit**
CIUHAEPTIS	Haepatic tissue	**Cell therapy infusion unit**
CIUNEURTIS	Neuronal tissue	**Cell therapy infusion unit**
CIUOPTHTIS	Opthalmic tissue	**Cell therapy infusion unit**
CIUPNCRTIS	Pancreatic tissue	**Cell therapy infusion unit**
CIUTUMRTIS	Tumour tissue	**Cell therapy infusion unit**
CIUOTHSRC	Other tissue source	**Cell therapy infusion unit**
CIUOTHRSPC	Other tissue source, specify	**Cell therapy infusion unit**
CIUCELULYM	Unselected lymphocytes	**Cell therapy infusion unit**
CIUCELCD4	CD4+ lymphocytes	**Cell therapy infusion unit**
CIUCELCD8	CD8+ lymphocytes	**Cell therapy infusion unit**
CIUCELMESN	Mesenchymal	**Cell therapy infusion unit**
CIUCELDNDR	Dendritic cells	**Cell therapy infusion unit**
CIUCELCD34	CD34+	**Cell therapy infusion unit**
CIUCELNK	NK Cells	**Cell therapy infusion unit**
CIUCELMON	Mononuclear cells	**Cell therapy infusion unit**
CIUCELEPRG	Endothelial progenitor	**Cell therapy infusion unit**
CIUCELOLIG	Oligodendrocytes	**Cell therapy infusion unit**
CIUCELCARDC	Cardiac progenitor cells	**Cell therapy infusion unit**
CIUCELISLC	Islet cells	**Cell therapy infusion unit**
CIUCELOTHR	Other cell type	**Cell therapy infusion unit**
CIUCELOTSPC	Other cell type, specify	**Cell therapy infusion unit**
CIUBSAMTHD	Bone marrow aspirate	**Cell therapy infusion unit**
CIULEUKMTHD	Leukapheresis	**Cell therapy infusion unit**
CIUBYSMTHD	Byopic sample	**Cell therapy infusion unit**
CIUMTHDOTH	Other method	**Cell therapy infusion unit**
CIUMTHDSPC	Other method specify	**Cell therapy infusion unit**
CIUCOLLDAT	Date of the 1st collection	**Cell therapy infusion unit**
CIUNUMCOLL	Number of collections	**Cell therapy infusion unit**
CIUMOBAGNT	Mobilising agent(s) used	**Cell therapy infusion unit**

MEDAORB	Form about to be entered	Patient
CIUMOBASPC	Mobilising agent(s), specify	**Cell therapy infusion unit**
CIUMOBAOTH	Other agent, specify	**Cell therapy infusion unit**
CIEXVIMANI	Manipulation of the product	**Cell therapy infusion unit**
MANIONSLPF	Onsite, by local processing facility	**Cell therapy infusion unit**
MANIOFSNCF	Offsite, by a non commercial facility	**Cell therapy infusion unit**
MANIOFSCF	Offsite, by a commercial facility	**Cell therapy infusion unit**
MANIDRUG	Drugs (any type)	**Cell therapy infusion unit**
MANIDRGMIT	Mitogens	**Cell therapy infusion unit**
MDRGMITSPC	Mitogens, specify	**Cell therapy infusion unit**
MANIDRGGF	Growth factor	**Cell therapy infusion unit**
MDRGGFSPC	Growth factor, specify	**Cell therapy infusion unit**
MANIGRDOTH	Other type	**Cell therapy infusion unit**
MDRGOTHSPC	Other type, specify	**Cell therapy infusion unit**
MANIGENE	Gene manipulation	**Cell therapy infusion unit**
MANIGENTRN	Gene transfer	**Cell therapy infusion unit**
GENTRNRETV	Retroviral vector	**Cell therapy infusion unit**
TRNRETVSPC	___ Retroviral vector, specify	**Cell therapy infusion unit**
GENTRNLEN	Letiviral vector	**Cell therapy infusion unit**
TRNLENSPC	___ Lentiviral vector, specify	**Cell therapy infusion unit**
GENTRNOTH	Other vector	**Cell therapy infusion unit**
TRNOTHSPC	___ Other vector, specify	**Cell therapy infusion unit**
NUMGENCYCL	__ No. of gene transfer cycles	**Cell therapy infusion unit**
TRNGENCAR	Transgene CAR	**Cell therapy infusion unit**
GENCARSPC	___ Transgene CAR, specify	**Cell therapy infusion unit**
TRNGENSUG	Transgene suicide gene	**Cell therapy infusion unit**
GENSUGSPC	___ Transgene suicide gene, specify	**Cell therapy infusion unit**
TRNGENTCR	Transgene TCR	**Cell therapy infusion unit**
GENTCRSPC	___ Transgene TCR, specify target	**Cell therapy infusion unit**
GENTCRSPCH	___ Transgene TCR, specify HLA restriction element	**Cell therapy infusion unit**
TRNGENOTH	Transgene other	**Cell therapy infusion unit**
GENOTHSPC	___ Transgene other, specify	**Cell therapy infusion unit**
MANIGENEDT	Gene editing	**Cell therapy infusion unit**
GENEDTCR5	CCR5	**Cell therapy infusion unit**
GENEDTFIX	Factor IX	**Cell therapy infusion unit**
GENEDTFVII	Factor VIII	**Cell therapy infusion unit**
GENEDTOTH	Other gene	**Cell therapy infusion unit**
EDTOTHSPC	___ Other gene, specify	**Cell therapy infusion unit**

MEDAORB	Form about to be entered	Patient
MANIGENOTH	Other manipulation	**Cell therapy infusion unit**
MANIOTHSPC	___ Other manipulation, specify	**Cell therapy infusion unit**
RECGTARANT	Target/ antigen recognition	**Cell therapy infusion unit**
VIRALANTG	Viral	**Cell therapy infusion unit**
TARANTADNV	Adenovirus	**Cell therapy infusion unit**
TARANTBKV	BK virus	**Cell therapy infusion unit**
TARANTCYMV	Cytomegalovirus	**Cell therapy infusion unit**
TARANTEBV	Epstein-Barr virus	**Cell therapy infusion unit**
TARANTHHV	Human herpes virus 6	**Cell therapy infusion unit**
TARANTHIV	Human immunodeficiency virus	**Cell therapy infusion unit**
TARANTOTH	Other virus	**Cell therapy infusion unit**
TRGANTSPC	Other virus, specify	**Cell therapy infusion unit**
FUNGANTG	Fungal	**Cell therapy infusion unit**
TARANTCAN	Candida	**Cell therapy infusion unit**
TARANTASP	Aspergillus	**Cell therapy infusion unit**
TARANTFUS	Fusarium	**Cell therapy infusion unit**
TARANTZYG	Zygomycetes	**Cell therapy infusion unit**
TARANTOTF	Other fungus	**Cell therapy infusion unit**
TRGANTSPF	Other fungus, specify	**Cell therapy infusion unit**
TUMRCANANT	Tumor/ cancer antigen	**Cell therapy infusion unit**
CANCANTSPC	Tumor/ cancer antigen, specify	**Cell therapy infusion unit**
RECTRGTOTH	Other target	**Cell therapy infusion unit**
RTRGOTHSPC	Other target, specify	**Cell therapy infusion unit**
CTIUSELECT	Selection	**Cell therapy infusion unit**
CTIUSELPOS	Positive	**Cell therapy infusion unit**
CTIUSELNEG	Negative	**Cell therapy infusion unit**
PURTYPERC	Purity	**Cell therapy infusion unit**
YIELDPERC	Yield	**Cell therapy infusion unit**
CTIUEXPNS	Expansion	**Cell therapy infusion unit**
EXPNSDAYIC	Number of days in culture	**Cell therapy infusion unit**
EXPNSPASS	Expansion passage	**Cell therapy infusion unit**
EXPNSFOLD	Expansion fold	**Cell therapy infusion unit**
CTIUINDIFF	Induced differentiation	**Cell therapy infusion unit**
CTIUFREEZ	Freezing	**Cell therapy infusion unit**
MULTINFEPI	>1 infusion episode	**Treatment**
NUMINFEPI	Number infusion episodes	**Treatment**
NAMCTIPKG2	Name given to the cell infusion unit (CIU)	**Cell therapy infusion episode**

MEDAORB	Form about to be entered	Patient
RTSYSINTR	Systemic including intravenous	**Cell therapy infusion episode**
RTINFULOC	Local	**Cell therapy infusion episode**
RTLSINART	Intra-arterial	**Cell therapy infusion episode**
RTLSINTIS	Into tissue	**Cell therapy infusion episode**
RTLSINPRT	Intraperiteonal	**Cell therapy infusion episode**
RTLSINBON	Intra bone	**Cell therapy infusion episode**
RTLSINTHC	Intrathecal	**Cell therapy infusion episode**
RTLSINTMS	Intramuscular	**Cell therapy infusion episode**
RTLSINMED	Intramedular	**Cell therapy infusion episode**
RTLSINTORG	Intraorgan	**Cell therapy infusion episode**
RTINFOTH	Other route	**Cell therapy infusion episode**
RINFOTHSPC	Other route, specify	**Cell therapy infusion episode**
CIEUNSLYMPH	Number of lymphocytes	**Cell therapy infusion episode**
UNSLYMUNIT	Units for lymphocytes	**Cell therapy infusion episode**
CIECD4LYMP	Number of CD4+ lymphocytes	**Cell therapy infusion episode**
CIECD4UNIT	Units for CD4+ lymphocytes	**Cell therapy infusion episode**
CICD8LYMPH	Number of CD8+ lymphocytes	**Cell therapy infusion episode**
CIECD8UNIT	Units for CD8+ lymphocytes	**Cell therapy infusion episode**
CICD3LYMPH	Number of CD3+ lymphocytes	**Cell therapy infusion episode**
CIECD3UNIT	Units for CD3+ lymphocytes	**Cell therapy infusion episode**
CIESPTCNUM	Number pathogen specific lymphocytes	**Cell therapy infusion episode**
CIESPTCUNIT	Units for pathogen specific lymphocytes	**Cell therapy infusion episode**
CIETCSPCFY	Specify the pathogen	**Cell therapy infusion episode**

MEDAORB	Form about to be entered	Patient
CIECSTLYMP	Number tumour specific lymphocytes	**Cell therapy infusion episode**
CIECSTCUNIT	Units for tumour specific lymphocytes	**Cell therapy infusion episode**
CIECSTSPCFY	Specify the tumour	**Cell therapy infusion episode**
CIETCELREG	Number of regulatory T-cells	**Cell therapy infusion episode**
CITCELUNIT	Units for regulatory T-cells	**Cell therapy infusion episode**
CIEMESNCHY	Number for mesenchymal cells	**Cell therapy infusion episode**
CIMSCHUNIT	Units for mesenchymal cells	**Cell therapy infusion episode**
CIEDNDRCEL	Number for dendritic cells	**Cell therapy infusion episode**
CIDNDRUNIT	Units for dendritic cells	**Cell therapy infusion episode**
CINFECD34	Number for CD34+ cells	**Cell therapy infusion episode**
CINF34UNIT	Units for CD34+ cells	**Cell therapy infusion episode**
CIENKCELLS	Number for NK cells	**Cell therapy infusion episode**
CIENKUNIT	Units for NK cells	**Cell therapy infusion episode**
CIEMONNUCL	Number for mononuclear cells	**Cell therapy infusion episode**
CIMONUCUNIT	Units for mononuclear cells	**Cell therapy infusion episode**
CIENDOTHEL	Number for endothelial progenitor cells	**Cell therapy infusion episode**
CIENDOUNIT	Units for endothelial progenitor cells	**Cell therapy infusion episode**
CIEOTHUNSP	Other cell type	**Cell therapy infusion episode**
CIOTHCTSPC	Other cell type, specify	**Cell therapy infusion episode**
CIEOTHCELT	Number for other cell type	**Cell therapy infusion episode**
CIOTHCTUNIT	Units for other cell type	**Cell therapy infusion episode**
CIECONMTRT	Concomitant treatment	**Cell therapy infusion episode**
CICNTRTSPC	Concomitant treatment, specify	**Cell therapy infusion episode**

MEDAORB	Form about to be entered	Patient
CIESIMULT	Simultaneous	**Cell therapy infusion episode**
CIEPCLTHRP	Post cell therapy	**Cell therapy infusion episode**
PROCED	Was there a procedure associated with this cell therapy?	**Treatment**
PROCEDS	Specify the procedure	**Treatment**
TIMEPROC	Timing of the procedure	**Treatment**
TUMRSA2	Best response	**Treatment**
DATRESP	Date response achieved or assessed	**Treatment**
LABSTAT	Laboratory parameter response	**Treatment**
LABPAR	Specify the laboratory parameter	**Treatment**
RESPGVHD	GvHD response to treatment	**Treatment**
RESPGRAFT	Graft function response to treatment	**Treatment**
IMMRRESP	Immune reconstitution response to treatment	**Treatment**
AGVHGRMX	Acute graft versus host disease (aGvHD) maximum grade	**Assessment(1)**
AGVHDSKI	aGvHD stage in skin	**Assessment(1)**
AGVHDLIV	aGvHD stage in liver	**Assessment(1)**
AGVHDLGI	aGvHD lower GI tract	**Assessment(1)**
AGVHDUGI	aGvHD Upper GI tract	**Assessment(1)**
AGVHOTHR	Other disease site	**Assessment(1)**
CTHRELATED	Cell therapy related	**Assessment(1)**
VGVHDRES	aGvHD resolution	**Assessment(1)**
GRAVHOSD	Chronic graft versus host disease (cGvHD)	**Assessment(1)**
VCGVHDG	Extent of cGvHD	**Assessment(1)**
MAXNIHSC	Maximum NIH score during this period	**Assessment(1)**
VOTCO100	Non infectious complication	**Assessment(1)**
AUIMPRES	Complication present or absent	**Treat Compl**
VOTCOMPS	Other complication, specify	**Treat Compl**
WHOSCORE	Grade/ CTC score	**Treat Compl**
DBEGCOM	Date complication first noted	**Treat Compl**
CELTHCOMPL	Complication related to cell therapy	**Treat Compl**
ONGOING	Ongoing on the date of this assessment	**Treat Compl**
DENDCOMPL	End date	**Treat Compl**
LGRAFTL	Late graft loss	**Assessment(1)**
SECONDDI	Secondary malignancy / clonal complication	**Assessment(1)**
VRELPROG	Relapse or progression after transplant	**Assessment(1)**

MEDAORB	Form about to be entered	Patient
VDISESTA	Disease status	**Assessment(1)**
CHRACU	Status at therapy of main indication	**Assessment(1)**
DISCLI	Disease detected by clinical/haematological method	**Assessment(1)**
VPATSTAT	Survival status on this date	**Assessment(1)**
PRSTSTDONE	Persistence detection test	**Assessment(1)**
PRSTSTDATE	Date of persistence test	**Assessment(1)**
MOLPCR	Molecular (PCR)	**Assessment(1)**
FLWCYTOMTR	Flow cytometry	**Assessment(1)**
CHIMAETECH	Chimaerism	**Assessment(1)**
IMAGETECH	Imaging	**Assessment(1)**
IMHISTECH	Immunohistochemistry	**Assessment(1)**
OTHTSTTECH	Other technique used	**Assessment(1)**
OTHTECHSPC	Other technique used, specify	**Assessment(1)**
CELPRDTDET	Were cells detected	**Assessment(1)**

4.5. EBMT and CIBMTR forms

In general terms, EBMT and CIBMTR forms overlap substantially. For some data points, CIBMTR forms contain explicit detail e.g. they have many more coded causes of death. Given the recent roll-out of the Cellular Therapy form, EBMT's assessment was that this level of detail is not necessary at this point but if our assessment changes, new fields can be added to the new MACRO platform. The need for changes to the dataset are determined by the Cellular Therapy and Immunobiology Working Party and the EBMT Scientific Council.

Overall, EBMT's current forms are meant to be minimal datasets and are intended to collect information across different treatments, centres and countries. It is fair to add that this approach was taken so as not to intimidate centres with extensive datasets given that they provide data voluntarily without financial compensation. These forms should be considered as a backbone on which we are building more specialised data collection forms for more specific treatments as needed either due to scientific interest or our collaboration with other stakeholders including pharmaceutical companies. The new MACRO platform in particular will greatly facilitate this form-building process.

CIBMTR forms 4000R4.0, 4006R2.0 and 4100R2.0 are available at https://www.cibmtr.org/DataManagement/DataCollectionForms/Pages/index.aspx

A comparison of the top-level areas of data collected by EBMT and CIBMTR is laid out in Table 3 below.

Table 3 EBMT-CIBMTR Data Collection Forms comparison

General sections	Main differences	EBMT Minimum Essential Data (MED) for cellular therapy	CIBMTR Cellular Therapy Essential Data
Centre identification		x	X
Patient	Ethnicity in the CIBMTR	x	x
Indication for the cell therapy		x	X
Disease assessment at Last Evaluation Prior to Cellular Therapy		X	X
Donor		x	X
Prior HSCT	The details are not asked in the EBMT registry. What is asked is that they enter this information as usual.	X	X
Prior cell therapy	The details are not asked in the EBMT registry. What is asked is that they enter this information as usual.	X	X
Treatment context (Clinical Trial, etc.)		X	X
Planned infusions	Only infusions that are actually performed are requested in EBMT	X	x
Systemic Therapy Prior to Cellular Therapy		X	X
Functional status of the patient		X	X
Cell Therapy			
Cellular Therapy Product Identification		x	X
Description & collection		x	X
Manipulation		x	X
Product infusion(s)		x	X
Response		x	X
Follow-up			

Last contact date		x	X
Graft vs. Host Disease		X	X
Toxicity in first 6 m	More detail in the CIBMTR	x	X
Secondary malignancy		x	X
Graft assessment / cell persistence		x	X
Subsequent cellular infusion(s)		X	X
First relapse/progression		x	X
Last disease status		x	X
Survival status		x	X
Death	More detail in the CIBMTR	X	X

4.6. Potential availability of unbiased controls

Currently the registry - by definition - does not include a non-transplant population (with exception of Severe Aplastic Anaemia and immunosuppressive treatment)

- Treatment comparisons within the fields listed under Base Population
- Possible to allocate historical cases within certain disease areas

4.7. How data are entered

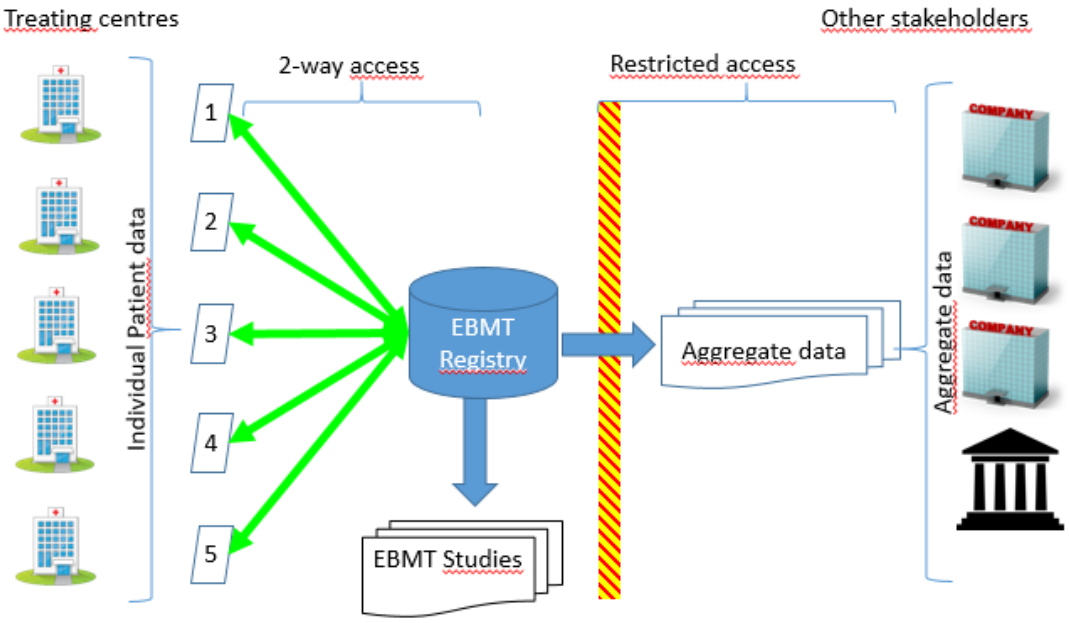
- Over 80% of data are entered by the transplant centres directly to the registry
- Data is reported by centres in from a wide range of EU countries thus allowing for detection of differences in practices and outcomes across the EU.
- Some national registries e.g. Germany, Austria may enter data on behalf of the centres based on paper forms submitted to them

4.8. Data access

- Restricted to EBMT research staff
- Transplant centres have continuous access to their own data
- Centres can request that EBMT gives access to specified external research organisations to their own data e.g. national registries
- All access is by unique non-transferable user access
    - There is an audit trail for users and their actions within in the Registry
- Pharmaceutical companies who have an agreement with EBMT do not have direct access to the data but can request that EBMT create specific reports for their use encompassing the data they are authorised to see.
    - Within MACRO this is called ‘read only access’ - by clicking on the specific report on the home page, pharma will be able to receive a pre-defined report on all their reported cases.
    - This report can contain all items and can be accessed 24/7.
- Regulators could have access to individual patient data only if the centre requests EBMT to give them access.

- The centre will have to ensure that the patient has given consent for such access and EBMT will also have to apply its own criteria in these cases.

Figure 1 Access by stakeholders to EBMT registry



4.9. Data sharing

In the spirit of facilitating data registration for centres and of increasing the use of scientific data worldwide, the EBMT can enter into data sharing agreements with organisations to whom centres are separately submitting similar data. The agreement will allow these organisations to access data already submitted by the centres to the EBMT, if the centre makes this request. The end result is that centres need to submit the same data only once, and still fulfil their data provision commitment with other partners e.g. the Stem Cell Transplant for Immune Deficiencies in Europe (SCETIDE), Eurocord, etc.

Post-submission note: Since 5 June 2018 the transfer of data from EBMT to CIBMTR is temporarily suspended whilst a GDPR review is ongoing.

More information at https://www.ebmt.org/registry/data-sharing.

4.10. Timeline for adding new variables

- Adding variables includes approval, definition, testing, and validation before implementation.
- Current database platform (ProMISe) – In very approximate terms the range extends from 1 day to 1 week per variable but it is completely context-dependent including the complexity of the requested data collection form.
- With the new MACRO platform, adding variables will take substantially less time.

4.11. Completeness of key data

EBMT uses 3 types of forms for data collection:

(1) MED-A which has the minimal essential data and is mandatory for full EBMT members
(2) MED-B which is more extensive, is regularly done only by a fraction of the centres on a voluntary basis, but is the framework for most studies
(3) MED-C which contains those fields specific for a study that are still not present in the MED-B forms

Estimates of completeness based on an overview performed half-way through 2017 and encompassing MED-A data from 2013 until then, are good with missing percentages below 1% in most items measured. For donor fields such as donor sex and CMV status, missing data was slightly higher but always below 1.5%. *Ex vivo* manipulation saw missing levels of up to 4% and GvHD parameters were missing in almost 10% of cases.

The main problem continues to be the follow-up as it is very time consuming for the centres. However, follow-up tends to be very good within sponsored studies as centres have committed themselves to do it.

There may be a delay of up to 6 months by some centres in reporting data.

Prospective non-interventional studies (PASS) tend to score much higher in completeness of all data and tend to be faster in receiving data.

4.12. Coverage and representativeness of population

Estimates of population completeness based on 2015 data, the last year for which we have a comparison.

- Autologous transplants – 75%
- Allogeneic transplants – 80%
- We estimate that around 80% of European transplant centres report to EBMT registry.
- The EBMT Activity Survey can serve to identify centres that are transplanting but not reporting data to the Registry.

4.13. Quality assurance procedures/Audit process

- Exact Definitions
    - All items are completely defined before being placed in the data collection forms
    - Same items in different collection forms must mean the same
    - A Definitions group[†††††] made up of expert representatives (physicians) of Working Parties and Study offices are always at hand to answer queries
    - Harmonization with US in progress
- Database with internal quality controls
    - Over 4000 triggers control the accuracy and internal consistency of what is entered in the database at the point of entry
    - Data quality reports can be run by users at any point to check for missing or unusual data
    - Regular follow-up requests issued by the Registry and Study Offices
    - Periodic queries on missing / incorrect data and follow-up requests
    - Missing data is queried in the context of studies from the Registry and Study Offices to the centres
    - Statistical analyses allow to detect bias, data quality and unusual trends
    - Statistical guidelines (see 4.17.8)
- Studies
    - Academic prospective non-interventional studies where data is collected prospectively and are therefore more complete with good follow-up. Data requests actively sent to the centres to complete missing data and to collect additional MED-C data.

[†††††] https://www.ebmt.org/registry-structure

- Within several Working Parties there are different Data Quality Initiatives to improve the data quality and follow-up of retrospectively collected patients.
- There are regularly studies underway which improves the data quality substantially.
- EBMT has statistical staff specially trained to analyse complex outcome like overall survival, relapse free survival, relapse incidence and non-relapse mortality. Many analyses include the incidence of engraftment, GvHD or secondary malignancies using competing risk models.
- EBMT uses different methodological strategies to investigate the data and to perform the statistics necessary. From Kaplan Meier estimates, cox regression models, match pair analyses, propensity scoring or multistate models, every set of data is different and should be treated as a unique data set.
- EBMT has published statistical guidelines (see 4.17.8)

- Education & Training
  - Training sessions available for data managers on the use of registry
  - Educational sessions on clinical knowledge specifically aimed at data managers
  - User manuals and clinical manuals are available and maintained on the EBMT web site (see link)
  - Continuous support is provided by the Registry office and by the Definitions group

4.14. Availability and use of SOPs, Instructions and Guidance

- SOPs, work instructions, manuals and guidelines are maintained by the Registry and Study Offices with version control

4.15. Other governance measures

- Dedicated, knowledgeable team for designing, managing and conducting patient/disease registries

- Working Parties (clinical lead disease/topic-specific groups within EBMT) are responsible for clinical content of data collection forms
- Definitions Groups: formed by clinicians who are experts in their field and appointed by Working Parties are continuously available to respond to specific queries and requests
- A member of the EBMT Board represents Registry issues at organisational governance level

4.16. Study set-up and timings

- After signing the PASS contract, EBMT starts the Ethical Committee approval procedures within the selected centres. EBMT's experience is that centres do the EC approval themselves with help of the EBMT regulatory officer.
- In general to open a country for a study we have seen timelines between 3 - 9 months. When a country is open, a new site can be opened within 1 - 3 months. All centres needs a centre site contract between EBMT and the centre. We use standard templates for these contracts but often centre site specific issues need to be adapted into the contract.

4.17. External certification

- ProMISe database is certified according to ISO/IEC 27001:2013 and NEN7510:2011.
  - Certificate holder is Leiden University Medical Center (LUMC) who hosts the database
- MACRO
  - Designed to support the requirements of internationally recognised ICH Good Clinical Practice, FDA 21 CFR Part 11 and the EU Clinical Trials Directive.

- Data centre is ISO 27001 Information Security Management certified.
- See also 5.3.

5. Annex

5.1. EBMT Clinical Manuals and Reference Documents including definitions

4.17.1. Registry function

4.17.2. Basic transplant registration: comprehensive guide to data collection, using the MED-A as a guide, with information on EBMT and data submission.

4.17.3. MED-AB Forms Manual: Guide to completion of the MED-AB forms.

4.17.4. List of disease classifications: Disease synonyms and sub classifications as applied in the Registry database

4.17.5. List of drug names and synonyms: List covering the different names drugs may be known by in different countries or contexts. It also contains some information on chemotherapy protocols.

4.17.6. Summary of Disease status and Response by disease: Tabular description of disease status or responses relevant for each disease.

4.17.7. Definitions of Infectious Diseases and Complications after Stem Cell Transplant

4.17.8. Statistical Guidelines for EBMT (see also Iacobelli, 2013[18])

All documents available at https://www.ebmt.org/registry/data-collection

5.2. Study flow per site example: CALM-study related documents

5.2.1. **Ethics Committee approval** *(if needed for NIS, country specific requirements)*

5.2.1.1. EC approval session 13.12.12.pdf

5.2.1.2. EC approval session 13.12.12.*pdf*

5.2.2. **Site contract** *(if needed, site specific requirements)*

5.2.2.1. CALM site contract ICO.pdf

5.2.3. **Financial Agreement** *(all sites)*

5.2.3.1. CALM Financial Agreement CIC230.pdf

5.2.3.2. Amendment_Financial_Agreement_instut_Pa.pdf

5.2.4. **Study management**

During study, regular updates: Biweekly/monthly TC with sponsor / 2 times a year Steering Committee meeting (Annual congress (March) and fall meeting Leiden (October / November)

5.2.4.1. EBMT CALM Powerpoint 2015032.ppt

5.2.5. **Data collection**

MED B -> Multiple Myeloma and Lymphoma + Autologous transplant form + follow-up form / MED C -> study specific questions

- **Data entry/check > Missing data request/ queries**

5.2.5.1. CALM process missing data.ppt

5.2.5.2. CALM_dataquality_baseline_anonymous.xls

5.2.5.3. CALM_overview_missing_anonymous.xls

5.2.6. **Finalization dataset**

- Anonymous SPSS data file of all collected patients
- Final patient selection done using the Statistical Analysis Plan (SAP)

5.2.7. **Analysis**

- According to the SAP that was agreed upon between EBMT statisticians and Sanofi statisticians (document not added is confidential))

5.2.8. **Closure** *(financial and study closure)*

5.2.8.1. Example_CALM_Financial_Closure_invoice.pdf

5.3. ProMISe and MACRO Certification

ProMISe

ProMISe (Project Manager Internet Server) is a web based relational database management system for the design, maintenance and use of (clinical) data management. ProMISe provides custom made databases for scientific medical research, including an application for on-line data entry, quality checks, online questionnaires and reporting. It also provides a tool for data retrieval to facilitate statistical analysis. ProMISe can be applied for single- as well as for multi-center studies.

ProMISe is ISO/IEC 27001:2013 and NEN7510 certified; data stored within ProMISe automatically comply with the most recent requirements regarding the storage and privacy of medical data.[‡‡‡‡‡] The certificate-holder is Leiden University Medical Center (LUMC) who hosts the database.

5.3.1. ADM Information Security Policy Statement

5.3.2. Certificaat ISO27001 (ID 5055)

5.3.3. CERTIFICERING2013 (ID 1523)

5.3.4. Information Access Policy Statement

MACRO

MACRO is a web based clinical data management system developed by InferMed/Elsevier. MACRO has been used for clinical data management in commercial and not-for-profit clinical research. It is widely used in European academic research units. MACRO has been designed to support the requirements of internationally recognised ICH Good Clinical Practice, FDA 21 CFR Part 11 and the EU Clinical Trials Directive. It is based on a client-server architecture and runs on Windows Operating System. Data centre is ISO 27001 Information Security Management certified.[§§§§§]

5.3.5. MACRO™ ELECTRONIC DATA CAPTURE

[‡‡‡‡‡] https://www.msbi.nl/promise/. Accessed 21/11/2017

[§§§§§] Information taken from MACRO information leaflet MACRO™ ELECTRONIC DATA CAPTURE [undated]

5.1. EBMT Clinical Trial and Study Office list of SOPs

EBMT Clinical Trial Office SOPs

- Writing, Reviewing and Layout of Standard Operating Procedures
- Training
- Insurance and Indemnification
- Application for a EudraCT number
- Submission for Clinical Trial Authorisation
- Submission for Ethical Approval
- Protocol Development and Protocol Amendments
- Criteria for Site Selection
- Vendor Selection and Management
- Contracts
- Identifying and Reporting of Serious Breaches, Fraud and Misconduct
- Outsourced Monitoring
- Site Initiation
- Close Out of Sites
- Audit and Quality Management
- Preparing for an External Audit or Regulatory Inspection
- Pharmacovigilance
- Coding of Adverse Events
- Development Safety Update Report Preparation and Submission
- Version Control of Documents
- IT Security, Backup and Restore
- Trial Set-UP in the Clinical Trial Management System
- Computer System Validation
- Set-up, Maintenance and Archiving of a Trial Master File
- Set-up, Maintenance and Archiving of an Investigator Site File
- Patient Registration and Randomisation
- Registration of a Clinical Trial on a Public Database
- Case Report Form Design
- CRF Tracking
- Data Entry
- Data Validation and Quality Assurance
- Completion of Case Report Forms
- Patient Information Leaflet and Informed Consent Form
- Preparing files for Statistical Analysis
- End of Trial
- IMP Management
- Independent Data Monitoring Committee
- Publication

EBMT Study Office SOPs

- Data office management
- Study management

5.2. EBMT Governance

The EBMT's Board of Association provides governance, transparency, and accountability. The Board consists of the President, President-Elect, Secretary, Treasurer, President of the EBMT Nurses Group and four members elected by and from the Scientific Council. The President of the forthcoming EBMT Annual Meeting is elected onto the Board for the year preceding the annual meeting as a non-voting member. Decisions are taken by majority voting. The Board of Association is responsible for defining the strategic direction of EBMT, operational responsibility and decisions that are not required to be taken by the General Assembly.

The EBMT President, Treasurer, Secretary and the Executive Director together constitutes the Executive Committee (EXCOM).

EBMT has 11 Working Parties (WP) which develop their respective scientific plans and supervises their output. Every WP has a chair. All positions in the board except the Executive Director are on voluntarily bases and are elected by the members of EBMT.

See also https://www.ebmt.org/anbi-data.

Financial reporting is part of the Annual Report and is subject to independent audit. For 2016 see

5.2.1. 2016 EBMT Annual Report

Also available at https://www.ebmt.org/sites/default/files/migration_legacy_files/document/Annual%20Report%202016_EBMT.pdf

5.3. List of abbreviations

ATMP	Advanced Therapy Medicinal Product
BMT	Bone Marrow Transplantation
CAR	Chimeric antigen receptor
CIBMTR	Center for International Blood and Marrow Transplant Research
CIC	Centre Identification Code
CT	Cellular Therapy
EBMT	European Society for Blood and Marrow Transplantation
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
GVP	Good Pharmacovigilance Practices
ICSR	Individual Case Safety Reports
ISCT	International Society for Cellular Therapy
JACIE	Joint Accreditation Committee ISCT-EBMT
MAH	Marketing Authorisation Holder
NIS	Non-interventional study
PRAC	Pharmacovigilance Risk Assessment Committee
PRIME	PRIority MEdicines
RWD	Real World Data
SAE	Severe Adverse Event
SAP	Statistical Analyses Plan
SCETIDE	Stem Cell Transplant for Immune Deficiencies in Europe

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