EUnetHTA Joint Action 3 WP5 Strand B:

Post-launch evidence generation (PLEG) and registries

EUnetHTA WP5B PLEG Pilot on Qualification procedure

EBMT in the context of CAR-T assessment

Written Recommendations June 2021

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DOCUMENT HISTORY AND CONTRIBUTORS

This document represents the written HTA recommendations that were addressed to the EBMT in the framework of the EUnetHTA Qualification procedure on EBMT registry in the context of CART-cell assessment. It represents the view of the participating HTA bodies only.

Pilot Team

Responsibility/role	HTA Body/affiliation
Pilot lead and coordination	Haute Autorité de Santé (HAS) / HTA international
Pilot members	Agenzia Italiana del Farmaco (AIFA)
	Asesoramento Científico-técnico (Avalia – T)
	Gemeinsamer Bundesausschuss (G-BA)
	Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (INFARMED)
	National Institute for Health and Care Excellence (NICE)
	Norwegian Medicines Agency (NOMA)
	Zorginstituut Nederland (ZIN)

Disclaimer

This output corresponds to a Qualification advice. The recommendations presented are non-binding and do not engage HTA authorities in any possible way. They reflect the state-of-the-art of medical science and national requirements at the time of the advice.

All HTAbs involved in the production of these recommendations have completed the EUnetHTA Declaration of interest and confidentiality undertaking (DOICU) statement form. No conflict of interests in relation to this procedure was detected.

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LIST OF ACRONYMS/ABBREVIATIONS

AIFA	L'Agenzia Italiana del Farmaco (Italian Medicines Agency)
Avalia-T	Asesoramento Científico-técnico (The Galician Agency for Health Technology Assessment)
CART-cell	Chimeric antigen receptor T-cell
EBMT	European Society for Blood and Marrow Transplantation
EMA	European Medicines Agency
EUnetHTA	European Network for Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss (The Federal Joint Committee, Germany)
HAS	Haute Autorité de Santé (French National Authority for Health)
HSCT	Haematopoietic stem cell transplantation
HTA	Health Technology Assessment
INFARMED	Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (National Authority of Medicines and Health Products, I.P., Portugal)
NICE	The National Institute for Health and Care Excellence (UK)
NOMA	Statens Legemiddelverket (Norwegian Medicines Agency)
RWD	Real world data
WP	Work package
ZIN	Zorginstituut Nederland (The National Health Care Institute, Netherlands)

1. Background information

Real world data collection requests

At the time of initial Health Technology Assessment (HTA) of a new drug, HTA bodies may require collection of additional data in routine clinical practice, called real world data (RWD). The objective is to collect data to cover uncertainties on a drug's effectiveness or long-term safety, or to inform on a drug's condition of use. These data are used afterwards to inform drug re-assessment.

Most HTA bodies encourage the use of existing registries of good quality to generate the required RWD.

When approved in the EU, CART-cell (Chimeric antigen receptor T-cell) immunotherapies were typically in this situation of great uncertainty with many remaining research questions on long-term benefit risk ratio, their place in the therapeutic strategy, their conditions of use and associated organizational and economic impact.

EBMT proposal

The European Society for Blood Marrow Transplantation (EBMT) is a Dutch-registered international not-for-profit organization founded in 1974. Among EBMT's first initiatives after its creation was the establishment of a registry of bone marrow transplants to become a source of data in the haematological field for clinical research for retrospective clinical studies, epidemiological trends, and feasibility studies for prospective clinical trials. In addition, the Registry collects donor follow-up information and data on cell therapies.

The EBMT sent a request for the **qualification** of the use of its patient registry to support CART-cell therapies to the European Medicines Agency (EMA). The proposal was accepted within the EMA procedure for the Qualification of novel methodologies for medicine development (called Qualification procedure hereinafter). The outcome of this EMA procedure was a Qualification **opinion** on the cellular therapy module of the EBMT registry.[1]

EUnetHTA participation

On invitation from the EMA and in agreement with the EBMT, HTA bodies (HTAb) participated as observers to the procedure. HTAb could not engage actively when the EMA qualification started because none of the CART-cell therapies (specific objective of the EMA qualification) had been assessed at that moment. The HTA-EBMT collaboration took place later, under a distinct procedure described in this document.

Eight HTA bodies participated in the procedure and their positions are presented in this document.

EUnetHTA Coordinator:	WP5B lead partner (HAS)[2]
Participating HTA bodies (in alphabetical order):	AIFA, Avalia-T, G-BA, HAS, Infarmed, NICE, NOMA, ZIN

Procedure overview

1. Establishment of pilot team
2. In parallel:
    a) HTA agreement on the variables to be collected in the registry (HTA minimum data set) – drafted on the basis of conclusions of national HTA reports of CART-cell therapies, provided by the pilot participants

[1] More details on the output of EMA qualification procedure are here: https://www.ebmt.org/sites/default/files/2019-03/EMA%20qualification%20opinion%20on%20Cellular%20therapy%20module%20of%20the%20EBMT%20Registry-28022019.pdf
[2] International relations team

b) HTA Registry quality analysis via REQueST – on the basis of the information provided by the registry holders in REQueST forms.

- EBMT filled in REQueST Tool May 2019- EUnetHTA send request for clarification August 2019- EBMT updated REQueST tool in November 2019

3. EUnetHTA sent their List of Issues End of January 2020
4. EBMT answered in writing to the List of Issues Beginning February 2020
5. F2F meeting EUnetHTA/EBMT to discuss the List of Issues Beginning February 2020

   – Meeting minutes produced by EUnetHTA pilot coordinator

   – Additional information from EBMT included in meeting minutes October 2020
6. Agreement between HTA participants on the final version of the HTA minimum data set (shared with registry holder in January 2021) and the registry quality analysis via REQueST.
7. Production of the final report (incorporating the HTA minimum data set and the results of the REQueST quality analysis).

2. Common recommendations from participating HTA bodies

The participating HTA bodies would like to welcome the initiative proposed by the EBMT, to harmonize data collection across countries and enhance data sharing.

Moreover, they would like to acknowledge EBMT's efforts to approach regulators and HTA bodies in order to adapt the data collections to the needs of different stakeholders.

All in all, they encourage EBMT's objectives and further developments that are ongoing. They are particularly interested in the expansion to the field of cellular therapies/gene therapies for hematology with potential linkage to other hematology disease registries to complete missing data and avoid duplication of data collection. They also appreciate the more inclusive approach which should improve patient-centeredness and the quality of data collection.

With regard to the variables included by the EBMT, HTA bodies agree on the minimal data set (MDS) in the two indications targeted by CART-cell i.e. acute leukemia and lymphoma. Please find the MDS recommendations in the tables 1 and 2 on the following pages.

EBMT as the registry holder is open to requests for adaptations to the standard data collection form and is currently performing a review of the cellular therapy form including input from users and stakeholders e.g. regulators, industry, HTAb, national registries and centre representatives. Adaptations to the minimum data sets are evaluated according to their scientific merit and technical and operational feasibility for EBMT and the centres who collect and report the data on a voluntary basis.

Results of the registry quality analysis via REQueST are described in table 3 with suggestions for improvement in the column entitled comments. Recent evolutions of the EBMT platform after HTAb analysis is mentioned in last column.

Finally, HTA bodies welcome and encourage early discussions with companies and EBMT (well in advance of product launch when defining pivotal data development strategies) if they plan to use the EBMT platform for generation of post-launch evidence for other health technologies.

Table 1: Minimum Data Set Acute Leukemia

Item N°	TOPIC	Outcome	Variable	Mandatory or nice to have variable
1	**Profile of target population (both eligible for treatment and actually treated)**	Demographics	Date of birth	Mandatory
2			Gender	Mandatory
3		Patient functional status	ECOG-PS or Karnofsky (>16y)/Lansky(<16y)	Mandatory
4			Comorbidity index	Mandatory
5		Characteristic of the disease - at the time of diagnosis/eligibility decision - at the time of administration - at the time of relapse/progression	Date of initial diagnosis	Mandatory
6			Expression of CD19	Mandatory
7			Percentage of blast cells	Mandatory
8			Extramedular invasion	Mandatory
9			Ph status	Mandatory
10			MRD status	Mandatory
11		Patient treatment history	Nature of previous treatments (product name or type of previous treatment)	Mandatory
12			Number of previous treatments (lines of therapy)	Mandatory
13			Date of last therapy	Mandatory
14			Type of previous treatment failure (relapse/refractory).	Mandatory
15			Date of the decision to treat with CAR t therapy	Mandatory
16			Date of leukapheresis	Mandatory
17			Bridging therapy: product name and dose	Mandatory
18			Bridging therapy: date of administration	Mandatory
19			Lymphodepleting chemotherapy: product name and dose	Mandatory
20			Lymphodepleting chemotherapy: date of administration	Mandatory
21		Treatment dosing and administration	Car-t therapy: date of administration	Mandatory
22			Car-t therapy: product and dose	Mandatory

Item N°	TOPIC	Outcome	Variable	Mandatory or nice to have variable
23		Reasons for delay of CAR t infusion	production failure	<Mandatory
24			clinical reason	Mandatory
25			patient choice	Mandatory
26			other (free text)	Mandatory
27		Reasons of absence of CAR-T infusion	production failure	Mandatory
28			clinical reason	Mandatory
29			patient choice	Mandatory
30			other (free text)	Mandatory
31		Content of the bag	Cell composition (description of the types of cells in the pouch (while taking into account the confidentiality))	Nice to have
32			Number of CAR-T cells infused	Mandatory
33	**Efficacy, safety and subsequent treatments**	Overall survival	Date of death	Mandatory
34			Cause of death	Mandatory
35		Type and duration of response	Complete remission	Mandatory
36			Complete remission with incomplete haematological recovery	Mandatory
37			Minimum residual disease (MRD < 0.01% or 10-4) by inmunophenotypic bone marrow assessment	Mandatory
38			Refractory disease	Mandatory
39			Relapse or progression	Mandatory
40			Not evaluated	Mandatory
41			Date of response	Mandatory
42		The persistence of CAR t	The persistence of CAR t	Mandatory
43		Adverse effects	Intensive care unit admissions (number of admissions and duration of stay)	Mandatory in case of economic assessment

Item N°	TOPIC	Outcome	Variable	Mandatory or nice to have variable
44			Appearance of cytokine liberation syndrome (timing, grade)	Mandatory
45			CAR-T cell related neurotoxicity (timing, grade)	Mandatory
46			Development of hemophagocit syndrome/macrophagocitic activation	Mandatory
47			Development of the tumor lysis syndrome	Mandatory
			Fœtal or Newborn anomalies	
48			Development of cytopenia grade 3 or 4 (type and recovery)	Mandatory
50			Development of CAR-T related hypogammaglobulinemia	Mandatory
51			Development of lymphocyte B aplasia	Mandatory
52			Development of secondary neoplasias (date, type)	Mandatory
53			Death due to CAR t toxicity	Mandatory
54			Infection	Mandatory
55			Other adverse events (free text)	Mandatory

Item N°	TOPIC	Outcome	Variable	Mandatory or nice to have variable
56		Quality of life	Suggested questionnaires thus far: **G-BA:** EORTC QLQ C30, FACT-Leu, PedsQL **NICE, NOMA*, Avalia-t, HAS:** EQ5D** **AIFA:** PedsQL * NOMA recommends one generic and one specific, not necessarily an immediate preference for the disease specific ; ** EQ-5D is not the preferred choice for G-BA, G-BA will only consider the VAS results to assess morbidity (and not quality of life).	Mandatory
57		Subsequent management	Immunoglobulin (date and dose)	Mandatory. It is necessary to collect details on various types of subsequent management but no need to split in the form
58			Tocilizumab (date and dose)	Mandatory
59			Corticosteroid treatment (date and dose)	Mandatory
60			Subsequent Stem cell transplant rate (date, type and reason)	Mandatory
61			Subsequent Antineoplastic pharmacological treatments (type, date and reasons)	Mandatory
62			CAR t reinjection (in countries where allowed) (date and dose)	Mandatory

Table 2: Minimum Data Set Lymphoma

Item N°	TOPIC	Outcome	Variable	Mandatory or nice to have variable
1	**Profile of target population (both eligible and actually treated)**	Demographics	Date of birth	Mandatory
2			Gender	Mandatory
3		Patient functional status	ECOG-PS or Karnofsky (>16y)/Lansky(<16y)	Mandatory
4			Comorbidity index	Mandatory
5		Characteristic of the disease: -at the time of diagnosis/eligibility decision - at the time of administration - at the time of relapse	International prognostic index	Mandatory
6			Date of initial diagnosis	Mandatory
7			Nature of the disease (according to WHO classification)	Mandatory
8			Stage of the disease (according to Lugano classification)	Mandatory
9			Immunophenotyping before treatment/CD19 expression	Mandatory
10		Patient treatment history	Nature of previous treatments (product name or type of previous transplantation)	Mandatory
11			Number of previous treatments (lines of therapy)	Mandatory
12			Date of last therapy	Mandatory
14		Treatment process and duration	Date of the decision to treat with CAR t therapy	Mandatory
15			Date of leukapheresis	Mandatory
16			Bridging therapy: product name and dose	Mandatory
17			Bridging therapy: date of administration	Mandatory
18			Lymphodepleting chemotherapy: product name and dose	Mandatory
19			Lymphodepleting chemotherapy: date of administration	Mandatory
20		Treatment dosing and administration	CAR t therapy: date of administration	Mandatory
21			Car-t therapy: product and dose	Mandatory
22		Reasons for delay of CAR t infusion	production failure	Mandatory

Item N°	TOPIC	Outcome	Variable	Mandatory or nice to have variable
23			clinical reason	Mandatory
24			patient choice	Mandatory
25			other (free text)	Mandatory
26		Reasons of absence of CAR-T infusion	production failure	Mandatory
27			clinical reason	Mandatory
28			patient choice	Mandatory
29			other (free text)	Mandatory
30		Content of the bag	Cell composition (description of the types of cells in the pouch (while taking into account the confidentiality))	Nice to have
31			Number of CAR-T cells infused	Mandatory
32	**Efficacy, safety and subsequent treatments**	Overall survival	Date of death	Mandatory
33			Cause of death	Mandatory
34		Type and duration of response	Complete response (according to Lugano consensus)	Mandatory
35			Partial response	Mandatory
36			Stable disease	Mandatory
37			Progression	Mandatory
38			Not evaluated	Mandatory
39			Date of response	Mandatory
40		Relapse rate in patients with complete response	Relapse status in patients with complete response	Mandatory
41		Persistence of CAR t	Persistence of CAR t	Mandatory
42		Adverse effects	Intensive care unit admissions (number of admissions and duration of stay)	Mandatory in case of economic assessment
43			Appearance of cytokine liberation syndrome (timing, grade)	Mandatory

Item N°	TOPIC	Outcome	Variable	Mandatory or nice to have variable
44			CAR-T cell related neurotoxicity (timing, grade)	Mandatory
45			Development of hemophagocit syndrome/macrophagocitic activation	Mandatory
46			Development of the tumor lysis syndrome	Mandatory
			Fœtal or Newborn anomalies	Nice to have
47			Development of cytopenia grade 3 or 4 (type and recovery)	Mandatory
49			Development of CAR-T related hypogammaglobulinemia	Mandatory
50			Development of lymphocyte B aplasia	Mandatory
51			Development of secondary neoplasias (date, type)	Mandatory
52			Death due to CAR t toxicity	Mandatory
53			Infection	Mandatory
54			Other adverse events (free text)	Mandatory
55		Quality of life	Suggested questionnaires: **G-BA:** EORTC QLQ C30, FACT-Lym; **SNHTA:** EORTC QLQ C30 ideally supplemented by QLQ HDC29 module **NICE, avalia-t, HAS, NOMA*:** EQ5D** **AIFA, INFARMED:** FACT-Lym ***one generic and one disease specific, not necessarily an immediate preference for the disease specific ** EQ-5D is not the preferred choice for G-BA, G-BA will only consider the VAS results to assess morbidity (and not quality of life).	Mandatory

Item N°	TOPIC	Outcome	Variable	Mandatory or nice to have variable
56		Subsequent management	Immunoglobulin (date and dose)	Mandatory. It is necessary to collect details on various types of subsequent management but no need to split in the form
57			Tocilizumab (date and dose)	Mandatory
58			Corticosteroid treatment (date and dose)	Mandatory
59			Subsequent Stem cell transplant (date, type and reason)	Mandatory
60			Subsequent antineoplastic pharmacological treatment (type, date and reasons)	Mandatory
61			Reinjection of CAR-t (in countries where authorized)(date and dose)	Mandatory

Table 3: REQueST Tool Output

Item N°	Area	Item and format required format required EBMT response	Does the information meet the HTA study's needs?	Comments *Completed by the HTA*	Updated information from EBMT (June 2021)
1	**Type of registry**	*Specify the type of registry which defines the patient population (disease/condition, pharmaceutical, medical device, procedure, or other), and all health interventions included in the registry.* The EBMT Registry, established in 1974, is the backbone of the EBMT's research and educational activities. As of 2018, the Registry has acquired data on over 660,000 patients who have received a haematopoietic stem cell transplantation (HSCT) or cellular therapy procedure.	Partially met	EBMT is not a disease specific but a transplantation/cellular therapy specific registry. Therefore, for indications like lymphoma (one of the currently approved indications) or multiple myeloma (future indication), where transplantation is not the only standard of care, it does not seem that EBMT will be fully able to provide comparative data against a representative control population. The possibility of linking and exchanging information with other data sources would be encouraged.	As of 2020, the number of HSCTs has increased to over 740.000 patients
2	**Objectives and research questions**	*Specify the registry objectives and research questions covered by the registry.* The purpose of the Registry is to provide a pool of data to EBMT members to perform studies, assess epidemiological trends, and ultimately improve patients' lives. Any primary or secondary research objectives are set by the various	Satisfactory		

Item N°	Area	Item and format required format required EBMT response	Does the information meet the HTA study's needs?	Comments *Completed by the HTA*	Updated information from EBMT (June 2021)
		working parties (WP) (see https://www.ebmt.org/who-we-are/scientific-council-working-parties for full list of WP) prior to data collection. The Registry itself does not have defined research questions beyond the broad purpose described above			
3	**Geographical and organisational setting**	*Specify the geographical area of the registry and organisational setting. List the data providers (type of providers and the number of sites) participating in the registry.* Europe and other world regions. Over 500 centres performing HSC transplantation report to the EBMT registry. Reporting centres are considered to be Full members of the society and can be identified at the membership listing accessed from https://www.ebmt.org/ebmt-membership-list. Membership status is indicated at the end of each centre's listing. The number of EU centres performing CAR-T cell therapy is increasing but there is in effect a restriction on reporting commercial products until the PASS protocols are approved by	Satisfactory		Over 550 centres performing HSC transplantation report to EBMT registry. The membership list is no longer made public due to data protection measures. The number of EU centres performing CAR-T cell therapy is increasing. Active data collection on commercial products is designed to ensure completeness and accuracy of data but can only take place after contracts are signed between the marketing authorisation holder and the registry holder. PASS protocols and study design are approved by EMA's PRAC.

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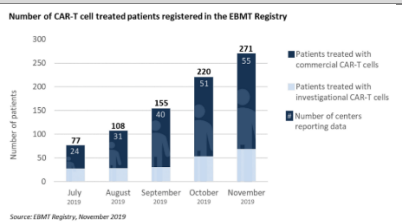
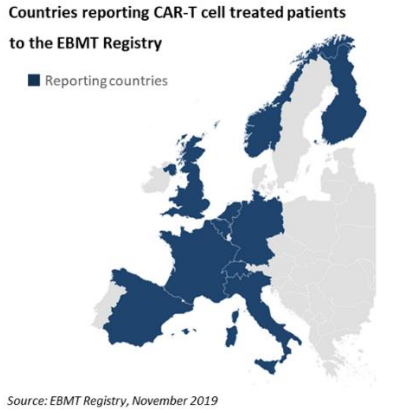
		EMA's PRAC which is expected in mid-October 2019. Assuming that EBMT and the MAHs subsequently reach agreement on using the EBMT Registry for PASS purposes, the number of reported patients is expected to increase significantly. In the meantime, EBMT has begun to publish global CAR-T data on the EBMT website which includes the number of treated patients, the number of centres and their countries. Please see graphs below or https://www.ebmt.org/ebmt/news/car-t-cell-treated-patients-registered-ebmt-registry-0 for the November 2019 data. This will be updated on a regular basis and also published via the monthly EBMT newsletter and the dedicated web page https://www.ebmt.org/registry/data-collection-car-t-cells.			

Item N°	Area	Item and format required format required EBMT response	Does the information meet the HTA study's needs?	Comments *Completed by the HTA*	Updated information from EBMT (June 2021)
		  Regarding identifying centres, each centre would have to consent to their being identified specifically as reporting data.			
4	**Duration**	*Specify the start and, if relevant, final date of data collection (duration). Can the registry be used as a platform for prospective registry studies?*	Satisfactory		A full description of how studies are performed can be found in the *EBMT GUIDELINES FOR THE CONDUCT OF REGISTRY BASED STUDIES USING THE EBMT DATABASE* available at

Item N°	Area	Item and format required format required EBMT response	Does the information meet the HTA study's needs?	Comments *Completed by the HTA*	Updated information from EBMT (June 2021)
		For transplantation data is collected at: Day 0, Day 100 and follow-Up must be performed every year if the patient was transplanted less than 10 years, ago, every 2 years if the patient was transplanted 10 - 20 years ago and every 5 years if the patient was transplanted more than 20 years ago therefore an average time-point duration is difficult to define. For Cell Therapy in the context of the Post-Authorisation Safety Studies (PASS): milestones are currently: Day 0, Day 100, 6 months and annual follow up for 15 years. Yes, the Registry can be used for prospective studies. EBMT has experience with both clinical trials and Post Authorisation studies. See https://www.ebmt.org/registry/data-submission A full description of how studies are performed can be found in the *EBMT GUIDELINES FOR THE CONDUCT OF REGISTRY BASED STUDIES USING THE EBMT DATABASE* available at			https://www.ebmt.org/non-interventional-prospective-studies Please note that this document requires revision in the light of more recent developments concerning for instance, GDPR, primary versus secondary data use, and related issues.

Item N°	Area	Item and format required format required EBMT response	Does the information meet the HTA study's needs?	Comments *Completed by the HTA*	Updated information from EBMT (June 2021)
		https://www.ebmt.org/non-interventional-prospective-studies.			
5	**Size**	*Provide the total number of patients included with the date when the number was calculated.* *Numeric* *Provide the percentage of the eligible patient population which has participated in the registry.* *Percentage* 666,000 transplant registrations (end-2018) Coverage: • Autologous transplants – 75% • Allogeneic transplants – 80% 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. For **CAR-T data**, see the information provided under item 3**Erreur ! Source du renvoi introuvable.**	Satisfactory		740,000 transplant registrations (end-2020) Approximate coverage: • Autologous transplants – 75% • Allogeneic transplants – 80% 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. Centres identified from the Activity Survey as performing transplants, but not reporting to the EBMT registry tend to be autologous-only teams with low annual activity.

Item N°	Area	Item and format required format required EBMT response	Does the information meet the HTA study's needs?	Comments *Completed by the HTA*	Updated information from EBMT (June 2021)
6	**Inclusion and exclusion criteria**	*Identify the inclusion and exclusion criteria.* **Inclusion criteria** Patients • who have undergone a haematopoietic stem cell transplantation (HSCT) procedure patients • with bone marrow failures receiving immunosuppressive therapies • receiving non-haematopoietic cell therapies Donors • donor information pertaining to collection and donor follow up • **Exclusion criteria** • patients whose own health does not display a malignant or non-malignant medical condition. • Who do not require an HSCT as a result of an underlying condition captured on our various data collection forms. • Patients experiencing last line of treatment and do not require cellular or gene treatment.	Partially met	As previously stated, due to the nature of the registry, patients who do not require a transplantation, a cellular or gene therapy for their disease might be missed. Moreover, it is of high interest for HTAb to have data on patients who were foreseen for CAR-T therapy but did not actually receive it due to different reasons (disease progression, manufacturing problems).	*Note: Exclusion criteria are specific to individual studies but there is no exclusion criteria per se for reporting to the registry.* *Please note that this document https://www.ebmt.org/sites/default/files/2019-03/Cellular%20Therapy%20Manual.pdf) is currently under revision.*

Item N°	Area	Item and format required format required EBMT response	Does the information meet the HTA study's needs?	Comments *Completed by the HTA*	Updated information from EBMT (June 2021)
		• Specific study-related inclusion/exclusion criteria would be stipulated in the study protocol from the MAH (study criteria) as not all CAR-T patients will have an associated HSCT. • **Criteria for entered data to the Cell Therapy Registry (CTR)** A centre must fill in a Cell Therapy MED-A data collection form only if the cell therapy was actually performed at that centre. The centre should **not** fill in the form if: - they have acted only as a referral centre - are only involved in following the patient after therapy which has been performed elsewhere - the harvest has been performed at this centre but the re-infusion has been performed elsewhere - the cells are hematopoietic stem cells and the treatment is an HSCT; in this case submit the HSCT Med-AB data collection forms https://www.ebmt.org/registry/data-collection			

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		The **CTR** aims to collect data on stem cells, progenitors or mature cells, such as T-lymphocytes, unmanipulated, such as DLI, or sorted and/or cultured and/or genetically manipulated, such as CAR-T cells, and including advanced therapeutic medicinal products (ATMP), used for treatment other than hematopoietic stem cell transplantation (HSCT) as well as data on the clinical characteristics and outcome of the treated patients. The cells can be infused in combination with other treatments, including hematopoietic stem cell transplantation, or by themselves. Novel cell therapies include cell preparations defined by various criteria and may be applicable to patients suffering from autoimmune, neurologic and hematologic disorders, heart disease and so on. The therapeutic potential of, for example, cytotoxic T-cells, tumour vaccines and mesenchymal stem cells (MSCs) is undergoing extensive clinical testing in areas such as cancer, tissue repair of connective tissue			

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		disorders, heart repair and immunomodulation in the setting of stem cell transplantation. Although these therapies may be promising and prove to be of clinical use, clinical trials are often small with a limited follow up. The detection of long-term beneficial effects, as well as late and rare side effects would require a large number of patients followed over many years. Pharma companies are currently developing medicinal products that are classified as gene therapy medicinal products (subcategory of advanced therapy medicinal products) from a regulatory point of view. Similarly CAR-T Cells are classified as gene therapy medicinal products. In all cases, however, the medicinal product is made of living hematopoietic cell that are genetically engineered *in vitro* to express the wild-type form of a gene that is mutated in the patient, or a fully artificial molecule such as CAR, allowing for improved recognition of target antigens; thus all these products functionally and clinically qualify as "hematopoietic cellular			

Item N°	Area	Item and format required format required EBMT response	Does the information meet the HTA study's needs?	Comments *Completed by the HTA*	Updated information from EBMT (June 2021)
		therapies", and whenever available will add or substitute to BMT. The CTR collects data on patients treated with these novel cell therapies, to allow for analyses of their risk and benefits. **Donor Outcome** forms have been implemented under the guidance of the EBMT Donor Outcome Committee and in collaboration with the Swiss Transfusion SRC. It consists of two forms, one for the collection procedure and one for follow-up. A manual on how to complete the forms is also available. Join us in this very important exercise by completing these forms regularly. *(Taken from https://www.ebmt.org/sites/default/files/2019-03/Cellular%20Therapy%20Manual.pdf)* . The full list of **Disease Classifications** is available from https://www.ebmt.org/sites/default/files/2019-09/List%20of%20Disease%20Classifications.pdf			

Item N°	Area	Item and format required format required EBMT response	Does the information meet the HTA study's needs?	Comments *Completed by the HTA*	Updated information from EBMT (June 2021)
7	**Follow-up**	*Describe the methodology for the follow-up. What is the average follow-up period per patient in months? How do you predict and prevent loss to follow-up?* In the Registry, 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. In prospective study settings, a higher or lower frequency can be established depending on the study requirements. Frequency can be adjusted only for in the study design of prospective studies based on primary data collection but not for studies based on secondary use of registry data which are based on standard registry procedures. The main problem continues to be the follow-up as it is very time consuming for the centres and may also be subject to patient-related factors that can complicate or disrupt follow-up, e.g. patient moves address. However, follow-up tends to be very good within sponsored studies as centres have committed themselves	Satisfactory		

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		to do it and there are likely to be financial incentives for reporting. There may be a delay of up to 6 months by some centres in reporting data. Prospective non-interventional studies (PASS) with an active data collection approach tend to score much higher in completeness of all data and would be expected to be faster in receiving data. The 2 documents available at https://www.ebmt.org/registry/data-retrieval under "Database Structure" give a description of the ProMISe database structure. It is expected that a similar overview will become available for the new Registry platform after full implementation is completed.			
8	**Registry protocol**	*Provide the registry protocol.* The registry protocol can be found on https://www.ebmt.org/ebmt-patient-registry	Satisfactory	The respective protocol for the specific registry study must be checked individually, but it seems that the registry offers the possibility to adjust the protocol according to the research question. Of note, the information on the website seems quite fragmented. Having one single	A full description of how studies are performed can be found in the EBMT GUIDELINES FOR THE CONDUCT OF REGISTRY BASED STUDIES USING THE EBMT DATABASE available here. Please note that this document requires revision in the light of more recent developments

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		A full description of how studies are performed can be found in the EBMT GUIDELINES FOR THE CONDUCT OF REGISTRY BASED STUDIES USING THE EBMT DATABASE available here Analysis is addressed in section 16		registry protocol would be much more convenient.	concerning for instance, GDPR, primary versus secondary data use, and similar.
9	**Governance**	*Describe the registry governance structure.* 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 Registry Function describes how it is governed.	Partially met		EBMT has now implemented the EBMT Code of Conduct and Policy on Conflicts of Interests policy as approved in 2019. In June 2021, there were 10 staff in the Registry department, working on Registry development, maintenance, membership, helpdesk, data collection and quality. 28 study coordinators and data managers, all working on collecting/reporting and data quality in the context of predominantly retrospective studies. There are 13 staff members that are working in the clinical study unit that performs prospective studies including clinical trials and post authorisation studies. EBMT has 10 statisticians support study conduct.

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		https://www.ebmt.org/sites/default/files/2018-12/EBMTRegistryFunction.pdf Other governance measures • Dedicated, knowledgeable registry 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 Representatives of EBMT are expected to perform their duties for EBMT independently and objectively. It is crucial that any and all business decisions are taken only in the interest			

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		of patients, the scientific community and EBMT. EBMT does not allow any private interest to be a factor in policy and decision-making. In order to guarantee and maintain the EBMT independence, objectivity and to provide transparency on EBMT activities, EBMT Representatives and Employees are bound to the EBMT Code of Conduct and perform a Declaration of conflict of Interests where they are asked to declare any conflict of interest that might influence the EBMT Representative business decisions and conduct affecting patients and scientific community interests. EBMT is currently implementing the EBMT Code of Conduct and Policy on Conflicts of Interests policy as approved in 2019			

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		 EBMT-P-007-01-EBMT Code of Conduct.  EBMT-P-008-01-Policy on Conflict of Int We have 11 data managers, all working on collecting/reporting and data quality In the clinical trial office, we have 3 staff members that are working on data collection/reporting/data quality, and one that is specifically collecting and reporting safety data. Their tasks include the following: • Contribution to the synopsis elaboration for retrospective studies and prospective non interventional studies regarding data requirement (contact with the principal investigator to modify and adapt the data requirements as necessary)			

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		• Data exportation from the registry & feasibility assessment • Development of specific databases and creation of questionnaires • Frequent communication with the EBMT centres for the studies • Management of the data collection, data entry (can represent 2/3 for the time), data checking and validation • Management of the study initiation (with help to centre for submission to the local authorities when if needed for prospective) • Preparation of the study database to be transmitted to the statistician for statistical • Selection of data according to the synopsis			
10	**Quality assurance**	*Specify the quality assurance activities.* **Quality assurance procedures/Audit process**	Partially met	HTAb welcome the ongoing developments aiming at enhancing the quality of data and reducing missing data within the registry. The current analysis shows the need for further developments on the following points: - Centralize the quality assurance handling	In support of the EBMT strategic plan 2018-2020, EBMT has moved forward in the implementation of a Quality Assurance Management System (QAMS) which includes: - Document control system which standardises all EBMT review and approval processes and documentation.

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		For the Registry the following specific elements are in place: 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		- Define key indicators for missing data - Define timelines for data entry, e.g. at least a maximum accepted time frame for data entry - Produce reports on the data quality (e.g. % of missing data, % of duplicates, % of coverage, process of standardization of data collection).	- Documented Standard Operating Procedures which standardise the EBMT activities - Internal Audit System - Management of Deviations and Corrective actions - KPI monitoring Studies are regularly performed (on average more than 120 publications/year over the last 3 years) and are a means to substantially increasing data quality. EBMT has developed a clinical outcome benchmarking model. The first version of the outcome benchmarking reports was released to the qualifying centres in February 2021 for transplants performed during 2013-2016. The next exercise will be performed in June 2021 for transplants performed during 2015-2019. The scheme is subject to ongoing review based on centres' feedback and development of the statistical model. Benchmarking requires minimum data completeness for centres to be included in the scheme and is expected to make a significant contribution to improvements to the Registry in this regard.

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		○ 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 **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 • 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			

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		incidence and non-relapse mortality. Many analyses include the incidence of engraftment, GvHD or secondary malignancies using competing risk models. o 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 5.1.8) • 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)			

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		• Continuous support is provided by the Registry office and by the Definitions group Additional questions: **are key indicators for missing data defined,** **is data triangulation used to check for missing data and accuracy,** **what are the timelines for data entry,** **what is the percentage of retrospectively collected data,** **are reports on the quality of registry data available?** Answers: a) EBMT is developing a report for all reporting centres on data completeness as data completeness is a precondition to rolling out a clinical outcome benchmarking initiative in 2020. A prototype format has already been developed by the biostatistical unit at Leiden UMC, The Netherlands as part of a wider project and final agreement on the exact elements to be included are to be defined in			

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		November and December. 2019. A preliminary draft of the report can be accessed by clicking on the PDF icon.  Data completeness exercise.pdf b) As above c) Timelines for data entry: this is variable as it depends on the centre and the resources that they can dedicate to data entry. d) See section 7 for details on data capture. Data capture occurs at the centre level who are responsible for observing the timing of data capture. Data submission may take place at a later point in time i.e. data is not expected to be in real-time due to the practical aspects of reporting a significant volume of detailed data in a timely fashion. e) No, these reports are not available			

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11	**Financing**	*Provide a financial plan (or similar) of the registry.* The Registry is directly supported by the EBMT as part of its infrastructural and running costs. See 2018 EBMT Annual Report at https://www.ebmt.org/sites/default/files/2019-03/EBMT%20Annual%20Report%202018.pdf See also the worksheet 'EBMT Financial details'	Satisfactory		EBMT Annual Report 2020 https://www.ebmt.org/annual-report-2020
12	**Data collection**	*Describe the data collection procedure.* Data originates with the centres who in most cases enter the data directly. Centres report data on a voluntary basis and are not financially reimbursed. The exception could be in the context of externally funded studies where financial compensation may be offered to centres.	Satisfactory		

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		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 also common that the profile of persons entering data varies and can include physicians, data managers and research nurses among others. However, regardless of the profile, data is entered in the same way via the data forms with the important proviso that staff can 'translate' the data from the patient's file into the correct fields in the registry. EBMT offers training and other support for data entry to help ensure common understanding. EBMT has developed a specific Cellular Therapy form for reporting data on these novel therapies.			
13	**Minimum data set**	*Provide a minimum data set.* The Cell Therapy Registry (CTR) aims to collect data on stem cells, progenitors or mature cells, such as T-lymphocytes, or sorted and/or cultured and/or	See MDS tables		This form is currently under review. During 2021, feedback from EUnetHTA is being evaluated for inclusion.

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		genetically manipulated, such as CAR-T cells, used for treatment in combination with hematopoietic stem cell transplantation or alone, and including advanced therapeutic medicinal products (ATMP), as well as data on the clinical characteristics and outcomes of the patients. The form also collects details of laboratory manipulation for all types of cells before they are infused into the patient. They include: selection, modification, genetic engineering and others. The forms and manual for reporting are available in the Cell Therapy forms section. See https://www.ebmt.org/registry/data-collection > Cellular Therapy Forms (Cellular Therapy MED-A Day 0 Form; Cellular Therapy MED-A Day 100 Form; Cellular Therapy MED-A 6M and Annual Follow Up Form).			

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14	**Data dictionary**	*Provide a documented data dictionary.* See Table 1 EBMT Registry Cell Therapy subset (this table also appeared in the EMA Qualification Opinion EMA/CHMP/SAWP/329105/2018) This dataset is further explained in the Cell Therapy MED-A Form Manual at https://www.ebmt.org/sites/default/files/2019-03/Cellular%20Therapy%20Manual.pdf	Satisfactory		This document https://www.ebmt.org/sites/default/files/2019-03/Cellular%20Therapy%20Manual.pdf is currently being updated.
15	**Standard definitions, terminology and specifications**	*Specify the national/international data standards that are used for organising, storing, managing or protecting the data sets.* WHO Classification, HLA/ WMDA dictionary, http://hla.alleles.org/wmda/index.html For clarification, MED-A and TED are the EBMT and CIBMTR terms respectively for the data collection forms which centres use to report their data. They are not data standards.	Satisfactory		

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		FACT-JACIE refers to standards for administration, collection and processing of hematopoietic cellular therapy. JACIE is the EBMT's accreditation scheme. Whilst many centres have achieved accreditation, not all centres are accredited, and accreditation is not a condition for reporting data to the registry. Another question is if accreditation is compulsory in a given country e.g. The Netherlands and/or whether manufacturers' own criteria for site inclusion includes JACIE accreditation. As an indicator, of those EU centres reporting transplant activity for 2017, we calculate that 73% of centres performing allogeneic transplantation had either applied, been inspected or achieved accreditation at some time. Of those performing autologous transplantation only, the same number was 25%.			
16	**Confounders**	*Specify your techniques to prevent or control the potential counfounders*.	Partially met	The general information provided is satisfactory for the scope of this exercise.	

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		In all the EBMT studies, we take into account for potential confounding factors associated both to the treatment under study and to the outcome, and not part of the causal pathway between exposure and outcome. **In the design phase:** - All potential factors that are known to influence the outcome are listed and collected in order to avoid unmeasured confounding - Prevention of confounding can be done using restriction: the study population is reduced to patients with a specific value of the confounding variable. **In the analysis phase:** We first compare the characteristics of the groups of interest (patients and disease characteristics, donor characteristics, treatment received, etc…) and performe univariate analysis for all the variables. Then, control for confounding can be performed in different ways according		The question of confounders can only be fully addressed on a study by study basis and will be further tackled in that context. However, the disease specific confounder identification must be done as early as possible, as the confounding factors need to be collected in the registry. Otherwise relevant information of the confounder on a study basis will be missing and adequate confounder-adjusted analysis could not be performed.	

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		to the population study and the clinical question: - **Exact pair-matching** that constrains subjects in different exposure groups to have the same value of potential confounders. - **Propensity scores matching** or **propensity scores weighting** to control for imbalances on observed variables. - **Stratification**: the study population is divided into a number of subsets of subjects having the same characteristics for the confounder (either each stratum is analyzed separately or adjustment is done using the Mantel-Haenszel method or a similar method). Most often using a **multivariate regression model** including all potential confounding factors For example: Potential confounders would be the brand name of medication varying per country and the generic names not always being made available or only specific to a given country.			

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		Regular communication with centres to ensure that essential medication (branded and generic) are coded correctly. Avoiding duplication of patient numbers for new patients within the same centre. This also applies across centres in instances where access needs to be granted to patients who have received an HSCT in another centre.			
17	**Data cleaning**	*Describe the data cleaning plan.* The EBMT has internal quality control measures to support and verify data quality in routine practice. Currently, the data are entered in the system by the center using 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.	Satisfactory	Of note, a centralized data cleaning process would be welcome.	

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		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. A detailed description of how Registry reports can be used to clean data is provided in the video at			

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		https://www.ebmt.org/ebmt/documents/using-reports-clean-your-data-video			
18	**Protection, security and safeguards**	Describe in detail the data security risks, policies and procedures specific to the registry. Free text The EBMT works in partnership with local healthcare providers to collect data on patients undergoing bone marrow or stem cell transplantation, cell therapies, and immunosuppressive treatments for any disease. The EBMT has a single centralised database where all the data requested through the standard DCF (Data Collection Forms) is stored. The database is hosted in the EEA and protected by safeguards that ensure security, including compliance with ISO27001 certification and a stringent access control policy.	Satisfactory		The registry upgrade project has faced delays but preparations for a validated electronic data capture system continue apace. As part of these ongoing preparations, during 2021, EBMT is participating in the EMA-funded MINERVA meta data project and has recently been accepted by the EHDEN project as a data provider to map EBMT data to the OMOP common data model (CDM). The ProMISe system will continue in use in the meantime.

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		The data will be entered and maintained through an internet management system (MACRO). which allows the users to access it from any machine with a web browser connected to the internet, through a secure socket layer encryption and digital signatures. The data captured and stored is accessible 24 hours 7 days a week on an SQL server database. Following appropriate EBMT authorisation, a user account is created for every MACRO user with a unique password controlled and created by the EBMT Registry in order to use the system. There are different levels of access per user implemented in MACRO, in order to prevent unauthorised access and guarantee that each user has access only to the relevant data in relation to the purpose for which the data is processed. MACRO is a well-established, validated electronic data capture system that will be replacing the ProMISe database used/accessed by EBMT Registry staff. It is compliant with ICH-GCP, EU Clinical Trial Directive, and Medicines for			

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		Human Use (Clinical Trials) Regulations & FDA 21 CFR Part 11. Other features of MACRO include: Successfully audited by MHRA (UK) ISO27001 certified data centre Audit log and audit trail Double time stamp (source : https://www.elsevier.com/solutions/macro/features#compliance)			
19	**Informed consent**	*If the registry requires individual informed consent for recording personal data (registry's primary purpose), please provide the document (document file format). Or, if regulations exist for the management of data in the absence of informed consent, describe* Patients must grant their permission to process and use their data in full knowledge of the possible benefits and risks of their participation and of the measures applied to mitigate risks. Patients must also be aware that they	Satisfactory		

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		can restrict the scope of their consent and withdraw the consent at any time. EBMT provides the centres with the EBMT Consent form for data registration with EBMT which is a template that each centre shall adapt to guarantee that the respective national laws are followed. EBMT makes patient consent a prerequisite for submitting the data and provides all necessary information about usages of the data, to ensure appropriate consent is obtained in all cases. The informed consent is collected by the individual centres or donor registries submitting data to the EBMT and it is the responsibility of the treating centre to ensure that patients have consented to the recording and use of their data by EBMT. The implementation of technical and functional separation between the EBMT registry and the treating centre is key in order to protect the patient			

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		privacy rights. Medical records or other sensitive patient information showing the identity of the patient are recorded in the treating centres and are not reported to EBMT. The data reported and processed in the registry is pseudonymised, therefore no directly identifiable data is reported to the EBMT Registry. The following documents support consent procedures: https://www.ebmt.org/patient-privacy-statement https://www.ebmt.org/ebmt/documents/consent-form-data-registration-ebmt			