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The making of a pan-European organ transplant registry

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Summary

A European patient registry to track the outcomes of organ transplant recipients does not exist. As knowledge gleaned from large registries has already led to the creation of standards of care that gained widespread support from patients and healthcare providers, the European Union initiated a project that would enable the creation of a European Registry linking currently existing national databases. This report contains a description of all functional, technical, and legal prerequisites, which upon fulfillment should allow for the seamless sharing of national longitudinal data across temporal, geographical, and subspecialty boundaries. To create a platform that can effortlessly link multiple databases and maintain the integrity of the existing national databases crucial elements were described during the project. These elements are: (i) use of a common dictionary, (ii) use of a common database and refined data uploading technology, (iii) use of standard methodology to allow uniform protocol driven and meaningful long-term follow-up analyses, (iv) use of a quality assurance mechanism to guarantee completeness and accuracy of the data collected, and (v) establishment of a solid legal framework that allows for safe data exchange.

Introduction

What is the 5-year post-transplant survival rate for all patients treated in Europe with a renal allograft? How many patients were transplanted in Europe who suffered from the hemolytic uremic syndrome? What donor and recipient factors influence outcome after organ transplantation? Are there different strategies toward organ replacement therapies and related outcomes between the different countries in Europe? At present we cannot answer questions such as these, but a European Transplant Registry will enable us to do so.

Despite well established European networks of transplant experts such as the European Society for Organ Transplantation (ESOT), and despite the existence of two well-functioning multinational organ sharing organizations, Scandiatransplant [1] and Eurotransplant [2], there is no pan-European registry of post-transplant outcome data that contains information on all national transplant activities and outcomes.

The need for a European Registry for organ transplant outcome stemmed from a survey carried out in 2003 by the Commission of the European Communities of the European Union (EU) that revealed discrepancies in quality and safety requirements within the EU Member States [3].

This demonstrated that European collaboration is crucial for the evaluation of measures intended to enhance post-transplant results and to make the use of organ donors more effective and safe. This in turn led to the creation of an Action Plan for strengthening the cooperation between the countries. One of the key elements derived from this Action Plan was the need to develop a European registry of national registries to monitor and evaluate post-transplant results. This should be carried out on the basis of a com-

mon European methodology, thereby ensuring the maximum health and safety standards in all Member States [4].

A project to develop a framework for realizing a pan-European Registry on post-transplant outcome data was established and called the *E*uropean *Fr*amework for *E*valua*t*ion of *O*rgan *T*ransplants (EFRETOS) [5].

The aim of the EFRETOS project was to describe the optimal content of a European Transplant Registry, based on the existing registries in Europe and current expertise. In addition, an appropriate functional framework, a feasible technical approach, and the organizational prerequisites for realizing a pan-European registry had to be designed.

The registry data set

One of the key stakeholders of the new European Registry is the European transplant community. To guarantee that a future European Registry will be built according to the high scientific standards and receive their support, the ESOT, one of the partners in the project, was asked to nominate three teams of experts. These groups of experts – one for kidney/pancreas, one for heart/lung, and one for liver/intestine transplants – undertook the crucial task of identifying variables to be taken up in the new registry.

Four types of variables were listed, these included donor factors, data on transplant candidate characteristics, peri- and early post-transplant outcome data, and post-transplant follow-up data. The complete report of the EFRETOS project is available as a digital complement including the full list of the variables.

It was recognized that at the start of the new Registry not all EU countries would be able to deliver information for all these variables. Therefore, it was agreed to design a list of basic variables that every contributor should with relative ease be able to provide on a regular basis.

The registry will be formed from three tiers of data (Figure 1). The first tier consists of the fundamental data on donor and recipient following a solid organ transplant. Provision of these data will be mandatory to provide for a core set of data for each country and to avoid any bias that may arise from selective reporting of outcomes. This requirement for mandatory data is not expected to be an impediment to participation in the European Registry because all countries are likely to collect these data.

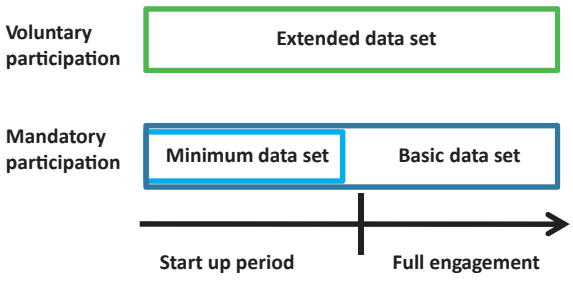

Figure 1 Three tier data base system.

The second tier data, or basic data set are those data that are generally acknowledged to be of interest by medical experts. These data are also considered mandatory data. However, in the initial phase of data delivery, not all countries will have information on these data fields. This data set will be essential for obtaining case mix adjusted survival rates.

The expanded data set or third tier of data are all other variables needed for novel studies in organ transplantation and also include information on socio-economical variables.

Data collection

Data will be sent from national registries to a centralized database by uploading standardized files. All uploaded data will be available for analysis through on-line analysis tools and download of defined files.

For secure communication with Internet and secure communication of the users with the database a separate redundant Internet web server has to be installed. The network has to be a secure network according to common standards in information technology.

Once an uploaded file has passed all validation checks, the data will be merged into the file containing cumulative data for a particular country, and released for uploading into the European Registry database. In the case of erroneous data the data in the uploaded file will not be merged into the country cumulative file, and corrective action will be undertaken by the country.

Analysis of registry data

Release of information by the new European Registry, is subject to compliance with policies to be agreed upon by cooperating national registries represented by the scientific community and the representatives of the competent authorities. This data release policy is expected to become the biggest hurdle as at present the countries that participated in the EFRETOS project do not allow free access to the data (Table 1).

Data access and data release is to be governed by policies that are approved by the Management Board of the new Registry. A Review Committee will consider all requests for data, other than for summary statistics that are provided as standard data sets for the web site and other communications. This procedure should safeguard against any traces of unauthorized usage of national data.

Legal policy

The legal basis for the collection of medical data can be found in specific regulations in the national transplantation

Table 1. Data release policy in the countries participating in EFRETOS.

Country	A center has full access to all of its own data, on request	A center has full access to all of its own data at any time	A center has full access to all data in the registry, on request (e.g. for specific projects)	A center has full access to all data in the registry	A center has access to own data but only in aggregated format	A center has access to all data but only in aggregated format
Austria	Y		Y			
Belgium	Y		Y			
Croatia	Y		Y			
Denmark	Y					
Finland	Y					
France	Y					Y
Germany	Y		Y			
Iceland	Y					
Italy		Y				
Luxembourg	Y		Y			
The Netherlands	Y		Y			
Norway	Y					
Slovenia	Y		Y			
Spain		Y	Y			Y
Sweden	Y					
UK	Y		Y			

acts predominately in combination with the consent of the data subject. It is essential to delineate the data set that is intended to be collected for recording in the European Registry and to define precisely the purpose for which the data will be collected. Based on this finding it needs to be ensured that required data collection is either permitted by law or covered by express consent of the individual patient.

During the EFRETOS project it was revealed that in a great majority of the countries no national registry exists (Table 2), while only France, Germany, and the Netherlands have a legal framework on mandatory data collection.

As data collection on national level is the fundamental basis for the European Registry, national legislation ensuring that transplant programs report on a mandatory and regular basis on outcome of their patients is required.

Depending on where the Registry will be established it has to be ensured that the operating institution complies with the national legal provisions in particular regarding the national legislation on data protection. As far as the transfer of data is concerned it is the providing organization that has to ensure that it collects, processes, and transfers the data in accordance with national provisions.

Table 2. Presence of a national transplant registry in the countries participating in EFRETOS.

Country	Kidney	Heart	Lung	Liver	Pancreas	Intestine
Austria	Y					
Belgium						
Croatia						
Denmark	Y					
Finland	Y					
France	Y	Y	Y	Y	Y	
Germany	Y	Y	Y	Y	Y	
Iceland	Y					
Italy	Y	Y	Y	Y	Y	
Luxembourg						
The Netherlands	Y	Y	Y	Y	Y	
Norway	Y					
Slovenia						
Spain			Y	Y	Y	
Sweden	Y					
UK	Y	Y	Y	Y	Y	Y

Pilot study

Within the EFRETOS project period a pilot study was carried out. This proof-of-concept exercise intended to establish whether data from two or more European countries could be successfully collected, combined, and analyzed. It focused on kidney transplantation performed over a short-time period limited to a small set of risk factors. These risk factors were agreed upon in advance with the participating countries and were known to already be collected by several national registries.

The pilot study was designed to evaluate 1- and 5-year graft survival rates following kidney-only transplantation. The study encompassed all types of donor, namely heart beating, nonheart beating, and living. Nonheart beating

donors were further categorized into controlled (Maastricht category 3, 4) and uncontrolled (Maastricht category 1, 2) [6]. All recipients receiving a transplant between 1 January 2000 and 31 December 2008 were included. The distribution of donor types across countries varied significantly ($P < 0.0001$), with Country B having the largest living donor transplants and nonheart beating donor transplants at 40.6% and 22.6%, respectively (Figure 2).

The pilot study provided a great deal of useful information for the design of a European Registry. As an example, Table 3 shows the graft survival rates following first adult deceased donor kidney transplantation in five European countries. In a multivariate model, this country effect was studied while adjusting for the following risk factors: donor and recipient age, donor and recipient gender, donor type, and the recipient's primary disease. Results from this analysis data indicate a significant difference in 5-year graft survival between countries after adjusting for these confounders; a European Registry is needed to identify reasons for these differences.

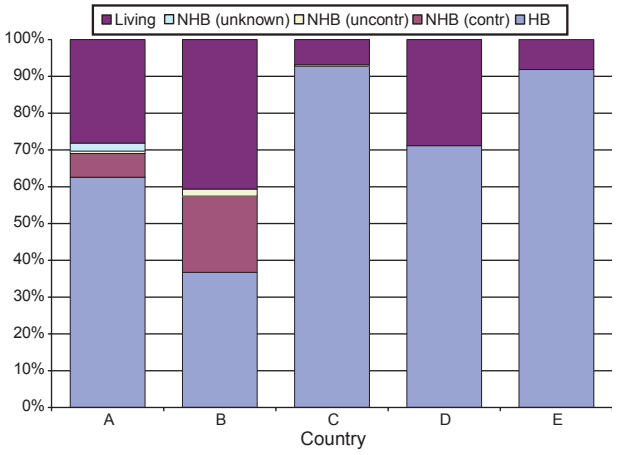

Figure 2 Donor type distribution across countries.

Table 3. One- and five-year graft survival estimates following first adult deceased donor kidney transplant, by country.

	One-year survival estimate	95% Confidence Interval	Five-year survival estimate	95% Confidence Interval
Country A (n = 17 625)	91.9	91.4–92.5	83.4	82.4–84.2
Country B (n = 5701)	89.7	88.5–90.8	80.2	78.2–82.0
Country C (n = 21 900)	95.1	94.7–95.4	87.9	87.3–88.5
Country D (n = 8417)	94.6	93.7–95.3	86.4	84.8–87.9
Country E (n = 11 551)	94.2	93.7–94.6	88.1	87.3–88.9
Log-rank test	$P < 0.0001$		$P < 0.0001$	

Five EFRETOS partner countries were able to supply national data, in a timely manner, for the pilot study. Three of the five countries participating provided data in a format that required less than ten minutes data manipulation to add to the database. In all five cases, some data manipulation was required, and so automatic procedures to integrate data provided to EFRETOS are unlikely to be feasible. In three cases, the data manipulation was minimal, but in the other two cases, this was more extensive. Data manipulation included changing the file type, changing textual dates to numeric dates, rounding data to the required number of decimal places, replacing missing values with the required 99 value, removing failure dates for deaths with a functioning graft, removing duplicate records, and grouping primary disease into the desired groups. This highlights the requirement for countries to devote sufficient time to formatting the data correctly, and also the requirement for central European Registry staff that is able to make these amendments where necessary.

Availability of data

Countries with an established national registry were able to contribute data to the pilot study in a timely fashion, but those without a national registry were unable to participate. Since a European Registry would aim to collect data from as many European countries as possible, this is an important feature to note and suggests that countries without an established central transplant registry may struggle to participate.

At least three countries needed to gain the permission of relevant stakeholders before they were able to submit data for the pilot study. This permission was obtained, but any European registry should be fully aware of these restrictions within countries and should seek to engage with the relevant stakeholders in countries to ensure their support for the registry and consequent data provision. Some countries were unable to provide data for the full time period of the study.

Definition of data set

Despite agreeing the choice of risk factors in advance of the pilot study, participating countries were sometimes unable to provide data on all factors for all transplants. Similarly, while the definition of each factor was also agreed, some countries were unable to provide data in the format requested because of limitations in the way the data are collected by the national registry, or because there was insufficient guidance on how to format risk factors into the required groups.

One country indicated that they were unable to distinguish between graft failure and deaths with functioning

graft effectively, particular in the early postoperative period. This highlighted one area where the data collected by national registries may not meet the requirements of a European Registry and may require changes to national registry data if the European Registry included such items in the basic data set.

When designing the pilot study, countries were asked to provide the data in a particular format, with consistent variable names, formatting of the data, codes to indicate missing values, and so on. None of the data sets received met all of these criteria. Participating countries must therefore be aware of the work required from them to participate in the European Registry, so that data can be formatted correctly prior to data submission to make compilation of the data as straightforward as possible. Those establishing the European Registry must also clearly specify all aspects of the data set they require in advance.

Figure 3 EFRETOS coverage among the European Union member states.

Table 4. Organ transplantation in 2009 in the European Union and in the countries participating in EFRETOS (based on Council of Europe data: Newsletter Transplant International Figures on donation and transplantation 2010).

Transplanted organs	EU total	EFRETOS total	EFRETOS (EU member states)	EFRETOS coverage of EU (%)
Kidney	17 886	17 427	16 958	95
Liver	6687	6662	6518	97
Heart	2090	2077	2030	97
Lung	1418	1434	1410	99
Heart/lung	48	47	47	96
Pancreas	779	786	757	97
Intestine	53	53	53	100

Coverage

A total of 21 countries participated in the EFRETOS project (Figure 3). The establishment of a European Transplant Registry founded by the EFRETOS partners would hence results in coverage of 95% of all renal transplants performed in the EU (Table 4).

Discussion

The EFRETOS project is an EU funded project in which 21 European countries collaborated with the aim of designing a blue print for the future establishment of a European Registry of registries on post-transplant outcome data. The establishment of a European Transplant Registry will have many advantages including the ability to investigate outcomes following transplantation for rare conditions, to explore outcomes following the transplantation of organs from extended criteria donors and to identify factors associated with the occurrence of rare adverse events following transplantation.

Levels of evidence

Clinicians use evidence to make decisions tailored to an individual patient's needs and circumstances. The highest level of evidence is provided by randomized controlled trial (RCT) studies [7]. In the context of organ transplantation, RCTs are often hampered by ethical concerns [8], therefore prospective cohort studies based on registry data are usually used as second best sources of knowledge, as evidenced by numerous scientific publications based on registry data [9–12]. But the platform for most of these studies are the country-based registries; while a joined European Register would in analog to the Scientific Registry for Transplant Recipients (SRTR) in the USA [13,14]; lead to a massive concentration of scientific data: 28 961 transplants performed in Europe and 28 464 in the USA in 2009 (Figure 4).

Uniformity data exchange

Lack of uniformity of the data fields is a major barrier to successfully foster an environment of data exchange. This point has recently been reiterated by Rosenblum *et al.* [15] who showed that the worldwide variability in deceased organ donation registries makes it hard to gauge a national initiative in a global context. We have specified recommendations for designing an effective registry, including a list of data fields with fixed formats that allow future studies into

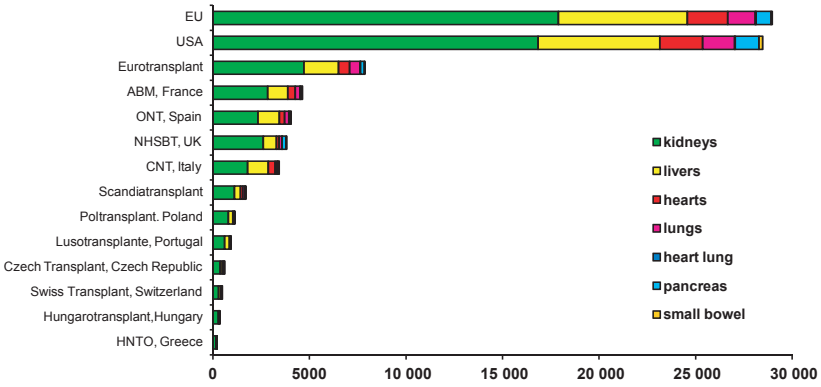

Figure 4 Number of transplants in 2009.

therapeutic strategies for the treatment of advanced organ failure patients. This blue print for a transplant registry can be of use both for countries without a national register as for those with an established register. All countries in Europe can participate once they are authorized by their national government to deliver data to the European Registry. Data from these existing registries will be uploaded in the central database according to the predefined formats. This submission process will also solve the European language issue as English is chosen as the lingua franca for the European Registry.

Data exchange with existing international registries

The new European Registry will provide an important opportunity for other multicenter registries, such as the International Society for Heart and Lung Transplantation Registry [16], and the European Liver Transplant Registry to share data [17]. The aim was to come to a close relationship with these established registries. It is envisaged that the new European Registry could draw historical data from the existing registries, while the new European Registry might, once the start-up phase has passed, forward data to these organ-specific international registries.

Tracking and tracing

The European transplant community is mostly organized into national organ procurement organizations (OPO) and national organ exchange organizations (OEO) where donors and patients are followed up as long as they stay inside the own OPO and OEO. There are only two international OEO, Eurotransplant and Scandiatransplant, where organs that cross border, albeit inside the own OEO, are tracked and traced. For instance, if organs retrieved from a Slovenian donor who died from carbon monoxide (CO) intoxication and used for transplantation in the Netherlands, the post-transplant course of these organs is recorded and the Slovenian clinicians will have access to this information via Eurotransplant. But a CO donor from the UK whose organs are transplanted in the Netherlands is lost to follow-up in the UK and no knowledge can be gained. The introduction of a European Registry would come with a European Registry identification number that will allow donor organ tracking and information retrieval across all borders inside Europe.

Data access and control

In contrast to the full data access policy in the USA [18], none of the countries that participated in the project claimed to have such a liberal attitude toward data delivery from their own regional or national register (Table 1). It is obvious that this attitude needs to be changed to ensure the viability of the new Registry, as interest in delivering data will fade if there is nothing in return. A first step has been made by providing a framework for the governance structure of the Registry, where data access regulation will be one of the future tasks of this governing body.

Legislation absence of national registries

One of the biggest surprises of the EFRETOS project was the finding that only a minority of the European countries have legislation that regulates mandatory registration of outcome after solid organ transplantation, and that only the UK has a national registry for all types of organ transplants (Table 2). Creating a European Registry based on national registries, at a time when even Spain has only regional renal transplant registries, seems an insurmountable obstacle. The process is slow and the transplant community should now focus on urging their national authorities to free funding for setting up and maintaining a national registry, and to install national legislation that should ensure that transplant programs report on a mandatory and regular basis on outcome of their patients.

Table 5. The major recommendations for setting up a European Registry.

- National or supranational registries on organ transplantation have to be established in all countries.
- The structure of the national registry should allow data delivery to the European Registry.
- Besides collection of the data on waiting list and transplant activities it is essential to also collect data on outcome of transplanted patients.
- National legislation should ensure that transplant programs report on a mandatory and regular basis on outcome of their patients.
- The necessary funding for setting up and maintaining this national registry should be made available by the competent authorities.
- There should be initial flexibility in the format of data provision to the European Registry, so that in the initial stages a variety of data formats could be permitted.
- Although the format of the required data set will be tightly specified, there will need to be flexibility in the early phase in accepting and converting submitted data to the required formats. It is recommended that any such conversion is performed by the European Registry itself.
- After data have been submitted to the European Registry, quality assurance procedures are necessary before data are uploaded to the Registry itself.
- The quality of the Registry data will need to be maintained by updating existing records on a regular basis and making any necessary corrections to the data.
- A relational database will be required to accommodate the data and web site produced that will allow data submission through the Internet.
- Regular reports that summarize the data held in the European Registry will need to be produced and disseminated.
- All proposals for audit and research projects based on data held in the European Registry should be scrutinized by a Review Committee set up for this purpose.

A European Registry that is developed and managed in line with the recommendations (Table 5) will be a great asset to the international transplant community as it will facilitate the refinement of patient selection for maximizing outcomes by studying actual donor-to-recipient combinations. Furthermore, results from this new European Registry will help in developing best practice guidelines to improve clinical management in case of transplants from extended criteria donors; and finally the use the Registry data will guide improvements in organ replacement therapies in Europe by publishing on collective data and by supporting research.

Authorship

JMS, JN, TB, and DC were assigned by the EFRETOS project team to write this article.

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Supplemental digital content

The full report of the EFREOTS project may be found as an appendix to the online version of this manuscript.

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