RWE data: EBMT Registry
Challenges in Data Collection & Use of Data (in PASS)

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1. Introduction

- The EBMT established in 1974, has a registry which is the backbone of EBMT's research & educational activities.
  It is used for other stakeholders' scientific purposes as well.

- <u>As of 2023, the EBMT Registry has acquired :</u>
  - ❖ Over **800,000 patients** that received a HSCT procedure.
  - ❖ Over **6,500 patients** that received CAR-T cell therapy.
  - ❖ Over **700 centers** reporting their HSCT and CAR-T treatments, including annual follow ups.

1. Introduction – New EBMT Registry

- The **New EBMT Registry was launched on** 24th of Aug 2023, including the first migrated data.
- This **innovative platform** replaces ProMISe & Castor.
- The **CAR-T data** from Castor are all **migrated** into new Registry
- The migration of the remaining data from ProMISe is done **in steps** throughout the rest of 2023 and in 2024.

The new EBMT Registry is **modern, agile and user-friendly platform**, which will undoubtedly facilitate the work of all centers that report data and will become an **indispensable tool** in the field of HSCT and cell therapy in the future.

2. Data collection forms

The EBMT has a set of forms divided into **core data set** and **extended dataset**:

- **Core dataset**: this is the minimum essential data that must be provided by all member centers for their consenting patients.

- **Extended dataset**: additional more detailed information on patient's medical history provided by centers or requested by the EBMT working parties, it includes items that are relevant to most WP studies.

  Data from the **extended dataset** is collected through several **additional forms** and can only be entered in addition to the **core dataset.**

2. Data collection forms – Content

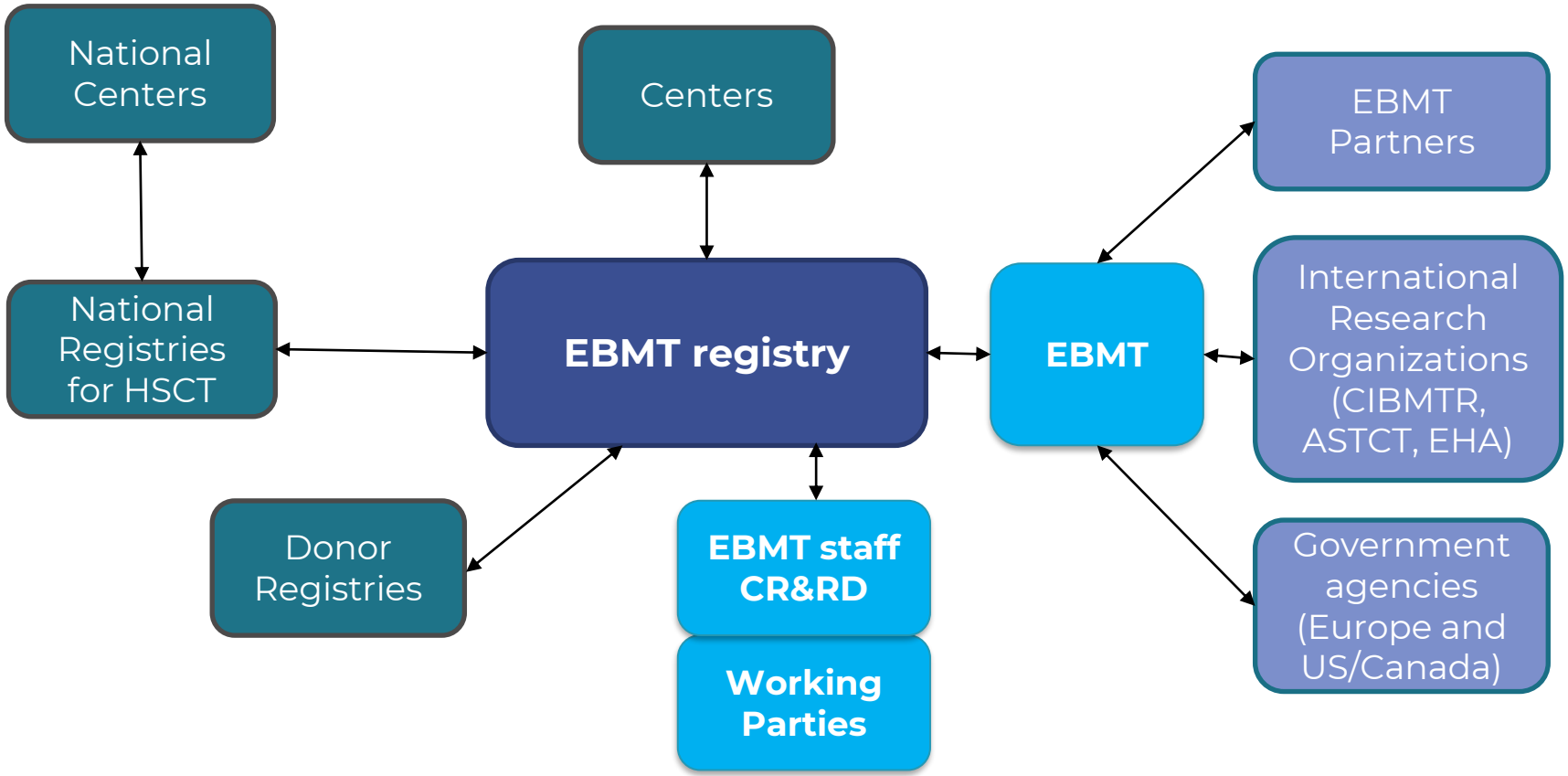
The EBMT Registry contains patient clinical data, including aspects of:

- Diagnosis & disease,
- First-line treatments,
- HSCT- or Cellular Therapy associated procedures,
- conditioning regimen,
- donor type,
- stem cell source,
- GvHD, HSCT related complications &, post-HSCT infections
- Outcome: items to calculate eg. OS, RFS/PFS, NRM, incidence of GvHD and incidence of relapse/progression.

In 2019 EMA issued a **positive qualification opinion** of the cellular therapy module of the EBMT Registry indicating that the Registry fulfills the essential needs

CAR-T dataset was **fully migrated** from Castor into the **new EBMT Registry** and the new Registry was launched on 24th of August 2023.

3. EBMT Registry users



4. Use of Registry data – GDPR

The EBMT ensures that all personal data under its responsibility is processed according to the **GDPR:**

- Patient consent (multiple data sharing options)
- Database in compliance with **ISO27001 certification**
- Accessible **only** by the EBMT members/centers, National Registries and staff following a stringent access control policy.
- Joint controllership agreements

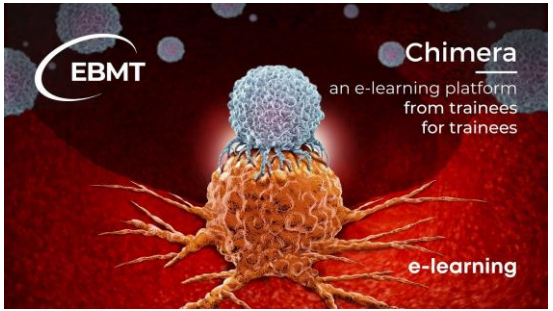
- Anonymization when data is used outside EBMT (aggregated reports)

4. Use of Registry data – Scientific Output

The data collected is used for:

- ❖ Medical research which aims to further develop the scientific knowledge in the field of HSCT, Cellular-, Gene- and immunosuppressive therapies

  - ✓ **11 Working Parties (disease-based or transversal) & a Nurses Group** resulting in:
    - ❑ developing scientific proposals
    - ❑ performing surveys, retrospective or non-interventional studies
    - ❑ contributing to definitions of guidelines and policies (consensus papers)
    - ❑ training of HSCT/CT physicians into HSCT/CT experts
    - ❑ sustain a continuous updated E-learning platform
    - ❑ hundreds of publications annually



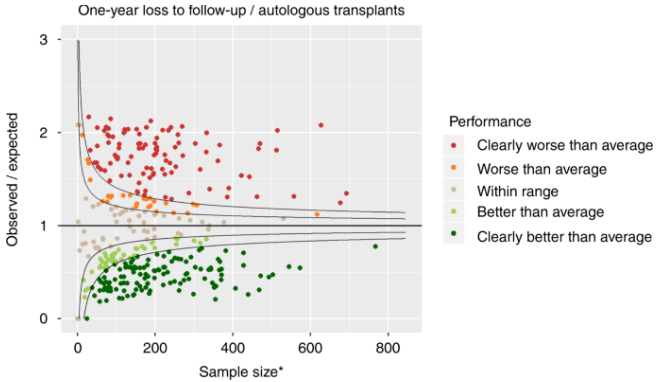
5. Purpose: Answering Scientific Questions

- Describe landscape in Europe by disease or treatment
- Identification of use of certain drugs or treatments
- Incidence of certain complications or infections
- Assess epidemiological trends
- Collect data on Advanced Therapeutic Medicinal Products
- Compare hospital or country specific results (Benchmarking)
- Publications

Clinical research supports the mission of the EBMT ‘ Saving patients lives’

5. Purpose: Benchmarking for the EBMT community

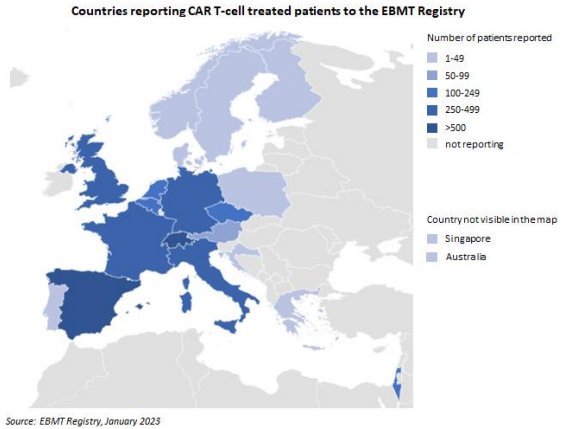
- **Benchmarking** (defined as “the process of comparing a practice’s performance with an external standard”) provides transplant professionals with a means to assess how their unit is performing compared to the wider BMT community
- **Benchmarking** has been developed as an integral part of Project 2020.
- **JACIE accreditation** standards have been a key driver.



- The current **model for 1-year overall survival** therefore includes only **higher reporting centers.** Prioritize improving the **quality of follow up reporting** with a **similar benchmarking model** for ‘data completeness’, which parallels the ‘funnel plot’ model for 1-year survival.

5. Purpose: Collecting data on CAR-T patients

- Mostly adult patients (only up to 25 yrs for Kymriah for ALL)
- Diagnosed with DLBCL, PMBCL, FL, MCL, MM, ALL
- Refractory to first-line chemoimmunotherapy
- that relapses within 12 months of first-line chemo-immunotherapy
- or with relapse after two or more lines of systemic therapy



6. Post-authorization Safety/Efficacy Studies

- The cellular therapy module of the EBMT Registry received a **positive qualification** opinion from the EMA, supporting **the use of Real-World Data** captured in the **EBMT Registry** to inform regulatory decision making by health authorities.

- The current protocols for the **PAS studies** are based on **secondary use of Registry data.** With this approach we prevent the creation of additional databases owned by MAHs.

  The EBMT Registry makes **data available** to the scientific community and it avoids the need for centers to report data to multiple registries.

  By using a **harmonized data collection form** for cellular therapies, it is easier to enter and compare data on different products.

  EBMT is used to collect long-term follow up. For CAR-Ts EMA endorsed **15 years of follow up**

Post-authorization Safety/Efficacy Studies

- Collaboration across stakeholders is key to **solving the main challenges** in the field of **cellular therapies**. In the context of the EMA-endorsed PAS studies it is important for EBMT to collaborate with the MAHs so we can ensure that the long-term follow-up data on CAR-T therapies are **not siloed** in private databases of MAHs but remains available **to academic research** and can further benefit patients.

We believe in 'collecting data once and re-use it, if possible'.

6. PAS / PAES: Data quality

- **Sites' data managers registry training** – training by EBMT and with support of National Registries (including e-learning course and exam).
- **Patients' written Informed Consent Forms (ICF)**
- **Standard Registry quality triggers -** built into the system to promote completeness, accuracy and internal consistency of the data entered.
- **Central data cleaning** – data review for all patients (checking data for completeness and consistency, identifying non-compliances, where possible in real-time).
- **Monitoring on-site** - source data verification for 10% of patients.
- **Site audits -** for cause, routine.
- **Reporting -** on-demand, interim and final report with review by MAH.

6. PAS / PAES: Challenges for Sites

- The Cellular Therapy form is substantial: It is a combination of EMA & MAH mandatory items (complications after CAR-T for monitoring safety) and EBMT items of scientific interest.
- The follow up form is a partial repetition of the CT form and contains a substantial amount of items to be filled.

- 'Registry study based on secondary use of data' does not fully fit into the ‘standard' categories for EC submissions; this causes delay in participation

- **Lack of resources** / sites are understaffed
- **Patient fee is too low** in respect to the amount of data to be provided
- Sites or national groups want **to publish** results first them self before sharing CAR-T data with MAHs
- **Double/extra reporting:** EBMT, National registries & HTAs for additional information at national level

- Opposite: Sites do not want or are legally not able to provide data for financial compensation: per patient fee is not mandatory to accept

EBMT registry contains much more data than from CAR-T sites participating in PASS (around 50/50)

6. Statistical aspects/challenges in (PAS) studies

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) approves the study protocol and will assess the outcomes of PAS studies

- **End points**: **Incidence of adverse events (complication section),** overall survival, relapse free survival, non-relapse mortality, relapse/progression incidence after CAR-T
- **Censoring** for HSCT, 2nd CAR-T
- **Follow up** - on day 100, after 6 months and annually for a period of 15 years.
- **Selection** of sites, the ones participating in PASS
- **Higher number** of CAR-T performed than initially anticipated; acceptable sample size
- **Mix of (generations** of) CAR-T products for same indication, also within 1 patient

6. Next generations of CAR-T; future challenges

There are 80+ clinical trials (ClinicalTrials.gov) evaluating the safety and efficacy of next-generation CAR-T cells.
Currently, there are **four distinctive approaches** tested in clinics:

- aim to increase efficacy by modulating immune checkpoint pathways
- aim to increase efficacy by induction of cytokine secretion
- with focus on implementing a safety-switch mechanism which enables the control of treatment-related adverse events, for instance, cytokine release syndrome (CRS), by disabling CAR-T cells with exogenous agents
- with focus on evaluating genetically edited CAR-T cells suitable for allogeneic use or designated to treat T-cell malignancies.

https://www.frontiersin.org/articles/10.3389/fimmu.2022.1034707/full

Thank you