

EBMT

European Group for Blood and Marrow Transplantation

REGISTRY FUNCTION

Per Ljungman

Carmen Ruiz de Elvira



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1 Background

When the EBMT started collecting transplant data, some of the disease dependent Working parties created their own registry. In some cases, there was a further subdivision in autograft and allograft registries. These registries were all physically isolated among them. The system required annual merging of all data with the consequent duplication of entries and lack of unique identifiers, and was based on a flat database with minimum quality checks.

EBMT member centres had to send their data, broken down by disease and, sometimes, by transplant type to several mail addresses. Since the data sent by centres was not necessarily as up to date as the data collected by the EBMT Registries directly, it was very difficult to ensure correct handling of the latest data.

The database was saturated and it become impossible to add new fields, let alone comprehensive data for new indications.

In the late 90's it was clear that the EBMT required a more sophisticated centralised database which could be accessed through the internet. This was achieved in two stages, first with the introduction of ProMISe in the year 2000, which allowed centralised and direct internet access for all users; and second, with the development of ProMISe2 in 2004, which allowed for the database to be upgraded to a more sophisticated model with a considerable increase in the quality control exerted on the data.

2 Current situation

Today the EBMT has only one Registry which encompasses all haematopoietic stem cell transplant (HSCT) procedures for all indications. It also stores immunosuppressive treatments for bone marrow failure syndromes (ie: aplastic anaemias), and cell therapy treatments other than HSCT. Ten national registries use the EBMT Registry database as their sole database and one donor registry uses the EBMT Registry database to store donor follow up. Most of the data is being entered directly by the centres and the amount of data which still needs to be mailed and merged has been considerably reduced although, unfortunately, has not completely disappeared.

The current situation would not have been possible without the development of ProMISe2 by Ronald Brand, and the cooperation of the EBMT and national registries staff which have put many hours of their time in furthering the development of both ProMISe2 and the database with their continuous debugging and suggestions.

3 Registry structure

The EBMT Registry has three components: the content which is made up of all the data that is collected; the hardware and software which make the collection and storing of the data possible; and the staff who run it.

3.1 Content and data collection forms

The content of the EBMT Registry is mostly decided by EBMT researchers. The EBMT is divided into Working Parties (WP) formed by voluntary representatives of member centres and headed by an investigator elected by the EBMT centres. These WPs are proactive in starting studies and assume responsibility for the clinical data that is collected through the design and auditing of the data collection forms (Med-AB Forms), and the participation of their representatives in the Registries Subcommittee and Definitions Committee. The responsibility for the data includes collaborating in the writing of the manual **Guide to completion of the MED-AB forms** prepared for the data managers of the centres and participating in the Data Management sessions during the annual meeting.

The EBMT has three types of forms for data collection:

- **MED-A for HSCT**, which contains the minimal essential data. All EBMT members need to forward these data to retain full membership.
- **MED-B**, which contains a large amount of disease and HSCT specific data. Although the disease specific Med-B are currently only used for HSCT, they can also be used for the Cell Therapy Registry if applicable.
- **MED-A for Cell Therapy other than HSCT or DLI**, which contains the minimal essential data for this type of treatment.

3.2 Hardware and software

The data is stored in an SQL Server database, housed in the Leiden University Medical College. The internet project manager, ProMISe, is run and maintained by Ronald Brand in that same location. While the EBMT is the owner of the SQL server and database, Ronald Brand remains the owner of ProMISe.

3.3 Staff

The EBMT Registry Office is located in London. The following tasks are the remit of the Registry: Designing, creating and maintaining the database infrastructure and the data collection forms necessary to collect and store the registry, entering data, requesting follow up and missing data, general quality checking. The office also suggests and implements procedures to improve data flow, data quality and support centres. The Registry helpdesk which is the main source of help and information for centres accessing the Registry through the internet is located in London, however help and training are extensively provided also by national registries.

4 Registry Users

Member centres are the primary users of the EBMT Registry. They use it to store their own data while simultaneously making it available to the EBMT. Each EBMT centre can be considered as the main owner of their data, although it is understood that the ultimate owner is the patient.

The EBMT through WP study coordinators, use data to further EBMT led studies. Although the EBMT Registry Office has the primary responsibility for entering, cleaning, and updating the data, the EBMT study coordinators contribute to this for specific studies.

National registries operating in some countries have become part of the EBMT data flow by mutual consent and are using the same central database. These national registries use the database for their own purposes, which may encompass national requirements for registration of transplants, research, demographics, etc. Where these registries exist, the responsibility of the EBMT Registry for the data may be partially devolved to them. Not all national registries operate in the same way and these differences are collected in the document **Guidelines for the Conduct of Registry Studies using the EBMT Registry Database**. This document is obligatory reading for anybody proposing to engage in a Registry based study.

The Agence de la Biomédecine, the public body in charge of transplantations in France, obtains data directly from the EBMT Registry. This is part of an agreement between l'Agence and the French national registry, SFGM (*Société Française de Greffe de Moelle*).

CIBMTR (Center for International Blood and Marrow Transplant Research) is the US based international transplant registry. Although the CIBMTR does not use the EBMT Registry directly, they are secondary users in that the EBMT forwards to the CIBMTR MED-A data taken directly from the EBMT Registry on behalf of centres who have requested this service from the EBMT.

The Swiss Blood Stem Cells Registry is using the structure of the EBMT database for their own purposes in following donors. These data is available only to the Swiss Blood Stem Cells Registry itself.

5 Data flow

The EBMT has a single centralised database where all the data requested through the standard data collection forms (MED-A and MED-B, see 3.1 in this document) is stored. The data is entered and maintained through an internet management system (ProMISe). Each EBMT centre, EBMT WP or national registry have access to a virtual representation of their data in this database. In addition, particular study groups can also be provided with a virtual representation of specific groups of patients. Users from a centre, an EBMT WP, a national registry or a study group within an EBMT WP or across WPs can view, modify, obtain reports from and download their own data once the necessary permissions have been granted by the principal investigator of the centre, or by the head of the national registry or EBMT WP. In addition all centres and national registries can obtain general overviews from the complete EBMT database. Different levels of access are possible (see appendix on **Remote Access** in this document).

5.1 Flow into the EBMT database

All member centres must submit the minimum essential data as recorded through the MED-A form. The MED-A data is a subset of the data collected in the more detailed MED-B forms. For this reason, centres submitting MED-B forms do not need to submit accompanying MED-A forms. These data must be submitted when 100 days have elapsed from the date of transplant, or when the patient dies, whichever comes first. For more information see document **Submitting data to the EBMT**

The data can reach the Registry through various channels:

- a) Direct entry through ProMISe by a centre. This is the preferred and most common method.
- b) Direct entry through ProMISe by the EBMT. This is performed mostly by the Registry Office, who is in charge not only of entering the data, but also of cleaning it and requesting follow up. For specific studies, data entry may be done by EBMT staff situated in other locations.
- c) Direct entry through ProMISe by a national registry.

- d) Uploads of converted data from non-integrated national registries. This is the least recommended method and has been almost completely phased out.

Centres can enter the data directly (option *a*), fill in the MED-A or MED-B paper forms and send it directly to the EBMT (option *b*), or fill in the MED-A or MED-B paper forms and send it to their national registry (option *c*). Some centres submit the data to non integrated national registries which in their turn submit the data in batches (once or twice a year) to the EBMT. These data have to be converted by the EBMT Central Registry Office before being uploaded to the central database. This method is time consuming and prone to errors and is not recommended. Currently the AEIOP (*Associazione Italiana di Ematologia ed Oncologia Pediatrica*) and the PRST (*Pädiatrisches Register für Stammzell Transplantationen*), Italian and German paediatric groups respectively, submit data through this method.

5.1.1 Data entered directly by the centre into the EBMT database

This method ensures immediate access by the EBMT and national registries –if in place- to the centre’s data. This is the preferred method. It involves no conversions, and all involved organisations can see the same data simultaneously. Errors or queries are solved in one go with immediate effect for all recognised users. Centres who use this system may be approached by the national registry –if they belong to one- or by the EBMT registry with requests for data corrections or clarifications.

5.1.2 Data submitted to the EBMT Registry Office

The Registry Office enters the data from all paper forms sent to it. This office is also in charge of checking the MED-A subset of data, feeding back to the centres on the quality of their submissions and requesting follow up information. All EBMT centres are welcome to use this method if they do not belong to a national registry and are unable to use ProMISe. Centres using this method can still use ProMISe to view and analyse their data, even if they are unable to do the data entry themselves.

5.1.3 Data submitted to a national registry

Usually national registries enter the MED-A and MED-B data sent to them. When this is not possible, the data is forwarded to the EBMT Registry Office (see 5.1.2 above). Queries raised by the EBMT registry on the existing data are routed back through the national registries which act as

the interface between the EBMT and the centres in those countries. Centres using this method can still use ProMISe to view and analyse their data, even if they are unable to do the data entry themselves.

5.1.4 Data submitted to a non-integrated national registry

Non-integrated national registries tend to have their own forms and ways of registering data. Although in some cases they have tried to create a data structure very similar to the EBMT, it is unavoidable that the lack of integration will lead to databases drifting apart. The data therefore needs to be converted –in terms of format and coding- and registrations uniquely identified before they can be uploaded to the EBMT database. The non-integrated national registries usually submit data to the EBMT once a year. In the past, the EBMT Central Registry Office created a conversion program and uploaded the data. Currently the task of converting the data has been left with the originating registry, but the EBMT still has to upload it. This usually raises large amounts of queries as existing EBMT data is overwritten by different data coming from the files submitted by the non-integrated national registries. These queries are sent back to the non-integrated national registries. Depending on the speed at which these registries answer, and also for those non-integrated national registries, which do not want to deal with these queries, it is normal for the EBMT to send the queries directly to the centres for answering. Centres using this method can still use ProMISe to view and analyse their data stored within the EBMT database, even if they are unable to do the data entry in ProMISe themselves.

5.2 Flow out of the EBMT database

All users of the EBMT Registry which have data from their centre or registry stored in it can obtain exports of their data. The EBMT Registry in itself does not feed into any other database but it does export data to the CIBMTR. Following the necessary request from centres, the EBMT Registry can also export data to study groups.

5.2.1 EBMT WP use

By far the most common use of the EBMT data is performed by the EBMT WPs undertaking retrospective or prospective clinical and scientific studies. These studies are always published in peer reviewed journals. Please, consult the Guidelines for Registry Studies for a more detailed explanation of this use.

5.2.2 *Data flow from the EBMT to the CIBMTR*

The EBMT and CIBMTR have reached an agreement whose aims are to prevent duplication of records when doing collaborative projects (registrations being used twice), prevent the publication of studies with overlapping data, reduce the workload of centres that wish to submit to both organisations. The CIBMTR is using the TED (Transplant Essential Data) as their data collection form, which is an adaptation of the EBMT MED-A form. The TED contains some items which are not considered compulsory for EBMT centres and which have been grouped in the Med-A Appendix. Within the on-going aim of facilitating data reporting to centres, the EBMT provides facilities within the central database so that centres can enter the data requested by the CIBMTR, including the Appendix. This ensures that centres need to enter any data item only once.

The EBMT forwards MED-A data to the CIBMTR if requested to do so by the centre. In order for this to happen, centres must send the completed form **Permission form to share Med-A data with the CIBMTR** to the Central Registry Office. Centres who want to take advantage of this facility, need to contact the CIBMTR directly so that they can be added to their centre's list. Failure to do so will mean that the EBMT will not be able to forward the data.

5.2.3 *Exports performed by other users*

All centres can use their own data for their own purposes. They can perform statistics on line or download their data onto their computer if they need to perform more sophisticated analyses. If forwarding data by e-mail, identifiable data must be excluded or password-protected. Any centre must abide by European Union (EU) data protection laws when downloading or viewing data, even if the data originated at the centre itself.

All national registries can use the data submitted by the centres belonging to that national registry. The rules by which these centres allow the national registries to use their data is agreed between each national registry and their respective centres. The EBMT Registry Central Office is only involved in making sure that the electronic permissions granted respect the wishes of the centres.

The study groups that exist within the EBMT Registry can use the data submitted for that purpose. The EBMT Registry Central Office is only involved in making sure that the electronic permissions granted respect the wishes of the centres.

6 Use of the Registry

The main use of the Registry data is clinical research, with the ultimate aim of improving patient outcome. There are other ways in which patient outcome can be improved, such as inspection, auditing and accreditation of transplant centres and the development of these activities means that the use of the EBMT Registry data is nowadays more complex. Unfortunately, the development in the use of the data has not been matched by a similar development in the system used to store it. For this reason, some of the solutions may seem cumbersome and may not necessarily represent exactly the original request submitted from some of the Registry users.

6.1 *EBMT led studies*

This is still the single most important use of the Registry data. The EBMT registry can use all the data submitted to them. It is understood that data submitted to the EBMT can be used for research and published by the EBMT WPs as long as the existing **Guidelines for the Conduct of Registry Studies using the EBMT Registry Database** and the **Authorship guidelines for EBMT publications** are followed.

6.2 *Centre led studies*

Centres or groups of centres can set up studies and use the EBMT Registry as their database. They can request that the EBMT set up study groups and its corresponding series of permissions to access the data.

6.3 *Studies led by other registries*

For those centres which submit data to both the EBMT and the CIBMTR, the CIBMTR receives part of their data directly from the EBMT Registry rather than from the centre itself. The CIBMTR then proceeds to use these data in their studies. The EBMT only forwards data from those centres who have submitted a **Permission form to share Med-A data with the CIBMTR**.

National registries may also initiate any studies using the EBMT database for that purpose. As long as the studies include only centres in their respective nations, national registries have no obligation to ask permission from the EBMT to do this.

6.4 *Accreditation*

It is mandatory for data to be reported regularly for the EBMT for a centre to receive EBMT accreditation. Centres must demonstrate, not only that a certain number of transplants have been performed, but also that they have been reported.

6.5 *Membership*

It is mandatory for a centre to provide Med-A data regularly in order to become a full member of the EBMT. Members that are transplant centres and do not report their data can only be associate members.

6.6 *Corporate members use*

Corporate members have the right to access the Registry database to obtain aggregate data, but cannot obtain outcome data. They can access the data directly, just like a centre member, or ask the Registry Central Office to provide it for them

6.7 *Government agencies*

Public agencies are becoming increasingly interested in the Registry data. This may happen directly, as in the case of France, or through the centres themselves which use the data they submit to the Registry to answer queries from their public agencies. Increasingly national registries are being opted into collaborating with public agencies, either through funding or due to changes in the law. This is another way by which EBMT Registry data may be used by governments.

6.8 *Donor registries*

The Swiss donor registry uses the EBMT Registry to follow patients transplanted with cells from Swiss donors. In addition, it uses the EBMT database to also follow the donors. The

Antony Nolan registry (UK) is using the EBMT Registry to follow patients transplanted with cells from their donors and it is possible that this type of use will increase in the future.

The DRST (Central Marrow Donor Registry of Germany) has requested that the EBMT Registry include tissue repository information within the donor section of the database. The items have been inserted in the Registry database but full implementation is awaiting DRST review.

7 Data protection and data security

The EU has produced a directive including regulations regarding data protection and the individual's right to privacy that has become law in most EU member countries. According to this directive, all patients residing in EU member countries must give approval for their personal data to be entered into registries such as the EBMT registry. Also many other countries outside the EU have similar laws. However, since it would be impossible for the EBMT to keep up-to-date with the laws in all countries where EBMT members centres exist, it must be the responsibility of the individual centre to make certain that the respective national laws are followed. The EBMT has requested that all centres outside the EU sign a **EU Regulations Statement** declaring they will follow EU regulations regarding data safety. As of 2006 this statement was added to the forms used to request access to the EBMT Registry **DATA ENTRY APPLICATION FORM** or **DATA DOWNLOAD APPLICATION FORM**. As of 2007, this statement has also been added to the EBMT membership application form.

The EBMT has the responsibility to register the central EBMT database according to the law in the country where EBMT is registered. Since EBMT is a Dutch foundation, the law of The Netherlands applies.

Another important part of the regulations is that data must not be transferred to countries outside the EU or the European Economic Space (EES) without explicit consent from the patients. This must be taken into account in three situations:

- a) When an EBMT WP is situated outside the EU/EES.
- b) When an investigator doing analysis on EBMT data is situated outside the EU/EES
- c) When data is transferred according to the centre's instructions to a registry collaborating with the EBMT (such as the CIBMTR) outside the EU/EES.

Since it cannot be assumed that the centres reporting patients know where an EBMT registry or individual investigator is situated; the responsibility of preventing situations a) and b) must belong to the EBMT. a) is the responsibility of the EBMT board while b) is the responsibility of the WP chairperson. Regarding c), data is only transferred to other institutions on the centre providing written consent and therefore it is the centre's responsibility to obtain appropriate approval from national authorities and patient consent for data export outside the EU/EES.

7.1 Data security regarding access

Within the EBMT Registry there are issues relating to the existence of data from centres which do not belong to the EU/EES countries, plus the fact that an EBMT WP may not be situated within the EU/EES countries, or that, even if they are, investigators of WP approved studies may be situated outside the EU/EES. What this means is that although the EBMT database is located within the EU, this database cannot be labeled as an EU database only. To cover these issues and ensure the legality of all procedures relating to the database the following must be implemented:

a) All centres inside and outside the EU must obtain informed consent from their patients before the data can be submitted to the EBMT. This informed consent must explicitly state that the data is to be kept in an “international” database (can be exported to a non-EU/EES country). This is to avoid misunderstandings pertaining to the data being kept in a national database or even in an EU database. If a centre fails to do this, it is the centre’s legal responsibility

b) All centres outside the EU/EES, which submit data to the EBMT, must submit a declaration to the EBMT that they undertake to abide by the EU laws as implemented in the Netherlands regarding data protection. It is the opinion of the Dutch data authorities that the EU/EES export restriction applies also to centers outside the EU/EES countries that want to look at their own data through ProMISe. If a centre fails to provide the EBMT with this declaration, the data can be kept, but that centre cannot be allowed access to the Registry through ProMISe, not even for its own data. It is the EBMT’s legal responsibility to ensure that no access is given to centers, which have failed to provide this declaration. Since the middle of 2007, the application for EBMT membership contains such a declaration, so centres applying for membership after this date, whether inside or outside the EU/EES, are covered.

7.2 *Data security implemented on site*

Keeping downloaded EBMT data with non-anonymous items on personal or home computers is not allowed. If the data is downloaded for backup purposes it should be immediately transferred to a system recognised to be reasonably safe (locked, encrypted, etc.). Users must abide by all their local and national rules regarding data protection and confidentiality.

The only purpose for which the data can be sent outside of an EBMT office is for statistical analysis by EBMT approved statisticians within the context of an EBMT approved study. If the data is to be sent outside of an EBMT office or remain in a personal computer for statistical analyses, all non-anonymous data whether of the patient or of the centre (names, hospital numbers, date of birth, all the fields indicating the centre where the transplant took place, contact person, etc) should be removed and records identified solely by the SQL server autonumber field(s). The CIC part of the EBMT Unique Identification Code (UIC) must also be removed since it provides information as to the transplant centre. If the transplant centre is to be a covariate in the analysis, a new field should be used by which the data can still be assigned to one centre, but which will not reveal the identity of that centre.

7.3 *Individual access*

All individual must submit an Access request form for internet access to the data. Accepted signatories are:

- Principal investigator of a centre (centre's data only)
- Working Party head (for data within the remit of that WP)
- The President of the EBMT (for data within the remit of an EBMT Committee)
- Director of an institution or study group with which we have a partnership (in this case, the partner must also submit a signed form from every centre involved granting access of their data to that institution)
- Registry head for EBMT Registry staff

Individuals who by the nature of their work have direct access to the EBMT Registry databases (IT system/server managers) have no access rights to the data and would be in breach of contract if they manipulate it.

Appendix – Remote access for centres

The EBMT Registry is accessed through ProMISe. In this context, ProMISe acts as an internet access system. It is free for all EBMT members and the only software it requires is Internet Explorer 7 or higher. Users of ProMISe can access their own data in which case they can request permission to do any of the following:

- data entry *
- lists of patient data *
- data download *
- frequency tables and cross tabulations
- survival analysis

The facilities with marked with * are restricted since they may include identification of the patients. This type of access can only be requested by the principal investigator (PI) of a centre for a set of nominated individuals. The request must be done in writing to the Central Registry Office and signed by the PI. E-mail requests are not accepted. The access provided is personal and cannot be transferred to other individuals, not even within the same centre. The Central Registry Office reserves the right to cancel access without warning if it is felt that patient confidentiality might be at risk.

The other facilities are available to all member centres. These statistical facilities do not allow patients to be identified. Requests to receive this password should be made to the Central Registry Office.