The general objective of this project is to provide a common definition of terms and methodology to evaluate the results of transplantation, by promoting a registry of registries on follow-up. A European registry will enable the monitoring of patients and the evaluation of transplant results.

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Thursday, July 14, 2011

Organ Transplant Waiting Lists Can Be Artificially Inflated, Comment Organ Transplant Experts

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Tuesday, April 12, 2011

HIV Infected Organs Should Be Available For HIV Infected Transplant Candidates

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Monday, March 07, 2011

EFRETOS Symposium 'Unifying data collection - creating new knowledge' , May 17, 2011

Wednesday, January 26, 2011

First Total Artificial Heart Implanted In California

Friday, October 29, 2010

Kidney Transplant Numbers Increase For Elderly Patients

Wednesday, October 13, 2010

Successful Kidney Transplantation Despite Tissue Incompatibility

Thursday, September 16, 2010

Dutch Kidney Foundation Awards 3 Million Euro To Renal Consortia

Wednesday, September 15, 2010

UK HealthCare Celebrates Pediatric Kidney Transplant

Wednesday, July 28, 2010

ISHLT Issues New Guidelines For The Care Of Heart Transplant Recipients, Published In The Journal Of Heart And Lung Transplantation

Monday, June 28, 2010

Common International Definition Will Benefit Heart Transplant Patients

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European Framework for the Evaluation of Organ Transplants

General and specific objectives

The general objective of this project is to evaluate the results of transplantation, by promoting a registry of registries on the follow-up of organ recipients.

Specific objectives:

- to prepare the specifications of a registry of registries concerning the evaluation of outcome of post-mortem solid organ transplantation;
- to promote common definitions of terms and methodology to evaluate the results of transplantation;
- to promote a registry or network of registries on the follow-up of organ recipients;
-

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to monitor health of patients who have undergone transplantation of organs;

to evaluate the results of the project in strong cooperation with the European Commission (EAHC) using the European Network of Competent Authorities;

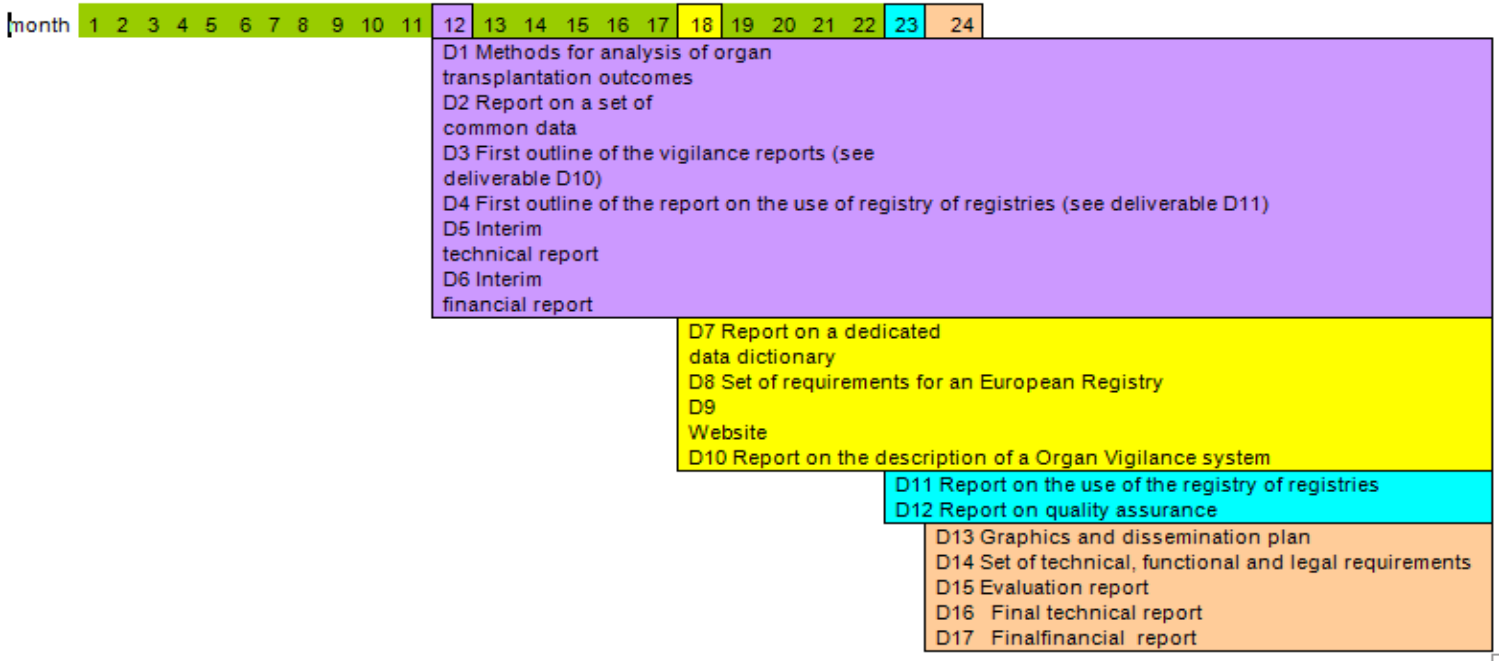
to disseminate the results of this innovative project, especially concentrating on the main stakeholders (patients medical experts, national authorities)

to set up a quality assurance system for obtaining high quality data on transplantation outcomes

Deliverable No	*Deliverable title*	*Delivery date*
D1	Methods for analysis of organ transplantation outcomes	M12
D2	Report on a set of common data	M12

D3	First outline of the vigilance reports (see deliverable D10)	M12
D4	First outline of the report on the use of registry of registries (see deliverable D11)	M12
D5	Interim technical report	M12+2
D6	Interim financial report	M12+2
D7	Report on a dedicated data dictionary	M18
D8	Set of requirements for an European Registry	M18
D9	Website	M18
D10	Report on the description of a Organ Vigilance system	M18
D11	Report on the use of the registry of registries	M23
D12	Report on quality assurance	M23

D13	Graphics and dissemination plan	M24
D14	Set of technical, functional and legal requirements for developing and maintaining a registry of registries	M24
D15	Evaluation report	M24
D16	Final technical report	M24+2
D17	Final financial report	M24+2



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Partners

Eurotransplant International Foundation (ET) – Project Leader

The Eurotransplant International Foundation is responsible for the mediation and allocation of organ donation procedures in Austria, Belgium, Croatia, Germany, Luxemburg, the Netherlands and Slovenia. The Eurotransplant region numbers well over 124 million inhabitants. Eurotransplant has well defined quality standards and practices. Important aspects of Eurotransplant's quality system involve the Eurotransplant Reference Laboratory and the audit system for evaluating the High Urgent status of patients on the waiting list. Specific objectives of the organization are:

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to achieve an optimal use of available donor organs and tissues;

.

to secure a transparent and objective selection system, based upon medical criteria;

.

to assess the importance of factors which have the greatest influence on waiting list mortality and transplant results;

.

to support donor procurement to increase the supply of donor organs and tissues;

.

to further improve the results of transplantation through scientific research and to publish and present these results;

.

the promotion, support and coordination of organ donation and transplantation in the broadest sense of the term.

ET is responsible for the overall leadership and management of the project, together with the internal evaluation of the project activities.

Centro Nazionale Trapianti (CNT) – Italy

The National Institute of Health (ISS) is a public technical and scientific body of the Italian National Health Service, under the Ministry of Health. The ISS manages and coordinates research and acts as consultant for the Ministry of Health, for the Government and the Regions. The Italian National Transplant Centre (CNT) is a technical body of the Ministry of Health. It was set up under Law 91 of 1999 and it is located at the ISS where it performs its activities as a department of the same body. CNT coordinates all activities concerning donation, allocation and transplantation of organs. It supports the Regions in the regulation of donation, banking and transplantation of tissues and cells by collating activity data, developing and disseminating practice guidelines, inspecting and certifying centres and managing a national vigilance programme. It also manages the Transplant Information System which collects data regarding donation, allocation and transplantation of organs, including transplanted organ quality, defines protocols about safety and security of organ donation and criteria for operational protocols for organ and tissue allocation, allocation of organs for urgencies and national programs. It fixes parameters for transplant quality assessment, promotes information campaigns for the general public, in collaboration with the Italian Health Ministry and patient Associations. Both ISS and CNT have a vast experience in project participation and coordination.

CNT is responsible for 2 workpackages: WP2 – Project Dissemination and WP7 – Quality Assurance

European Society for Organ Transplantation (ESOT)

The European Society for Organ Transplantation (ESOT) aims to become the umbrella organization under which all European transplant activities are organised. ESOT cooperates with many transplant organizations to structure and streamline these transplant activities in Europe. Several Organ Expert Sections within ESOT represent expert knowledge on the respective organs. ESOT trains and supports its members through an extensive educational and basic science programme and encourages excellence through an award and grant programme. Furthermore ESOT gathers the European and international transplant scene at its biannual Congress organised in a European city.

ESOT is responsible for WP4 – Development of data dictionary.

NHS Blood and Transplant (NHS) – UK

NHSBT is a Special Health Authority in the NHS with responsibility for optimising the supply of blood, organs, plasma and tissues and raising the quality, effectiveness and efficiency of blood and transplant services.

NHSBT is responsible for:

- encouraging people to donate organs, blood and tissues
- optimizing the safety and supply of blood, organs and tissues
- helping to raise the quality, effectiveness and clinical outcomes of blood and transplant services
- providing expert advice to other NHS organisations, the Department of Health and devolved administrations
- providing advice and support to health services in other countries
- commissioning and conducting research and development
- implementing relevant EU statutory frameworks and guidance

NHSBT is responsible for WP5 – Methods and legal and technical requirements.

Organizaciòn Nacional de Trasplantes (ONT) - Spain

ONT is an institution belonging to the Ministry of Health and Social Policy, in charge to develop the competencies related with provision and clinical utilization of organs and tissues. To carry out these tasks, it functions as a technical operative unit that fulfils its mission of coordinating the activities of donation, recovery, preservation, distribution, exchange, and transplantation of organs and tissues throughout the whole Spanish Health Care System.

Core activities of the Organization:

- Promotion and organization of all donation and transplantation activities;
- Extra-hospital coordination of all multiorgan recovery procedures;
- Elaboration of regulations and reports;
- Promotion of Agreements and Consensus Reports; Provision of information on donation and transplantation activities and health related topics; Information to the general public;
- Promotion and development of training courses; International Cooperation.

ONT is responsible for workpackage 6 – Safety Management.

Agence de la Biomédecine (ABM) – France

The Agence de la biomédecine was created by virtue of the Bioethics Law of August 6, 2004. It guarantees equity, ethics and transparency for the activities under its responsibility, and for anticipated developments.

The Agency is a public organisation under the supervision of the Minister of Health, operating in four key areas of human biology and medicine: (i) procurement and transplantation of organs, tissues and cells; (ii) assisted reproductive technologies; (iii) prenatal and genetic diagnosis; and (iv) embryo and stem cell research.

Among its numerous missions, the Agency is the Competent Authority, in coordination with Regional Authorities, for licensing and inspection of the procurement, processing, storage and distribution of reproductive cells for assisted conception. The agency is also in charge of the vigilance and surveillance of serious adverse reactions or events in the field of assisted reproduction.

ABM participates to the project activities, but does not lead any of the workpackages.

ScandiaTransplant

Scandiatransplant is a Nordic organ exchange organization and it covers a population of 24.5 million inhabitants in five countries, Denmark (5.4 million), Finland (5.2 million), Iceland (0.3 million), Norway (4.6 million), and Sweden (9.0 million). Scandiatransplant was founded in 1969 on the initiative of Nordic pioneers within the organ transplantation field. Today, Scandiatransplant includes a cooperation of all 12 Nordic transplant centers in addition to eight immunology laboratories.

According to the by-laws, the purpose of the Scandiatransplant association is fourfold:

(1) Scandiatransplant shall effect the exchange of organs and tissue between the participating transplant centers;

(2) It shall operate a database and communicate information from it;

(3) It shall contribute to promoting the provision of human organs and tissue for transplantation;

(4) It shall support scientific activities.

The members of the Scandiatransplant association are hospitals, each with an active program for organ transplantation. Iceland is now a fully member because they do kidney transplantations from living donors, having transplantations with organs from deceased organ donors done in one of the other Nordic countries.

The supreme authority is the Council of Representatives, where one or more professionals who must be clinically active in terms of organ transplantation represent each transplant center. The Board has responsibility for the day-to-day operation of Scandiatransplant. The Board has one member appointed by each of the five Nordic countries in addition to one chairman who is elected by the Council of Representatives. The office of Scandiatransplant is located at the University Hospital Skejby in Aarhus, Denmark.

Scandiatransplant participates to the project activities, but does not lead any of the workpackages.

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No Events available.

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WP1 - Project Management

Tasks of the project coordination and administration will be:

- Establishment of the project structure and procedures
- Surveillance on all procedures
- Preparation, chairing and minutes of project meetings
- Preparation of 6 monthly internal progress reports
- Scientific coordination of work packages, steering the workpackages based on progress and output
-

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Monitoring ethical issues and reporting to the PB.

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WP2 - Dissemination of the project

Dissemination activities are lead by CNT that will produce a Graphics and Dissemination plan as a fruit of discussion and input by all partners. This will include a list of the congresses and meetings at which the project and its output will be presented as well as a plan to ensure that all relevant stakeholders are aware of work progress and results. Dissemination will be managed both at national and international level.

The Partnership will periodically inform the European Commission and the Competent Authorities about the progress of the project. This will ensure a good fit between the project and policy related issues.

The need for dissemination to the general public will be also addressed by this WP. The website will include a publicly accessible part. The WP leader will ensure that suitable information and links are included on the website so that interested members of the public can be informed of the project's aims, methods and progress.

Dissemination tasks include:

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Definition of target groups and dedicated dissemination strategies per group;

Identification of events and dissemination methods;

Definition of information to be disseminated;

Building and sustaining of EFRETOS project website;

Monitoring of participation in chosen events;

European Framework for the Evaluation of Organ Transplants

WP3 - Evaluation of the Project

With respect to the evaluation of the project, the management board will appoint an evaluation manager who will assess all critical elements of the project, the management board, the dissemination strategy and the technical work packages. In particular, the evaluation manager will evaluate the deliverables (in time, quality, quantity, contribution by all participants) and the outcomes of the work packages.

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WP4 - Development of data dictionary

The aim of the WP is to develop a common data dictionary and definitions. In order to reach this goal, some tasks have to be carried out:

- To assemble and to compare data sets definitions currently used by organizations in Europe to evaluate outcome as well as quality and safety in deceased donation and organ transplantation.
- To develop a common data dictionary defining and describing all pertinent variables necessary to evaluate outcome and risk factors for quality and safety in deceased donation and organ transplantation.
- To determine a required "minimum" and optional "expanded" data set of variables to be collected by all participants of the consortium for analyzing outcome and risk factors in deceased donation and organ transplantation.

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The data dictionary will describe individual variables and define the data set that will allow risk-benefit analyses in donation and transplantation of kidney, pancreas, liver, intestine, heart and lung. Building on the outcome of the survey and recommendations described under the first task, existing definitions will be discussed and if acceptable confirmed.

European Framework for the Evaluation of Organ Transplants

WP5 - Methods and legal and technical requirements

The objective of this WP is twofold: to develop methods for analysing outcomes on organ transplantations and to develop legal, and functional and technical requirements for future registries. This work package builds on the work that was facilitated by the Alliance-O project.

The first step is to devise methods for the analysis of the data sets that are formulated in WP4. Discussions amongst statisticians and epidemiologists in the participating organizations will lead to a specification of statistical techniques for data summary, as well as more sophisticated methods based on statistical models that were summarised in the Alliance-O Project. Attention will also be given to the way in which the results of such analysis might be reported.

Once a common data set and method of analysis has been agreed, data for individual countries will be obtained where possible. This would be done in compliance with all data protection and confidentiality frameworks, and in particular would not involve the transmission of person identifiable information assessment of outcome will be done at OEO level. Outcomes following transplantation using expanded criterion donors will

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be studied, so as to inform organ allocation.

One of the major deliverables (D5) of this project will be achieved in this work package: the detailed description of technical, functional and legal requirements as base for the future development of the registry of registries.

This deliverable will serve as input indicator of work package 6 and work package 7.

European Framework for the Evaluation of Organ Transplants

WP6 - Safety management

The objective of this WP is to develop a common safety management procedure. Specific objectives of this WP are:

- to review the current available information on criteria applied to transplanted organs from donors with specific conditions. This includes the evaluation of the state of the art on the use of donors with the above mentioned conditions in the participating European countries, the technical conditions required and the legal issues related to their use. Moreover, a systematic review of the available information on the criteria applied to utilize organs from donors with specific conditions will be carried out, as well as on the risks/problems related to their use. A link with the EU funded project, DOPKI will be also established for this purpose.
- to provide a set of recommendations on the use of such organs;
- to develop a harmonized system for organ vigilance in organ transplantation, incorporating legal, functional and

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technical requirements for the management of this system (broad European level):

- Definition of requirements
- Definition of responsibilities
- Definition of safety problems after transplantation to be reported
- Information to be collected on safety problems after organ transplantation

European Framework for the Evaluation of Organ Transplants

WP7 - Quality assurance

The objective of this WP is to set up a quality assurance system for obtaining high quality data on transplantation outcomes.

A survey will be performed through the circulation of a questionnaire sent to all partners. On the basis of this analysis a consensus document that identifies an agreed quality assurance methodology will be worked out for this particular field. Following such analysis, a consensus document for a best practice of quality assurance of transplant outcome, data collection, production pathways and auditing methods via the organizations that delivered the data will be laid down.

The definition of quality indicators for organ transplantation is a prerequisite for increasing quality of health in this field. Ensuring the quality of data that are used for assessing transplant outcome is pivotal in this process, as quality assurance of registry data allows comparative analysis. This quality assurance study will evaluate the following processes: data delivery, data validation, data storage, follow-up data refreshing and data dissemination according to the legal, functional and technical requirements that have been defined in WP5

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and WP6.

In this work package we will find consensus on a common shared methodology for assessing the quality of post-transplant outcome, the validation of these data sources and their handling. Since this WP represents the final moment of the evaluation process, it will start with the results and inputs from other work packages.

In order to achieve this goal, existing methods through which transplant organizations represented in the project presently ensure quality of data production and input for transplant outcome evaluation have to be analyzed. Such analysis will focus on transplant processes and on how defined outcome data are produced, collected and handled by different organizations in different countries.

EFRETOS

Report on the use of the European Registry of Registries

Project Acronym: **EFRETOS**
Project Title: **E**uropean **Fr**amework for the **E**valua**t**ion of **O**rgan Transplant**s**
Contract Number: 20081101
May 2011

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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 Haemolytic Uremic Syndrome? What donor and recipient factors influence outcome after organ transplantation? Are there different strategies towards 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 like the European Society for Organ Transplantation (ESOT), and despite the existence of two well-functioning multinational organ sharing organisations, Scandiatransplant and Eurotransplant (ET), there is no pan-European registry of post-transplant outcome data that contains information on all national transplant activities and outcomes.

The history of making a European Registry for organ transplant outcome started with 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.[1]

The Commission then realized 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 has 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 in order to monitor and evaluate post-transplant results. This should be carried out on the basis of a common European methodology, thereby ensuring the maximum health and safety standards in all Member States.[2]

A project to develop a framework for realizing a pan-European Registry on post-transplant outcome data was born and called the **E**uropean **Fr**amework for **E**valua**t**ion of **O**rgan Transplant**s** (EFRETOS).[3]

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 organisational prerequisites for realizing a pan-European Registry had to be designed. Because the recently approved *Directive 2010/53/EU* sets down common quality and safety standards of human organs intended for transplantation, it was also the intention of the EFRETOS project to provide a comprehensive approach to safety issues related to organ transplantation, including both the specific assessment of recipients transplanted from non-standard risk donors (NSRD) and the development of an organ vigilance system.

1.2 Registry design and Data dictionary

One of the important stakeholders of the new European Registry is the European transplant community. In order to guarantee that a future European Registry will be built according to high scientific standards and receive their support, the European Society for Organ Transplantation (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.

It was furthermore 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 short list of basic variables that every contributor should, with relative ease, be able to provide on a regular basis.

The Registry will contain national data at patient level. The data will be collected to an agreed standard of quality, and to agreed functional, technical and legal requirements.

The Registry will collect data in three tiers (Figure 1). The first tier (minimum data set) consists of fundamental donor and recipient data following a solid organ transplant. Provision of these data will be mandatory in order to join the European Registry. This way a basic data set will be available for each country avoiding 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.

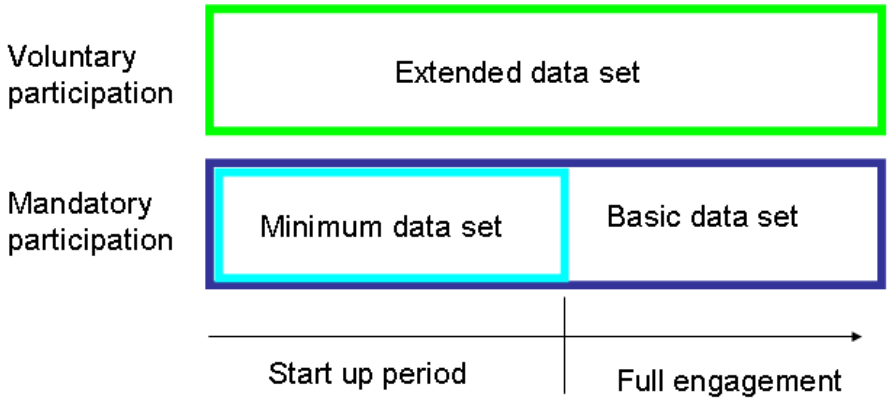


Figure 1. Three tier data set in the new European Registry

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. However in the initial phase of data delivery, not all countries will have information on these data fields available in an electronic format. Therefore a transition period is conceded for all countries joining the Registry for providing this data set. Nevertheless the data set is considered important because it will be essential for obtaining case mix adjusted survival rates. It will include characteristics of donors and organs that are needed to undertake an adequate risk assessment in the use of organs from non-standard risk donors.

The expanded data set or third tier of data reflects data that are not routinely collected for all patients. They are needed for novel studies in organ transplantation that might be of great interest for specific subgroup studies. They will also go beyond purely medical factors and for example include information on socio-economic variables.

The ESOT expert committees not only identified the items for the different data sets, they also provided detailed definitions of the different variables in order to make comparisons and merging of data from different sources possible.

1.3 Data Collection

Data will be sent periodically (i.e. once a year) from national registries to a centralized data base 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 of the users with the data base via internet a separate internet web server has to be installed. The network has to be a secure network according to common standards in IT.

Defined data checks will be performed on all uploaded files. If no errors are detected the file will be merged into the cumulative country table and released for uploading into the European Registry data base (Figure 2). If one or more errors are encountered, the merging will not be performed, the file will be marked as not usable and an email will be sent to the user who uploaded the file. This e-mail contains an overview of all the errors encountered.

Figure 2 Schematic overview of the European Registry

During the start-up of a country it is, for a defined interim period, possible that the data do not comply completely with the definitions of the data sets. The data will be imported in the country file and will be converted in the uploading process to the Registry's database.

1.4 Analysis of registry data

Release of information by the new European Registry is subject to European data safety and privacy rules and complies with policies to be agreed upon by cooperating national registries, represented by the scientific community and the representatives of the competent authorities.

Data access and data release is to be governed by policies that define two categories of data requests complying with policies 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 communication.

National registries will be able to access their own national data. For all other types of requests the following table is proposed:

Categories of data requests		Data release to:
A	Standardized reports and related data requests that do not require specific authorization	all stakeholders
B	Data requests that require specific authorization	authorized stakeholders

The definition of these two sets and any transition of data later on between the different types is the responsibility of the Management Board. This procedure should safeguard against any traces of unauthorized usage of national data.

1.5 Data quality assessment

While data collection on organ donation, allocation and the transplant process itself is compulsory in most countries participating in the EFRETOS project, for post-transplant data collection only half of the consortium partners have a compulsory system in place. Follow-up data completeness is currently often low especially in those countries without a mandatory data reporting system. Therefore efforts have to be made to increase the level of post-transplant data collection at central (national) level.

With regard to data quality, currently all partners perform checks on data format, internal consistency, accuracy and reliability of the data reported to them. On the other hand less than 50% of the partners require a minimal standard of quality and most do not have a system of quality indicators to assure data quality. For this reason it is considered important to establish quality indicators to evaluate and where necessary improve the quality of the data provided to a European Registry.

After establishing a European Registry quality levels based on different indicators should be developed. This will increase the transparency level of the data provided and could be used to define certification levels for the reported data from the different national registries. To establish these quality levels, a “training period” will be required during which all partners should make an effort to reach a minimum level of data quality. The time period foreseen for setting up these different quality levels is about two years, during which data quality targets will be adapted based on the experiences with the data collected during this period.

1.6 Pilot study

Within the EFRETOS project period a pilot study was realized. This proof-of-concept exercise intended to establish whether data from two or more European countries could be successfully collected, combined and analysed. 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 provided a great deal of useful information for the design of a European Registry. A relatively small data set was collected from five EFRETOS partner countries, and successfully combined and analysed. Even this small data collection and analysis exercise yielded interesting findings showing the potential of a future European Registry (Figure 3).

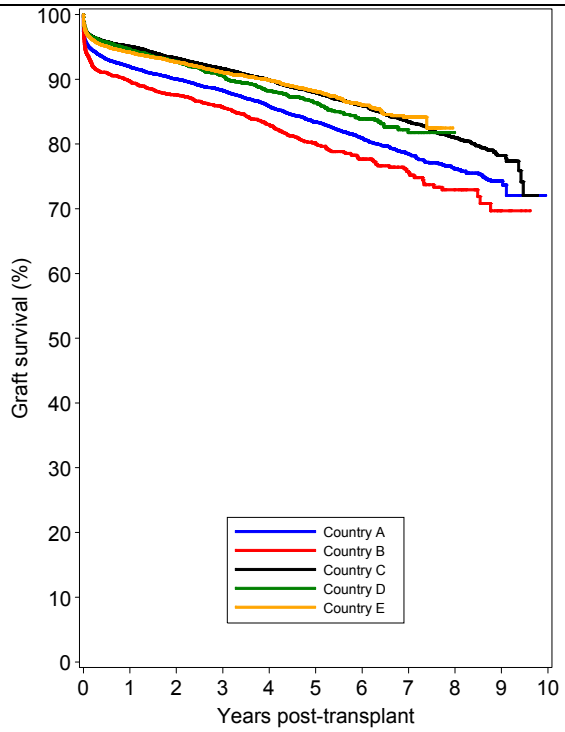


Figure 3. Graft survival following first adult deceased donor kidney transplants in five European countries EFRETOS pilot study

However, the process was not always straightforward and highlighted several issues. In particular:

- Countries without national registries are likely to find participation in a European Registry challenging;
- Stakeholders within countries must be well-informed and supportive of the Registry's aims and support data submission;
- The definition of fields in the European Registry must be highly detailed and give guidance on how existing coding structures should be mapped to any new categorization used by the Registry;
- The selection of fields for the basic data set must take account of the availability of those items in existing national registry data sets;
- Participating countries must commit sufficient time to preparation of the data set adhering to the common pre-specified format and must follow any data security requirements specified by the European Registry;
- Central registry staff will be required to process and analyse the data received;
- Missing data is a common problem that must be treated appropriately in any analysis.

By taking these issues into account a sound foundation will be laid for a European Registry.

1.7 Governance and administrative structure

The governance of the new European Registry intends to respect and safeguard individual privacy as well as the sovereignty of each Member State to identify and act upon national quality and safety issues related to the field of organ transplantation, and most importantly will strive for a harmonization with the existing national governance policies.

The main purpose of the establishment of a European Registry is to gain and increase knowledge in the field of solid organ transplantation. In order to fulfil its purpose the Registry should be set up to provide certain

services. These are: to provide access to inhabitants of the EU to an actual overview of the activities and profiles of national registries within EU Member States, including information on active transplant programs, annual number of transplants performed within each Member State and some basic demographic statistics; and to set up an information request service for data extracts and data analyses

A three layered governance structure is proposed. These are the Management Board, the Review Committee and the Central Staff (Figure 4).

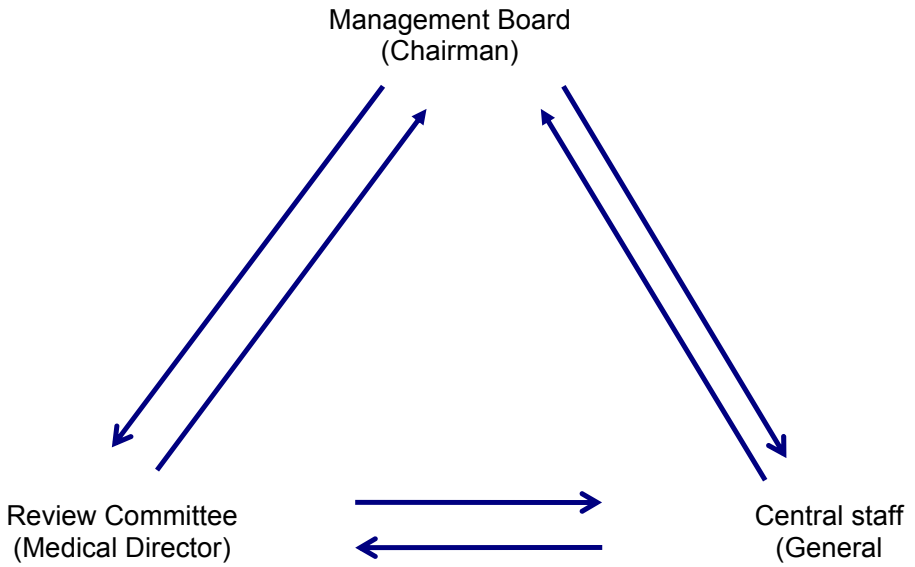


Figure 4. Governance structure

The Management Board acts as governing body for the Registry organisation. It is responsible for developing and sustaining a framework of policies that ensures that the registry can function in compliance with the existing legislative, scientific and ethical conditions. The Management Board is also responsible for the performance of the Review Committee and the Central Staff of the Registry.

The Management Board will consist of members appointed by national competent authorities or delegated bodies responsible for registry questions of the participating countries. All national or supranational registries delivering data to the European registries shall also send a representative to the Management Board.

Within the mandate of the Management Board: the Review Committee will review and evaluate proposals for registry adaptations, determine priorities in relation to available resources and make recommendations to the Management Board regarding approval of such proposals. One of the key tasks of the Review Committee will be the evaluation of data requests going beyond standard reports and analyses. It is the responsibility of the Committee to assess whether or not data requests are complying with approved policies from the Management Board and general principles of the European Registry. The Committee will also direct and oversee all activities performed by the Registry Central Staff.

The profile of the Review Committee members is intended to be of medical scientific nature. Therefore it is suggested that candidate members shall be proposed by the transplant community.

The Central Staff is responsible for data hosting, data collection, monitoring of the quality of the data and for data analysis. The Central Staff will be responsible for the implementation of all agreed policies and operating procedures. It is anticipated that the Registry Central Staff will be embedded in either an Organ Exchange Organisation (OEO) or an academic institution.

1.8 Legal policy

The legal basis for the collection of medical data can be found in specific regulations in the national transplantation acts predominantly in combination with the consent of the data subject.

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

The EU Data Protection Directive 95/46 lays down the minimum set of rights of the individual regarding the processing of personal identifying data. Individuals should be fully informed of the use to which information about them may be put and the extent to which it may be shared. Based on the implementation into national law data subject rights may nevertheless vary since Member States can always pass stricter regulations than those that have been published in the Directive.

A protocol must be developed in which the requirements and the authorizations in relation to the access to the identifiable data are laid down. These requirements have to be in compliance with European legal standards and the national legislation of the future host country of the Registry.

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 organisation that has to ensure that it collects, processes and transfers the data in accordance with national provisions.

1.9 Non-standard risk donors and vigilance

The final aim of the EFRETOS project is to contribute to improve the effectiveness, the quality and the safety of organ transplantation, by examining variations in outcomes. This will be done by providing a system for all Member States for the management of solid organ transplant data, which would be viewed by participating countries as a powerful, customized tool to foster their own research programs rather than being merely an additional reporting chore and expense. The evaluation of these post-transplant results through the use of common definitions will help to develop good medical practices in organ donation and transplantation.

Safety in solid organ transplantation has been addressed in a comprehensive way in the EFRETOS project: from the most common complications related to transplantation and immunosuppressive therapy to more specific issues as those related to the use of organs from non-standard risk donors (NSRD) and organ vigilance.

NSRD are defined as those posing a non-standard or non-assessable risk for disease transmission (ALLIANCE-O project). Some of the identified categories of NSRD include: donors with a past or present history of malignancy, donors with a positive serology for HCV, HBV or HIV, those with risk behaviours for viral infectious diseases or pitfalls in serology screening and donors with emergent or rare infectious diseases. Because many of these donors are infrequent or even not accepted in particular countries, obvious benefits could potentially derive from international data sharing on these donors and on the outcome of their recipients through the new European Registry, by helping to establish the safety limits in the use of particular organs for transplantation. EFRETOS has identified specific variables in this regard through a literature

review, the evaluation of currently run specific data collections and expert discussions. These variables and corresponding definitions have been incorporated into the previously described data sets (either as tier 1, 2 or 3).

Nevertheless, risk related to a specific donor or to the process from donation to transplantation can change after transplantation has been carried out. This variation in risk might even be identified after a complication arises in a particular transplant recipient. In the EFRETOS comprehensive approach to safety, these particular circumstances falling under the concept of vigilance and surveillance were considered to need a particular focus. This was especially relevant in the current scenario set down by Directive 2010/53/EU, which requires Member States to develop and implement a system for reporting what is defined as serious adverse events and serious adverse reactions (SARE).

EFRETOS has performed a review and a detailed description of current organ vigilance systems in countries represented at the consortium and in the United States. This review, combined with extensive expert discussions and analysis, has been followed by the release of a set of recommendations for the development of an organ vigilance system that can be useful for Member States when implementing provisions reflected in Directive 2010/53/EU. Moreover, the agreement achieved during the project lifetime will make possible a common EU understanding on organ vigilance of special relevance for organs exchanged between countries. International data sharing on SARE could be a further step in the understanding of the European Registry, noting that the reporting, assessment and management of SARE, as well as the required maintenance of traceability, is a national competence, not to be attained through the Registry itself.

1.10 Conclusions

The establishment of a European Transplant Registry will have many advantages and, amongst other things, will lead to the ability to investigate outcomes following transplantation for rare conditions, to explore outcomes following the transplantation of organs from extended criteria donors, to identify factors associated with the occurrence of rare adverse events following transplantation, and to establish a European vigilance system. A European Registry that is developed and managed in line with the recommendations summarized in this document will be a great asset to the international transplant community and beyond.

1.11 Frequently asked questions

What is the EFRETOS project?

The EFRETOS project is an EU funded project in which 20 European Member States have collaborated effectively with the aim of designing a blue print for the future establishment of a European Registry of registries on pre- and post-transplant outcome data. It comprehensively addresses safety issues related to organ donation and transplantation.

Why is it important to create a European Registry on post-transplant outcome?

The objectives of a future European Registry include, but are not limited to the following:

- to facilitate the refinement of patient selection for maximizing outcomes by studying actual donor-to-recipient combinations;
- to develop consensus in best practice guidelines to improve clinical management in case of transplants from non-standard risk donors;
- to use the registry data to guide improvements in organ replacement therapies in Europe by publishing on collective data and by supporting research.

What are the benefits of participating in the future European Transplant Registry?

The future Registry will be designed to simplify reporting of essential outcome data at national and at European level. This approach will serve the purpose of benchmarking and might lead to a quality improvement.

Which organisations collaborated in the EFRETOS project?

The EFRETOS consortium encompassed the following organisations:

- ABM - Agence de la Biomédecine (France)
- Autoridade para os services de sangue e de transplantacao (Portugal)
- CNT - Instituto Superiore de Sanità (Italy)
- Czech Transplant Society (Czech Republic)
- Derer University Hospital (Slovakia)
- DSO - Deutsche Stiftung Organtransplantation (Germany)
- ESOT - European Society for Organ Transplantation
- ET - Eurotransplant International Foundation (The Netherlands)
- HNTO - Hellenic National Transplant Organisation (Greece)
- NHSBT - NHS Blood and Transplant (UK)
- NTS - De Nederlandse Transplantatie Stichting (The Netherlands)
- ONT - Organización Nacional de Trasplantes (Spain)
- Poltransplant (Poland)
- SKT - Scandiatransplant (Denmark)
- Slovenija Transplant (Slovenia)
- Universitair medisch centrum Groningen (The Netherlands)
- University of Padua (Italy)

What is the population coverage rate of the EFRETOS project?

The collaborating organ exchange organisations served a total population of 459.7 million people thereby covering 95% of the EU population.

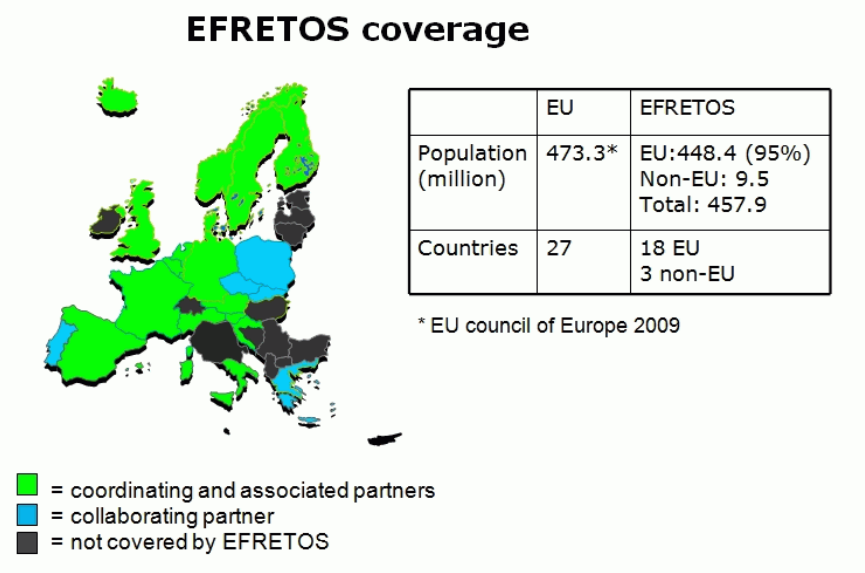


Figure 5. The EFRETOS consortium partners

Is any approval required to participate in the future European Transplant Registry?

Participation in the future Registry will require

- a participation agreement issued by the Ministry of Health or the responsible competent authority;
- a financial disclosure and conflict of interest statement;
- agreement to training of national partners cooperating with the European Registry;
- agreement to certification process.

The major recommendations for setting up a European Transplant Registry

Recommendation 1
National or supranational registries on organ transplantation should be established in all countries. The structure of these registries should allow data delivery to the European Registry.

Recommendation 2
Besides collection of data on waiting list and transplant activities, data on outcome of transplanted patients should be collected. National legislation ensuring that transplant programs report on a mandatory and regular basis on outcome of their patients would facilitate the data collection and reporting process.

Recommendation 3
The necessary funding for setting up and maintaining this national registry should be made available by the competent authorities.

Recommendation 4
Although the format of the required data set will be tightly specified, flexibility will be needed 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.

Recommendation 5
After data have been submitted to the European Registry, quality assurance procedures should be performed before data are uploaded to the Registry itself.

Recommendation 6
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.

Recommendation 7
A relational database will be required to accommodate the data and web site produced that will allow data submission through the internet.

Recommendation 8
Regular reports that summarize the data held in the European Registry will need to be produced and disseminated.

Recommendation 9
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.

Recommendation 10
In the early stages of the formation of the European Registry, a greater number of staff will be needed for setting up the Registry and accepting the first submissions of data from participating countries, but there will be a continuing need for staff to facilitate the uploading of data from countries that join the Registry at a later stage.

2 Introduction

Although many European countries have national registries that include data on outcomes following solid organ transplantation, there are many advantages in having a pan-European registry. These include the ability to investigate outcomes following transplantation for rare conditions, to explore outcomes following the transplantation of organs from “extended criteria donors” and “non-standard risk donors” and to identify factors associated with the occurrence of rare adverse reactions following transplantation

One of the aims of the EFRETOS project is to provide a detailed specification of the data requirements for a European Registry and to describe the appropriate functional framework, a feasible technical approach and the organizational and legal prerequisites for realizing a pan-European registry. The EFRETOS consortium with members from 20 European countries will therefore be taking a first step towards the creation of this Registry of registries. Ultimately, this new European Registry could be used to gauge actual versus expected outcome of transplantation in Europe, and to evaluate best practices to promote health and safety standards in all Member States. This European Registry would also allow public health researchers to perform studies on risk factors for defined donor and patient populations. These objectives could be extended according to the need of the Registry partners.

This document provides a description of the data that will be required for a European Registry, and will indicate how data will be collected, how the quality of the registry data will be monitored, how such data might be presented, and who might have access to the data, The document also describes the technical, functional and legal requirements for creating and maintaining the European Registry. However, we begin with background information that has led to the establishment of the EFRETOS project.

2.1 Authorship

The executive summary was written by Jacqueline Smits and Axel Rahmel (both ET) and was based on documents drafted by (in alphabetical order) Thomas Breidenbach (DSO), Mario Caprio (CNT), Dave Collett (NHSBT), Carlo de Cilia (CNT), Beatriz Domínguez-Gil (ONT), Marja Guijt (ET), Rosario Marazuela (ONT), Jan Niesing (ESOT), Daniela Norba (DSO), Murk Schaafsma (ET), Helen Thomas (NHSBT) and Maria Valentin (ONT).

The chapter on content was written by Jan Niesing (ESOT), Maria Valentin (ONT) and Thomas Breidenbach (DSO). Dave Collett and Helen Thomas (NHSBT) wrote the chapters on methods and the pilot study. The introduction chapter and the chapter on functional requirements was written by Jacqueline Smits (ET). The chapter on governance was written by Axel Rahmel, Jacqueline Smits,and Arie Oosterlee (all ET). The chapter on technical requirements was written by Murk Schaafsma (ET). Mario Caprio and Carlo de Cillia (CNT) wrote the chapter on the quality assurance system. Marja Guijt (ET) and Daniela Norba (DSO) wrote the chapter on legal and ethical requirements. The chapter on organ vigilance systems was written by Rosario Marazuela, Beatriz Domínguez-Gil and Maria Valentin, (all ONT). Brigitta Exterkate (ET) drafted the International code of conduct for data exchange and Dave Collett wrote the chapter called Key points and Recommendations.

2.2 Actions of the Commission of the European Communities

This chapter gives a historical overview of the actions of the Commission of the European Communities regarding organ transplantation by listing crucial milestones that lead to the development of a draft Action Plan and a proposal for a legal framework on quality and safety in organ transplantation.

A survey carried out in 2003 by the Commission of the European Communities on the legal requirements related to organ transplantation in the EU has revealed discrepancies in quality and safety requirements within Member States.[4]

The Commission therefore stated that European cooperation is crucial for the evaluation of measures intending to enhance post-transplant results and to make the use of organ donors more effective and safe. This can be addressed more efficiently from a community perspective.[5]

In May 2007 the Commission adopted a Communication on organ donation and transplantation in which two mechanisms of action were proposed: a legal instrument containing the basic quality and safety principles in organ donation and transplantation and an Action Plan for strengthening the cooperation between Member States.[6] This Communication on organ donation and transplantation proposed an appropriate and flexible European framework as an adequate community response to meet the mandate provided in Art.152.4 a) of the Treaty. The future legal instrument based on a separate impact assessment, could include the principles needed to establish a basic quality and safety framework, such as the creation of competent authorities[1] and relevant structures. The proposed Action Plan should complement the legal framework with the compilation of sufficient information in form of a register that can facilitate the evaluation of post-transplant results and contribute to the development of good medical practices in organ donation and transplantation. The key aspects are traceability of the organ, reporting of serious adverse events and reactions, basis protection of the organ and organ characterization.

The European Parliament resolution of April 22, 2008 on organ donation and transplantation expressed the following policy actions at EU level[7]: (as) The European Parliament:

- Recognizes that it is vitally important to ensure the quality and safety of organ donation and transplantation; points out that this will have an impact in terms of reducing transplant risks and will consequently reduce adverse effects; acknowledges that actions on quality and safety could have an effect on organ availability and vice versa; asks the Commission to help Member States develop their capacity to create and develop national regulations and a regulatory framework to enhance quality and safety, without this having a negative impact on the availability of transplant organs.
- Acknowledges that post-transplant and post-donation results should be monitored and evaluated; stresses that a common methodology of data analysis should be promoted, on the basis of the best practices currently employed by Member States, in order to allow optimal comparability of results across Member States.
- Asks Member States to increase the monitoring times for transplant patients to several years and preferably for as long as the patient lives and/or the graft still functions.

And in an explanatory statement of this same European Parliament resolution it is mentioned that:

- Long-term follow-up and monitoring of patients following transplantation are also needed to evaluate the best treatment outcomes for patients. The monitoring and evaluation of post-transplant results is crucial and should therefore be carried out on the basis of a common methodology, which ensures the maximum health and safety standards in all Member States.
- The Committee stresses that closer cooperation between Member States is vital; suggests that exchange of best practice in the field of donation and transplantation should be stepped up and calls for the setting up of a data bank at Community level for the purposes of donation and transplantation.
- The Committee calls on the Commission and the Member States to launch a pan-European data base and communication network or to support an existing one in order to interconnect the national data bases and provide them with a platform for fast exchange of comprehensive data on organ donation and transplantations and on living and deceased donors.

[1] The definition of Competent Authorities is still under debate

The EU Action Plan on organ donation and transplantation has three priority areas of action:

- improving quality and safety of organs;
- increasing organ availability and
- making transplantation systems more efficient and accessible.

As mentioned earlier in order to respond to these objectives two different mechanisms of action were suggested and published on December 8, 2008: an Action Plan and an EU legal framework (Directive) on quality and safety.

In this Action Plan[8] several priority actions are set out; where priority action 9 was called: "Evaluation of post-transplant results" and was subdivided in the following four actions:

- develop common definitions of terms and methodology to evaluate the results of transplantation;
- development of register or network of registers to follow-up on organ recipients;
- promote common definitions of terms and methodology to help determine acceptable levels of risk in the use of expanded donors;
- develop and promote good medical practices on organ donation and transplantation on the basis of results, including the use of expanded donors.

The aim of this priority action is to develop common definitions and methodology to evaluate the results of transplantation. This action would facilitate the promotion of an EU wide register on the comparability of the results of existing registers to follow-up on organ recipients, monitor their health and evaluate results. This will permit the elaboration and promotion of good medical practices on organ donation and transplantation on the basis of the results. The data can furthermore assist in determining the acceptable levels of risk in the use of expanded donors. Finally, falling under the scope of the Directive, a system will be designed that can ensure that all organs can be traced from donation to recipient and vice versa. An organ vigilance system must have the capacity to raise the alert if there is any unexpected complication. Such a system should therefore be put in place to detect and investigate serious adverse events and reactions, for the protection of vital interest of the individuals concerned.[9] The resulting action of this system is to improve quality and safety of medical practices in the field of solid organ transplantation.

2.3 Rationale and objectives of the EFRETOS project

2.3.1 Rationale of this assignment

The overall objective of the EFRETOS project is to contribute to improve the effectiveness, the quality and the safety of human organs intended for transplantation by examining variation in outcomes.

This will be done by providing a system for all Member States for the management of solid organ transplant data, which would be viewed by participating centres/countries as a powerful, customized tool to foster their own research programs rather than being merely an additional reporting chore and expense. The evaluation of these post-transplant results through the use of common definitions will help to develop good medical practices in organ donation and transplantation

In addition this compilation of sufficient information by the Member States will assist in determining the acceptable levels of risk in the use of organs from deceased donors in general terms, and of organs from Non-Standard Risk Donors (NSRD) donors posing a non-standard or non-assessable risk for disease transmission.

An assurance system for obtaining high quality data needs to be created. The assessment of the quality of data from national contributors to the new European Registry by the use of the quality certificate - defined in the EFRETOS project - will help in identifying those countries where the data collection on outcome of solid organ transplantation is insufficient.

Safety in organ transplantation will be addressed comprehensively by also addressing the concept of organ vigilance and surveillance, through the release of a set of recommendations for the development of an organ vigilance system that can be useful for Member States when implementing provisions reflected in *Directive 2010/53/EU*. International data sharing on serious adverse events and reactions following the provided recommendations could be a further step in the understanding of the pan-European Registry.

2.3.2 Primary objective

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

Furthermore, EFRETOS intends to provide recommendations to Member States on the development of an organ vigilance system, in line with provisions of *Directive 2010/53/EU*.

2.3.3 Beneficiaries

The stakeholder- specific objectives are:

The EC and national governments
- the identification and promotion of good medical practices in organ donation and transplantation;
- the harmonization of the definition of terms and the quality assurance system will guide in interpreting the outcome data;
- the recommendations for setting up a well-functioning organ vigilance system will protect an already frail patient population from further harm.

The medical experts
- a common data dictionary and definitions will allow the evaluation and comparison of outcome throughout the Member States, thereby increasing knowledge and improve the monitoring of patients;
- the exchange of data on the use of non-standard risk donors will help in understanding the risk of disease transmission and as such will facilitate in determining acceptable levels of risk;
- the future European Registry can be used for research and bench-marking purposes;
- data exchange between the future European Registry and other existing registries could be considered in the future.

The patients
- an adequate risk assessment will minimize the risks for the recipient and increase utilization of the available donors by directive matching, therefore will help in achieving shorter waiting times, by reducing the need for a re-transplantation;
- the organ vigilance system will aid in protecting or helping other recipients.

2.4 A European Registry of registries

The proposed European Registry will include data on transplant activity and outcomes following solid organ transplantation.

Data will be delivered by the responsible bodies in the Member States. As national outcome data will be the focus of the future European Registry, single centres cannot deliver data to the registry, unless mandated by the national authorities. Double data entry should be avoided.

The Registry will contain national data at patient level. The data will be collected to an agreed standard of quality, and to agreed functional, technical and legal requirements. The data items to be collected will be described by a team of European experts.

The European Registry will be formed from three tiers of data. The first tier consists of the fundamental data on donor and recipient following a solid organ transplant. Provision of these data will be mandatory in order to provide for a basic 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, and besides, there will be a strong motivation to participate in the European Registry.

The second tier data, or basic data set are those data that are generally acknowledged to be of interest by medical experts. This list is different for the different organ types. 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. This set of data will include characteristics on donor and organ needed to undertake an adequate risk assessment in the use of organs from non-standard risk donors.

The expanded data set or third tier of data will be determined by medical experts and will reflect data that are needed for novel studies in organ transplantation and will also include information on socio-economic variables.

Methods designed to ensure compliance, completeness, integrity and security of the registry will be described in this document. An assurance system for obtaining high quality data will be described. The assessment of the data quality form national contributors to the new European Registry will be made through a quality assurance check that will help in assigning a “Quality certificate” to the countries that wish to contribute to the European Registry. Different levels of certification will be foreseen on the basis of the quality analysis of the collected data. Recommendations on the level of risk on the use of non-standard risk donors and the follow-up assessment of the recipients of organs from these donors will be provided.

A common definition of terms will allow the elaboration of and promotion of good medical practices on organ donation and transplantation throughout Europe. The identification of best practices between countries will be done by applying an appropriate case mix adjustment method. This method will be developed further during the project.

A proposal for the tasks and composition of a Registry Review Committee and Registry Management Board will be made. Future investigator initiated protocols will require Review Committee submission and approval. Members of this Review Committee should be democratically elected. During regular public meetings on the European Registry transplant physicians should be encouraged to not only consult the European Registry but also to develop their own hypotheses for additional questions. The Review Committee will also be responsible for data dissemination in the form of presentations on the current state of the registry, yearly detailed reports in a medical journal and on the web and a discussion of new protocols.

The collection, cleaning, management and hosting of data will require the existence of a Registry Central Staff. A description of the constitution and tasks of this staff will be provided. The assigned Registry Management Board will have the responsibility for this staff. In addition to providing the yearly reports, responses to analysis requests will be handled by the Registry Central Staff.

2.5 Non-standard risk donors and organ vigilance

2.5.1 Concept

Safety in solid organ transplantation will be addressed in a comprehensive way in the EFRETOS project: from the most common complications related to transplantation and immunosuppressive therapy to more specific issues as those related to the use of organs from NSRD and organ vigilance.

Some of the identified categories of **NSRD** include: donors with a past or present history of malignancy, donors with a positive serology for HCV, HBV or HIV, those with risk behaviours for viral infectious diseases or pitfalls in serology screening and donors with emergent or rare infectious diseases. Because many of these donors are infrequent or even not accepted in particular countries, obvious benefits will potentially derive from international data sharing on these donors and on the outcome of their recipients through the European Registry, by helping to establish the safety limits in the use of particular organs for transplantation.

Nevertheless, risk related to a specific donor or to the process from donation to transplantation can change after transplantation has been carried out. This variation in risk might even be identified after a complication arises in a particular transplant recipient. In the EFRETOS comprehensive approach to safety, these particular circumstances falling under the concept of **vigilance and surveillance** will need a particular focus. This is especially relevant in the current scenario set down by *Directive 2010/53/EU*, which requires Member States to develop and implement a system for reporting and managing serious adverse events (SAE) and serious adverse reactions (SAR). A SAE is defined as ”any unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life-threatening, disabling, or incapacitating conditions for patients which results in, or prolongs, hospitalization or morbidity”. In parallel, a SAR is defined as “an unintended response, including a communicable disease, in the donor or in the recipient associated with any stage of the chain from donation to transplantation that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity”.

2.5.2 Actions

EFRETOS will identify specific variables relevant for the assessment of NSRD and the outcome of their recipients, through a literature review, the evaluation of currently run specific data collections and expert discussions. These variables and corresponding definitions will be incorporated into the previously described data sets (either as tier 1, 2 or 3).

From the perspective of organ vigilance, a set of recommendations for the development of an organ vigilance system that can be useful for Member States when implementing provisions reflected in *Directive 2010/53/EU* will be developed. Moreover, the agreement to be achieved during the project lifetime will make possible a common EU understanding on organ vigilance of special relevance for organs exchanged between countries. International data sharing on SAE and SAR could be a further step in the understanding of the pan-European registry, noting that the reporting, assessment and management of SAR, as well as the required maintenance of traceability, is a national competence, not to be attained through the European Registry of registries itself.

3 Content

3.1 Methodology

In deriving at the content of the new European Registry of registries, a thorough approach was chosen, as will be outlined in this chapter. As a first step, a survey was conducted of the major (mostly national) registries that currently exist in Europe. In addition the American Scientific Registry of Transplant Recipients (SRTR) was taken up in the survey, as this registry has been in operation and quality tested for many years.

After combining and ordering all the available variables in the existing registries, teams of experts were called in to carefully go through all these variables with the instruction to rate the variables according to their necessity of being included in the European Registry for proper evaluation of transplant outcomes. Several levels of importance were included.

After proper variable selection was concluded the third step of the process was to arrive at a consensus on the preferable and optimal description of the variable and the way it preferably should be scored (continuous, ordinal, nominal with value labels, etc.). With each variable, more than one outcome was possible, given its complexity and differences in gathering the variable in question in the different registries in Europe, from which the final European Registry is expected to draw its content. Also, it is possible that for some undeveloped variables a further development or refinement will be recommended.

The selection and definition of additional variables for the evaluation of organ transplants from non-standard risk donors, is part of this process and part of the efforts of the expert groups, and will be addressed at the end of this chapter.

3.1.1 Survey on currently used data sets

ESOT has been given the task of making an inventory of all available and all possible variables for creating a European Registry and the task of developing a common data dictionary. For this, information on the major transplantation registries with experience in data collection was gathered from the participants in the project. In short, information was received from the six participating European organ transplant organizations ONT, CNT, SKT, ABM, NHSBT and ET. This information was delivered either in electronic form or in the form of entry forms for the respective registry. This information was partly in English, but often translations had to be made in order to compare the contents of the different registries.

After having compiled and ordered the variables currently used in the diverse data bases, the following groups of variables were formed:

- variables on the recipient before transplantation (screening variables);
- variables on the transplant procedure, including the pre-transplant evaluation of the recipient and the follow-up of the recipient until hospital discharge;
- variables on the follow-up of the patient in the period following transplantation, until either graft lost or patient death;
- variables on the post-mortem donor and the organ retrieved for transplantation;
- variables on the living donor, as far as these variables had any possible connection to the function and quality of the donated organ after transplantation. Living donor follow-up was left out explicitly, because this fell outside of the scope of this project.

3.1.2 Expert groups

A project organization was set up in which three expert groups were formed around the different type of organ transplantations. Each expert group was chaired by one of the experts. Experts were selected from all over Europe.

The composition of the Expert Groups is as follows:

Kidney & Pancreas Transplantation Expert Group
1. Andries Hoitsma, The Netherlands, (Chair)
2. Frans Zantvoort, Bremen, Germany
3. Yves Vanrenterghem, Leuven, Belgium
4. Reinhard Kramar, Wels, Austria
5. Jean Paul Soulillou, Nantes, France
6. Paul Harden, Oxford, United Kingdom
7. Peter Friend, Oxford, United Kingdom
8. Roger Lehmann, Zurich, Switzerland

Heart & Lung Transplantation Expert Group
1. Andreas Zuckermann, Heart, Vienna, Austria (Co-Chair)
2. Bruno Meiser, Munich, Germany (Co-Chair)
3. Marisa Crespo-Leiro, La Coruna, Spain
4. Florian Wagner, Hamburg, Germany
5. Johan Vanhaecke, Leuven, Belgium
6. Lieven Dupont, Leuven, Belgium

Liver & Intestine Transplantation Expert Group
1. Patrizia Burra, Padua, Italy, (Chair)
2. René Adam, Villejuif, France
3. Andrew K Burroughs, London, United Kingdom
4. Paolo Muiesan, Birmingham, United Kingdom
5. Michele Colledan, Bergamo, Italy
6. Michael Olausson, Gothenburg, Sweden

Activities of the expert groups were steered and overseen by project leader Prof. R.J. Ploeg, Kidney & Intestine Transplant Surgeon, University Medical Centre Groningen (UMCG) Groningen, President of ESOT, while content for the expert group was provided by secretary and project coordinator Dr. Jan Niesing, scientific researcher UMCG/ESOT.

Communication between members of the expert groups took place on a regular basis through e-mail contact and with the use of an especially for this purpose created internet community on the ESOT web site.

3.1.3 Working methods and responsibilities of participants

The chairs of the expert groups:

- participated in the steering committee;
- recruited the members of their expert group, in cooperation with the project leader and the project coordinator;
- were responsible for the contributions of the experts to the end results;
- attended meetings of the expert groups and the WP4 working group, as well as Management Board meeting when invited.

All experts were regularly required to comment on the variables proposed and currently collected and give their approval or proposals for data dictionaries and measurement definitions presented to them.
The expert groups held several meetings to discuss the content of the European Registry.

The results of the expert groups were firstly to achieve consensus on a comprehensive list of variables that could be included in the European Registry, following classification rules as described in section 3.1.1 and 3.2. These lists were presented to the WP4 working group where, in the presence of the chairs of the expert

groups, the final decision was made on the proposed variables. The Management Board was responsible for the final decision on the data set.

After variables were selected for each of the categories presented in section 3.1.1 and 3.2, the currently used data dictionaries were added to the variables and sent to the expert groups for comments and recommendations. This process lasted from May to September 2010. This was quite a challenge, because each data set uses different definitions for the same variable. The purpose now was to achieve consensus on the preferable definitions.

This second rating process was again conducted via e-mail and the ESOT community at first, and saw finalization in an expert meetings.

The tasks above represent the major responsibilities of the expert groups.

3.2 Common data dictionary and common definition of terms

As explained earlier, the new European Registry will receive its data from existing national (or supra-national) registries. However, this European Registry might become a strong incentive to increase the number of variables collected by participating countries. It was therefore decided not to place any limits on variables to be recommend by the experts for inclusion and new or currently not widely collected or available variables could be included in the definitions for the data sets of the European Registry.

The main question that was emphasized was: “Is a variable valuable for the evaluation of (diverse aspects of) organ transplantation?” Experts were asked to look at this from a medical viewpoint, but also from a policy viewpoint.

The classification of the variables has two main levels: *basic* and *expanded*. The basic data are mandatory for participating countries, the expanded data are optional. Within the basic category, there is a subdivision into *minimum* mandatory data set.

3.2.1 Basic data

This set contains all variables, generally acknowledged as of vital interest for a comprehensive evaluation of transplant outcomes. All participating countries are required to collect all the basic variables for the European Registry. However, since this list is comprehensive, not all participating countries are currently collecting all of these variables. Moreover, some European countries that are just starting to register information on transplant outcomes on a national level, start of their collection with a relatively small number of variables and are years away from the collection of all variables in the basic category. Therefore it would be unwise to restrict participation in the European Registry to only those countries that can comply with this requirement. For this reason the basic category, although mandatory, will not be enforced as such. However, all participating countries will be required to state the timeframe within which they plan to be able to gather all variables in the basic category and deliver them to the European Registry.

3.2.2 Minimum mandatory data

A minimum mandatory set of the variables in the basic category is defined. The variables in this sub category of the basic category were deemed so important for any evaluation of transplant outcomes, that all countries willing to participate must be able to deliver this minimal set to the European Registry.

3.2.3 Expanded data

Included in the expanded data set is all data that is deemed medically interesting and relevant for evaluation of transplants, but not essential enough to be part of the basic data set at this time.

This data is of medical interest and relevant for evaluation of organ transplants, but not likely to become available in all current leading registries. The reasons for this can be various, i.e. they are only of regional interest, they pertain to population characteristics not prevalent in other regions, they are gathered using expertise not widely available, they represent advanced medical issues or study purposes not deemed important in other regions. However, the combination of even a small number of data sets (of several countries/registries) with these variables may be of great value.

Summarizing, participants in the European Registry will be required to deliver all variables in the minimum mandatory category in order to be allowed to participate. Furthermore they must draw up a timeline for the expansion of their data set to include all variables in the basic data set. Variables in the expanded category should be delivered to the new European Registry when available, but the collection of these variables is optional and the decision for collecting these is left to all participating countries.

3.3 Set of variables

3.3.1 Introduction

At the end of June 2010, the set of variables to be collected for the European Registry of Registries was decided upon by the Management Board of the project based on the recommendations of the ESOT expert groups and the variables proposed by WP6 with regard to non-standard risk donors. In the months that followed, the members of the different organ specific expert groups were requested to provide definitions for the selected variables taking into account already existing definitions in the different European countries or already existing multinational organ specific registries. This approach was aiming at optimal harmonization with existing registries and thereby laying the basis for broad acceptance in all European countries. For this purpose meetings of the expert groups took place in August and September 2010, followed by some individual meetings with the chairs of the organ specific subgroups to finalize the proposals.

The variables selected are divided into three tiers.

Basic data (Tier 1 and Tier 2 data)

These are all variables that are considered to be of upmost importance and therefore mandatory for the evaluation of organ transplantation. These variables have been divided into two sub categories.

Mandatory data (Tier 1 data)

There will be a minimum mandatory set of basic data. These variables are considered essential and are the same for all countries. To enter and for participating in the future European Registry of registries a country must be able to deliver this minimum mandatory data set to the European Registry right from the beginning of its participation.

Mandatory data with transitional time frame (Tier 2 data)

Collection of these variables by the European Registry is also deemed essential. However, it is recognized by the organ transplantation expert groups and the EFRETOS consortium members that these variables are currently not routinely collected by all National Registries. Therefore, each country that enters the European Registry is given a period of transition, in which it can adjust its organisation in such a way that the requested Tier 2 variables can be included in the National Registry and thus delivered to the European Registry. The exact period of transition allowed for each country entering EFRETOS will have to be decided upon by the body overseeing the data upload to the European Registry at that time.

Data definitions Tier 1 and Tier 2 data

For most variables a uniform definition could be agreed upon by the experts representing the different countries and the different organs. For a few variables on the other hand it was decided to allow data delivery with the coding systems used in the different national registries (donor cause of death, Primary (recipient) diagnosis, primary cause of graft failure, cause of death after transplantation, cause of graft failure). In addition these items will also be collected using a standardized, internationally established coding system (For liver and intestine: European Liver Transplant Registry (ELTR), for heart and lung: International Society for Heart and Lung Transplantation (ISHLT), for kidney and pancreas: ICD-10-code).

Expanded data (Tier 3 data)

Included in the Expanded data set are all variables that are deemed medically interesting and relevant for evaluation of transplants, but not essential enough to be part of the basic data set at this time.
These are data that are not likely to become available in all countries and/or not for 100% of all transplants. The reasons for this can be various, i.e. they are only of regional interest, they pertain to population characteristics not prevalent in other regions, they are gathered using expertise not widely available, they represent advanced medical issues or study purposes not deemed important in other regions. However, the combination of even a small number of these variables can be of great importance for research purposes.
These data shall be delivered to the European Registry when available, but completeness of the variables (100% filled) is not a requirement.

Conditional variables

For a number of variables, the label ‘Conditional’ is added. These are variables that are to be collected, only if a certain condition has been fulfilled. For instance, only if a tumour is present, a description of this tumour has to be delivered. The specific condition that has to be fulfilled is given in the ‘Definition’ column. These variables are not included in the overall count of variables per tier.

Option ‘Unknown’

The option “Unknown” as a possible answer is included in many variables. “Unknown” may only be entered, if the exact value is not available and can’t be obtained anymore and a transparent reason for the absence of this value is provided. All other data not provided will be considered as “Missing”. Using this definition, “Unknown” has a different status from “Missing”. In the calculation of completeness of a variable, “Unknown” is counted as a valid entry. Only “Missing” data reduce the calculated data completeness.

Marked variables

The variables marked with an asterisk *, correspond to those provided by the work package 6 (safety management). Definitions and explanations on these variables are available in Deliverable 3 and Deliverable 10 part I.

Multiple measurements of the same variable

For a number of variables, multiple measurements at different time points will be required, e.g. Serum Creatinine. Recipient data can be collected in three main timeframes: (1) “Pre Transplantation”, (2) Transplantation and Follow-up until Discharge from the hospital after transplantation (rehospitalisation not included), and (3) Follow-up after Discharge. A number of variables have to be collected in two or three of these periods. Although these variables are mentioned more than once, they are only counted once for the total number of variables included in the registry. In the case a variable is mentioned more than once, corresponding variable numbers are included between brackets.
Measurements of the same variable in donor and recipient on the other hand are considered as different variables.

Calculated or derived variables

These have no tier attached to them, because they are generated or derived from other variables included in the registry. If they are missing, the cause lies in the variables from which they are derived. The tier that applies to the underlying variables suffices.

Total number of variables for the different tiers

Many variables are assigned to the same tier for all organs, e.g. Donor and Recipient Gender. However, some variables are considered to be only of relevance for the evaluation of the transplantation of one type of organ, these variables form the organ specific part of the data set. In addition some variables should be collected for all types of donor organs and related transplants but they were considered to be more important for one type of organ (e.g. lungs) than for the others. Therefore a higher tier was assigned for the one type of organ (e.g. lungs) and a lower tier for the others. In the attached overview variables that have received the same tier for all organs (tiers common for all organs) are presented separately from those variables that have received organ specific tiers. In case a variable was rated Tier 1 for one organ and Tier 2 or 3 for another organ, this variable is mentioned twice, with the numbers of the corresponding variable added between brackets.
The total number of Tier 1 variables, common for all organs, is 37. For each of the individual organs, there are between 1 and 5 organ specific Tier 1 variables. Additionally, there are 22 Tier 2 variables, common for all organs, with each organ adding between 4 and 8 organ specific Tier 2 variables. As for Tier 3 variables, there are 66 common for all organs. As for Tier 3 variables, there are 66 common for all organs. The number of variables for each individual organ is 24 for kidney, 19 for pancreas, 70 for heart, 86 for lungs, 47 for liver and 54 for intestine. The difference in the number of Tier 3 variables reflects the complexity of the transplantation of the different organs.

Final Concept

This final concept was then discussed in detail in a meeting of the EFRETOS Management Board on November 19th 2010 at Schiphol Airport. At this meeting, the chairs of the expert groups were present to present and explain their choices and react to all proposals for adaptations from members of the Management Board. Because the number of variables was, and is, still very extensive, discussion was mostly, but not completely limited to variables suggested to be included in Tier 1 or Tier 2 of the European data set. The Tier 1 and Tier 2 variable selection and definition was finalized on the next Management Board meeting at Schiphol Airport on November 29, 2010.
Definitions of the Tier 3 variables were not discussed at this point in time. As the variables in Tier 3 of the data are not mandatory and will probably concern the most fluctuating part of the future European Transplant Registry, it was concluded that their definition has to follow at a later stage when the European Transplant Registry is already operational. Because the expert groups have agreed on the selection of the initial Tier 3 variables and some comments on variables of this tier were already collected, all three tiers are presented in this document.

3.3.2 Variable overview

Donor Variables

Tier 1 Donor Variables, common for all organs

Nr	Variable name	Definition	Unit or coding
D1.1	Donor ID	National ID code, same as used in the National or Regional registry that delivers the data.	Alphanumerical code
D1.2	Donor Gender	Donor's gender	M, F
D1.3	Donor Blood Group	Donor's blood group	A, B, AB, O, Unknown
D1.4	Donor Height	Donor's body height	in cm, no decimals
D1.5	Donor Weight	Donor's body weight	In kg, no decimals
D1.6	Donor Age in Years at Organ Donation	Donor age in years at time of organ donation. For children under the age of two the value will be recorded with an exact first decimal. For all other ages it will be recorded with “0” as the first decimal.	Years with one decimal point
D1.7	Donor Cause of Death	Two separate fields: one for coding system used and one for the respective death code	Alphanumerical code
D1.8	Unified Cause of Death	For Liver and Intestine: ELTR, For Heart and Lung: ISHLT For Kidney And Pancreas: ICD-10.	Alphanumeric
D1.9	Cause of death: acute intoxication*	For Non Standard Risk Donors	Yes, No
D1.10	Donor Type	Type of donor	DCD, DBD, Living
D1.11	Malignant tumours in the donor*		Yes, No, Unknown

Tier 1 Donor Variables, organ specific

Nr	Variable name	Definition	Unit or coding	Organ(s)
D1.12 (D3.24)	Donor HLA - typing A-B-DR (1-2) antigen	Split in six variables: A1, A2, B1, B2, DR1, DR2	Alphanumeric, letters and numbers. One string variable.	Kidney

Tier 2 Donor Variables, common for all organs

Nr	Variable name	Definition	Unit or coding
D2.1	Perfusion Fluid	Perfusion fluid used during procurement	Euro Collins, University Wisconsin, Phosphate Buffered Sucrose (PBS), Celsior, Bretschneider, Custodiol, Marshall, Soltran, Low Potassium Dextran, St Thomas’, Papworth Solution, Perfadex, Ringers, Other
D2.2	Anti-CMV	IgG	Reactive, Non-Reactive, Unknown
D2.3	Anti-EBV	IgG	Reactive, Non-reactive, Unknown
D2.4	HIV (I/II) Ab*	Antibodies against Human Immunodeficiency virus subtype 1 or 2.	Reactive, Non-reactive, Unknown

Nr	Variable name	Definition	Unit or coding
D2.5	HBsAg*	Surface antigen of hepatitis B virus.	Reactive, Non-reactive, Unknown
D2.6	HBsAb*	Antibodies against hepatitis B virus surface antigen.	Reactive, Non-reactive, Unknown
D2.7	HBc Ab*	Antibodies against hepatitis B virus core antigen.	Reactive, Non-reactive, Unknown
D2.8	HCV Ab*	Antibodies against hepatitis C virus.	Reactive, Non-reactive, Unknown
D2.9	Risk factor for infection: IV Drug user*		Yes, No, Unknown
D2.10	Moment of Diagnosis* **Conditional**	Organ specific variable. Condition: Only when Post Transplant Malignancy is `Yes`.	Previously known, Incidentally found before transplantation, Incidentally found after transplantation
D2.11	Cranial location of tumour*** Conditional**	Condition: Only when Post Transplant Malignancy is `Yes`.	Intracranial, Extracranial
D2.12	Kind of Intracranial Tumour* **Conditional**	Condition: Only when Kind of tumour Detailed is `Intracranial´	Medulloblastoma, Astrocytoma, Glioblastoma, Oligodendroglioma, Ependymoma, Meningioma, Other, Unknown
D2.13	Other Kind of Intracranial Tumour* **Conditional**	Condition: Only when Kind of Intracranial Tumour is ´Other´	String
D2.14	Kind of Extracranial Tumour* **Conditional**	Condition: Only when Kind of tumour is `Extracranial´	Renal Cell Carcinoma (RCC), Prostate Adenocarcinoma, Breast Cancer, Lung Cancer, Colorectal Cancer, Oesophagus Carcinoma, Pancreatic Carcinoma, Hepatocellular Carcinoma, Thyroid Carcinoma, Ovarian Cancer, Chorioncarcinoma, Sarcoma (including GIST), Malignant Melanoma, Non Melanoma Skin Cancer (Basal Cell Carcinoma, Spinocellular Carcinoma), Carcinoma in situ, Low grade Lymphoma, High grade Lymphoma, Leukaemia, Other, Unknown
D2.15	Other Kind of Extracranial Tumour* **Conditional**	Condition: Only when Kind of Extracranial Tumour is ´Other´	String

Tier 2 Donor Variables, organ specific

Nr	Variable name	Definition	Unit or coding	Organ(s)
D2.16	History of Cigarette Use	Accept all definitions in national registries.	Pack years	Heart, Lung
D2.17	INR: Prothrombin time		%	Liver, Intestine
D2.18	Total Bilirubin		mg/dl	Liver, Intestine

Tier 3 Donor Variables, common for all organs

Nr	Variable name	Definition	Unit or Coding
D3.1	DCD specification **Conditional**	Condition: only applies when Donor Type = DCD.	DCD Category I, DCD II, DCD III, DCD IV
D3.2	Donor Nationality	Nationality of donor. Only one nationality is registered. Which Nationality is entered is left up to the National Registry.	ISO-Code 3166
D3.3	Country of origin*		ISO-Code 3166
D3.4	Ethnic Origin	No clear standard exists. It is proposed to use a set of ethnicities with a "Yes, No" answer. More than one variable with "Yes" means there is mixed ethnicity.	
D3.5	Toxic substance involved* **Conditional**	Condition: If D1.9 is "Yes".	Amanita Phalloides, Barbiturics, Benzodiazepines, Carbon Monoxide, Chloroquines, Cocaine, Cyanur, Dextropropoxylen, Escstasy, Ethanol, Ethylenglycol, Hydrocarburs, Isoniacid, Lead, Methanol, Neuroleptic, Organophosphorade, Pesticides, Paracetamol, Rodenticides (dicumarin), Theophylline, Tricyclic antidepressants, Unknown, Other
D3.6	Other Toxic substance involved * **Conditional**	Condition: When 'Toxic substance involved' is 'Other'.	String
D3.7	Haemodilution*		Yes, No, Unknown
D3.8	HTLV (I/II) Ab*	Antibodies against Human T-Lymphotropic virus.	Reactive, Non-reactive, Unknown
D3.9	Inotropes		Yes, No
D3.10	Last dose		µg/kg/min
D3.11	HBV DNA*	Number of copies of HBV virus tested by PCR (polymerase chain reaction).	Number of copies
D3.12	HCV RNA*	Number of copies of HCV tested by PCR.	Number of copies
D3.13	Cardiac arrest	Cardiac arrest before donation procedure	Yes, No, Unknown
D3.14	Duration of cardiac arrest		Minutes
D3.15	Risky sexual behaviour*		Yes, No, Unknown
D3.16	Risk factor for infection: Recent travel to endemic country or region*	Risk factor for emergent diseases	Yes, No, Unknown
D3.17	Endemic country or region of recent travel*	Specification of country or region of recent travel.	String

Nr	Variable name	Definition	Unit or Coding
D3.18	Trypanosome Cruzi Ab*	Antibodies against Tripanosoma Cruzi (causal agent of Chagas disease.	Reactive, Non-reactive , Unknown
D3.19	Plasmodium spp*	Direct test to find plasmodium spps (causal agent of malaria)	Positive, Negative, Unknown
D3.20	Other emergent diseases*		String
D3.21	Tumour free time* **Conditional**	Period of time in which the neoplasia is considered cured (0 is considered a current process). Condition: Only when Tumour is "Yes" and Moment of Diagnosis is "Previously known".	Years, one decimal
D3.22	Tumour Grading* **Conditional**	Depending on the type of tumour. Condition: Only when Tumour is "Yes"	
D3.23	Tumour Staging* **Conditional**	Depending on the type of tumour. Condition: Only when Tumour is "Yes"	

Tier 3 Donor Variables, organ specific

Nr	Variable name	Definition	Unit or Coding	Organ(s)
D3.24 (D1.12)	Donor HLA - typing A-B-DR (1-2) antigen	Split in six variables: A1, A2, B1, B2, DR1, DR2	Alphanumeric, letters and numbers. One string variable.	Pancreas, Heart, lung, Liver, Intestine
D3.25	Donor Rhesus Factor	Donor's Rhesus Factor	Pos, Neg	Heart, Lung, Liver, Intestine
D3.26	Living donor specification **Conditional**	Living related: blood related, child or through parent or grandparent Living unrelated: partner or friend. Condition: Donor Type = Living.	Domino, Living related, Living unrelated, Altruistic	Kidney, Heart, Lung, Liver
D3.27	Living donor relation to recipient **Conditional**	Condition: Donor Type = Living.	Mother, Father, Sister, Brother, Son, Daughter, Cousin, Other family, Spouse, Friend, None	Kidney, Heart, Lung, Liver
D3.28	Machine Perfused		Yes, No, Unknown	Kidney, Pancreas, Heart, Lung
D3.29	Perfusion Completed Date/Time		Date, Time	Lung
D3.30	Perfusion Method		ECMO, Cold perfusion	Lung, Liver, Intestine
D3.31	Anti-toxoplasma		Reactive, Non-reactive, Unknown	Heart, Lung,
D3.32	Syphilis TPHA		Reactive, Non-reactive, Unknown	Heart, Lung,
D3.33	Diabetes		Yes Type I, Yes Type II, No	Kidney, Pancreas, Heart, Lung

Nr	Variable name	Definition	Unit or Coding	Organ(s)
D3.34	History of Hypertension	As assessed by the physician.	Yes, No, Unknown	Kidney, Pancreas, Heart, Lung
D3.35	Alcohol		No, Occasional drinker, Social drinker, Alcohol abuse	Heart, Lung, Liver, Intestine
D3.36	History of Cigarette Use		Pack years	Liver, Intestine
D3.37	Bacterial Infection		Yes, No, Unknown	Heart, Lung, Liver, Intestine
D3.38	Viral Infection		Yes, No, Unknown	Heart, Lung, Liver, Intestine
D3.39	Parasitic infection		Yes, No, Unknown	Heart, Lung, Liver, Intestine
D3.40	Mycosis		Yes, No, Unknown	Heart, Lung, Liver, Intestine
D3.41	Lowest Creatinine		µmol/l or mg/dl	Kidney, Pancreas
D3.42	Proteinuria	This is defined for an undetermined amount of urine, hence gram/l.	gram/l	Kidney
D3.43	Hematocrit		%	Heart, Lung
D3.44	Coronary Angiogram		Yes, No, Unknown	Heart
D3.45	Coronary Disease		Yes, No, Unknown	Heart
D3.46	Echocardiogram		Normal, Abnormalities, Not available	Heart
D3.47	Intubation Time		Hours	Lung
D3.48	Lungs: Results from chest radiograph	Results from chest radiograph	Clear, Not clear	Lung
D3.49	Left Lung Bronchoscopy:		Normal, Not normal	Lung
D3.50	Right Lung Bronchoscopy:		Normal, Not normal	Lung
D3.51	Blood gasses: %FiO2		Percentage	Lung
D3.52	Blood gasses: 40% PEEP 5		Number	Lung
D3.53	Blood gasses: 100% PEEP 5		Number	Lung
D3.54	Blood Gasses: %SAT		Percentage	Lung
D3.55	Blood gasses: PCO2		Number	Heart, Lung
D3.56	Blood gasses: PO2		Number	Lung

Nr	Variable name	Definition	Unit or Coding	Organ(s)
D3.57	Blood gasses: HCO3		Number	Lung
D3.58	Blood gasses: O2 Saturation		Percentage	Lung
D3.59	Blood gasses: HCO3		Number	Lung
D3.60	SGPT/ALT	ALT or AST has to been filled in, (=Tier 1).	U/l	Liver, Intestine
D3.61	SGOT/AST	ALT or AST has to been filled in, (=Tier 1).	U/l	Liver, Intestine
D3.62	Amylase			Intestine
D3.63	GGT		U/l	Liver, Intestine
D3.64	Liver Biopsy		Yes, No, Unknown	Liver
D3.65	% Macro vesicular fat		Number, percentage	Liver
D3.66	Donor pretreatment		Yes, No, Unknown	Intestine
D3.67	Donor feeding (>1000 kcal in last 24 hrs.)		Yes, No, Unknown	Liver, Intestine

Calculated or derived Donor Variables

Nr	Variable name	Definition	Unit or coding	Organ(s)
D4.1	Cause of Death coding system specific codes	Contains the values of the Cause of Death codes used by the National Registries.		All
D4.2	Expected TLC	Total Lung Capacity. Calculated from length.		Lung
D4.3	Serum Creatinine Unit		µmol/l or mg/dl	Kidney, Pancreas

Recipient Pre-Transplantation Variables

Tier 1 Recipient Variables, common for all organs

Nr	Variable name	Definition	Unit or Coding
R1.1	Patient's Gender	Patient's Gender	M, F
R1.2	Patient's ABO Blood Group	Patient's Blood Group Type	A, B, O, AB, Unknown
R1.3	Primary Diagnosis	All codings from National Registries are stored: one variable describing which coding system (see derived variables) is used and one with the National coding.	Alphanumeric
R1.4	Date of Birth	Date of birth of recipient	DD-MM-YYYY
R1.5	Unified Primary Diagnosis	For Liver and Intestine: ELTR, For Heart and Lung: ISHLT For Kidney And Pancreas: ICD-10.	Alphanumeric
R1.6	Country of Residence	Country where the recipient resides most of the year, or has its main address.	ISO-Code 3166
R1.7	Listing Date	Date recipient was added to the waiting list. Can be entered separately for every transplant (first, second, etc.).	DD-MM-YYYY

Tier 1 Recipient Variables, organ specific

Nr	Variable name	Definition	Unit or coding	Organ(s)
R1.7	Urgency of candidate at time of transplantation	Variable reflecting severity of disease. If transplantation is not registered as urgent or with high priority, it is elective.	Urgent, Elective	Heart, Lung
R1.8 (R3.25)	Last Absolute Creatinine before transplantation	Most Recent Absolute Creatinine before transplantation.	µmol/l or mg/dl	Liver
R1.9 (R3.26)	Date Candidate went on Dialysis **Conditional**	Date the recipient went on dialysis for the first time, before his first transplantation. For second and third transplantations, this variable is not entered.	DD-MM-YYYY, 99-99-9999 must be used for 'No Dialysis'.	Kidney, Liver
R1.10 (R3.36)	Serum Albumin	Serum Albumin (used for CPT)	g/l	Liver
R1.11 (R3.37)	Total Serum Bilirubin	Total Serum Bilirubin (used for MELD/CPT)	mg/dl, no decimals	Liver
R1.12 (R3.38)	INR	INR (used for MELD)	% Integer, No decimals	Liver

Nr	Variable name	Definition	Unit or coding	Organ(s)
R1.13	Indication: impaired quality of life	How this is judged is left open, because there are so many different possibilities. The intention is that for intestine recipients there has always been a measure of the quality of life. Whether and how these different measures can be compared is an open question for the future.	Yes, No, Unknown	Intestine
R1.14	Indication: loss of venous access		Yes, No, Unknown	Intestine
R1.15	Indication: TPN induced liver cirrhosis		Yes, No, Unknown	Intestine
R1.16	Indication: recurrent line sepsis		Yes, No, Unknown	Intestine

Tier 2 Recipient Variables, common for all organs

Nr	Variable name	Definition	Unit or coding
R2.1	HIV (I/II) Ab*		Reactive, Non-reactive, Unknown
R2.2	HBsAg*		Reactive, Non-reactive, Unknown
R2.3	HBsAb*		Reactive, Non-reactive, Unknown
R2.4	HBc Ab*		Reactive, Non-reactive, Unknown
R2.5	HCV Ab*		Reactive, Non-reactive, Unknown

Tier 2 Recipient variables, organ specific

Nr	Variable name	Definition	Unit or coding	Organ(s)
R2.7	Vaccination for hepatitis B*		Yes, No, Unknown	Liver
R2.8	B Delta **Conditional**	Condition: for HBV positive recipients registered for liver tx	Reactive, Non-reactive, Unknown	Liver
R2.9	Duration of Abstinence of drinking before transplantation	Will often need to be calculated from duration of abstinence at time of listing, and period between date of listing and transplantation date.	Months 999 = Never drank	Liver
R2.10	Life Support Medication	Inotropes.	Yes, No, Unknown	Heart, Lung
R2.11	Life Support Ventilation		Yes, No, Unknown	Heart, Lung
R2.12	Life Support Mechanical Assist Device	General variable combining use of life supporting mechanical assist devices ECMO, IABP, VAD, Novalung, ILA, and other devices	Yes, No, Unknown	Heart, Lung
R2.13	Prothrombin Time used for CPT		%, one decimal	Liver

Nr	Variable name	Definition	Unit or coding	Organ(s)
R2.14	Last Serum Sodium	Translate µmol/l into mg/dl (used for MELD Sodium or UK MELD)	mg/dl	Liver
R2.15	Recipient presence of Ascites prior to transplantation	Recipient presence of Ascites prior to transplantation (used for CPT)	None, Controlled with medication, Refractory (poorly controlled)	Liver
R2.16	Recipient presence of Encephalopathy prior to transplantation	Recipient presence of encephalopathy prior to transplantation (used for CPT)	Grading 1 to 4	Liver
R2.17	Number of central venous access sites		Number	Intestine

Tier 3 Recipient Variables, common for all organs

Nr	Variable name	Definition	Unit or coding
R3.1	Rhesus factor	Rhesus factor	Positive, Negative
R3.2	Recipient's Nationality	Nationality of recipient. Only one nationality is registered.	ISO-Code 3166
R3.3	Number of pregnancies	Include also abortions	Number
R3.4	CMV serology of recipient IgG	CMV serology of recipient IgG antibodies before transplantation	Reactive, Non-reactive , Unknown
R3.5	EBV of the recipient IgG	EBV serology of recipient IgG before transplantation	Reactive, Non-reactive , Unknown
R3.6	Risk factor for infection*	Risk factor for emergent diseases (born in an endemic country, recent travel to endemic country or region, parents or sexual partner coming from endemic area):	Yes/no/unknown
R3.7	Endemic country or region of recent travel*	Specification of country or region of recent travel.	String
R3.8	HTLV (I/II) Ab*	Antibodies against Human T-Lymphotropic virus.	Reactive, Non-reactive , Unknown
R3.9	Trypanosome Cruzi Ab*	Antibodies against Tripanosoma Cruzi (causal agent of Chagas disease).	Reactive, Non-reactive , Unknown
R3.1	Plasmodium spp*	Direct test to find plasmodium spps (causal agent of malaria).	Positive, Negative, Unknown
R3.12	Other emergent diseases*		String
R3.13	HBV DNA* **Conditional**	Condition: In case HBsAg is 'reactive'.	Number of copies
R3.14	HCV RNA*		Number of copies
R3.15	Cigarette use	Smoking daily before transplantation	Yes, No, Unknown
R3.16	Ethnic Origin	No clear standard exists. It is proposed to use a set of ethnicities with a "Yes, No" answer. More than one variable with "Yes" means there is mixed ethnicity.	

Nr	Variable name	Definition	Unit or coding
R3.17	Patient's Educational Status	Patient's Educational Status at registration.	Local Country Specific Education System codes.
R3.18 (F3.6)	Patient's Employment Status Pre Transplantation	Patient's Employment Status Pre Transplantation	Full time, part time by choice, part time due to disability, part time due to treatment, part time due to inability to find full time work, part time no reason, unknown, homemaker
R3.19	Diabetes		Yes, No, Unknown
R3.20	Cerebrovascular Disease	Positive if anamnesis shows history of cerebrovascular disease that required hospitalization.	Yes, No, Unknown
R3.21	Peripheral Vascular Disease	Positive if anamnesis shows history of peripheral vascular disease that required hospitalization.	Yes, No, Unknown

Tier 3 Recipient Variables, organ specific

Nr	Variable name	Definition	Unit or coding	Organs(s)
R3.22	Activation Date **Conditional**	Date waiting time clock started: Can only be entered for first time listing (first transplantation).	DD-MM-YYYY	Kidney, Pancreas, Heart, Lung
R3.23	Total active waiting time at time of transplantation	All separate active waiting status periods added together at time of transplantation.	Months, no decimal	Heart, Lung
R3.24	Duration of last urgency status at time of transplantation		Days, no decimal	Heart, Lung
R3.25 (R1.8)	Last Absolute Creatinine before transplantation	Most recent absolute serum creatinine before transplantation.	µmol/l or mg/dl	Kidney, Pancreas, Heart, Lung, Intestine
R3.26 (R1.9)	Date Candidate went on Dialysis **Conditional**	Date the recipient went on dialysis for the first time, before his first transplantation. For second and third transplantations, this variable is not entered.	DD-MM-YYYY, 99-99-9999 = 'No Dialysis'.	Pancreas
R3.27	Vaccination for hepatitis B		Yes, No, Unknown	Kidney, Pancreas, Heart, Lung, Intestine
R3.28	Serology for toxoplasmosis		Reactive, Non-reactive, Unknown	Heart, Lung
R3.29	Serology Syphilis		Reactive, Non-reactive, Unknown	Heart, Lung
R3.30	HBeAg		Reactive, Non-reactive, Unknown	Kidney, Pancreas

Nr	Variable name	Definition	Unit or coding	Organs(s)
R3.31	B Delta **Conditional**	Condition: for Liver HBV positive recipients	Reactive, Non-reactive, Unknown	Intestine
R3.32	Alcohol abuse	Subjective judgement of the physician. Accept what is used in national registries.	Yes, No	Heart, Lung, Liver, Intestine
R3.33	Duration of Abstinence of drinking before transplantation	Calculated from duration of abstinence at time of listing, plus period between date of listing and transplantation date.	Months 999 = Never drank	Heart, Lung, Intestine
R3.34	Other Tobacco Use	Any other tobacco use: Cigar, Tobacco chewing	Yes, No, Unknown	Heart, Lung
R3.35	Duration of abstinence of smoking		Number of months 999 = Never smoked	Heart, Lung
R3.36 (R1.10)	Serum Albumin		g/l	Heart, Lung, Intestine
R3.37 (R1.11)	Total Serum Bilirubin		mg/dl, no decimals	Heart, Lung, Intestine
R3.38 (R1.12)	INR		% Integer, No decimals	Intestine
R3.39	Prothrombin Time	Prothrombin Time used for CPT	%, one decimal	Intestine
R3.40	Last Serum Sodium	Translate µmol/l into mg/dl	mg/dl	Intestine
R3.41	Recipient presence of Ascites prior to transplantation	Recipient presence of ascites prior to transplantation	None, Controlled with medication, Refractory (poorly controlled)	Intestine
R3.42	Recipient presence of Encephalopathy prior to transplantation	Recipient presence of encephalopathy prior to transplantation	Grading 1 to 4	Intestine
R3.43	Cardiac Disease	Positive if anamnesis shows history of cardiac disease that required hospitalization.	Yes, No, Unknown	Kidney, Pancreas, Lung, Liver, Intestine
R3.44	Is growth hormone therapy used at time of listing		Yes, No, Unknown	Kidney, Pancreas
R3.45	Latest PRA, measured with DTT		%	Kidney, Pancreas, Heart, Lung
R3.46	Implantable Defibrillator		Yes, No, Unknown	Heart
R3.47	PCWP (mean)		mm/Hg	Heart
R3.48	Chronic Lung Disease	Positive if anamnesis shows history of chronic lung disease that required drug treatment.	Yes, No, Unknown	Heart
R3.49	Pulmonary arterial systolic pressure		mm/Hg	Heart, Lung

Nr	Variable name	Definition	Unit or coding	Organs(s)
R3.50	Pulmonary vascular resistance (PVR)		Wood, Dyne	Heart, Lung
R3.51	Pulmonary mean arterial pressure		mm/Hg	Heart, Lung
R3.52	CO		L/min	Heart, Lung
R3.53	Right Ventricular Pressure, diagnosed by echocardiography		mm/Hg	Heart, Lung
R3.54	FEV1 % predicted		Percentage, no decimals	Heart, Lung
R3.55	FVC % predicted		Percentage, no decimals	Heart, Lung
R3.56	FeV1/FVC		Numeric, two decimals	Heart, Lung
R3.57	TLC % predicted		Percentage, no decimals	Heart, Lung
R3.58	pO2		mm/Hg	Heart, Lung
R3.59	pCO2		mm/Hg	Heart, Lung
R3.60	6 minute walking distance		Meters	Heart, Lung
R3.61	Volume O2 max (during effort)		Litre, one decimal	Heart, Lung
R3.62	Oxygen Requirement at Rest		Yes, No, Unknown	Lung
R3.63	Prior Thoracic Surgery (non-transplant)	Thoracotomy, Sternotomy	Yes, No, Unknown	Heart, Lung
R3.64	Candidate in ICU		Yes, No, Unknown	Heart, Lung
R3.65	Peptic Ulcer Disease		Yes, No, Unknown	Heart, Lung
R3.66	Ventricular ejection fraction (heart tx candidate)			Heart, Lung
R3.67	New York Heart Association Functional Classification		Number	Heart, Lung
R3.68	Pan-Resistant Bacterial Infection		Yes, No, Unknown	Lung
R3.69	Corticosteroid Dependency		Yes, No, Unknown	Lung
R3.70	Pulmonary Embolism		Yes, No, Unknown	Lung
R3.71	Previous Upper Abdominal Surgery		Yes, No, Unknown	Liver, Intestine
R3.72	History of TIPPS or portocaval shunt		Yes, No, Unknown	Liver, Intestine
R3.73	History of Portal Vein Thrombosis		Yes, partial, Yes, total, No	Liver, Intestine
R3.74	History of Spontaneous Bacterial Peritonitis		Yes, No, Unknown	Liver, Intestine
R3.75	Hepato-renal syndrome		Yes, No, Unknown	Liver, Intestine
R3.76	Number of CVL infections		Number	Intestine

Nr	Variable name	Definition	Unit or coding	Organs(s)
R3.77	Loss of abdominal domain		Yes, No, Unknown	Intestine

Calculated or derived Recipient Variables

Nr	Variable name	Definition	Unit or coding	Organs(s)
R4.1	National ID number for Recipient	The National Registry ID is copied. Together with country code this is a unique number.	Alphanumeric	All
R4.2	TX organisation	(National) registry that delivers data for recipient	Alphanumeric ET, SKT, ONT, NHSBT, CNT, ABM, DSO, etc.	All
R4.3	Primary diagnosis system code	This variable contains the coding system used.	1 = ICD-10 2 = ICD-10 German 3 = ERA 4 = Snowmed 5 = EDTA ER 6 = ELTR 7 = ISHL	All
R4.4	Last Creatinine Unit	This variable is always coupled to a serum creatinine measurement	µmol/l or mg/dl	All
R4.5	Code system used for Malignancy specification	Will be delivered by WP6 on Safety		All
R4.6	Country Specific Education System Codes			All
R4.7	MELD	Calculated at time of listing and at time of transplant	Number	Liver, Intestine
R4.8	PELD	Calculated at time of listing and at time of transplant.	Number	Liver
R4.9	CPT	Calculated at time of listing and at time of transplant.	Number	Liver

Transplantation and Follow-up until Transplantation Discharge Variables

Tier 1 Transplantation Variables, common for all organs

Nr	Variable name	Definition	Unit or Coding
T1.1	Transplant Number ID	Local transplant number ID	Alphanumeric
T1.2	Transplant Date		DD-MM-YYYY
T1.3	Country	Country where recipient is registered as recipient at time of transplant.	ISO-Code 3166
T1.4	Previous Transplants	Specification of previous transplant(s). For each of the previous transplants the specification will be required. PM: Intestine is currently NOT included	Heart, Heart + Kidney, Heart + Liver, Heart + Liver + Kidney, Heart + Lung, Heart + Lung + Kidney, Heart + Lung + Liver, Kidney, Kidney + Pancreas, Kidney + Pancreas islets, Liver, Liver + Kidney, Liver + Kidney + Pancreas, Liver + Pancreas, Liver + Pancreas islets, Lung, Lung + Kidney, Lung + Liver, Pancreas, Pancreas islets
T1.5 (F3.4)	Height	Height is registered at time of transplantation	in cm, no decimal
T1.6 (F1.10)	Weight	Weight is registered at time of transplantation	in kg, no decimal
T1.7	Total Ischemic Time	Time elapsed between the time of clamping of the aorta and the time of declamping. For DCD: Time elapsed between circulatory arrest and the time of declamping.	Hours and minutes
T1.8	Organ Type	Since the entries on the registry will be on the transplant level, all organs and all possible combinations will be listed in this variable. PM: Intestine is currently NOT included. Multivisceral: multiple organs are transplanted, such as the stomach, pancreas, liver and small intestine.	Heart, Heart + Kidney, Heart + Liver, Heart + Liver + Kidney, Heart + Lung, Heart + Lung + Kidney, Heart + Lung + Liver, Kidney, Kidney + Pancreas, Kidney + Pancreas islets, Liver, Liver + Kidney, Liver + Kidney + Pancreas, Liver + Pancreas, Liver + Pancreas islets, Lung, Lung + Kidney, Lung + Liver, Pancreas, Pancreas islets
T1.9	Induction therapy	Induction therapy as it is given before transplantation. Entered only once. The induction therapy variable will have all names as separate variables with a “Yes / No” answer option. As all induction agents are stored separately, one has to be filled to achieve completeness (excluding Unknown). Each separate variable has a tier 3.	ATG, rATG, OKT3, Basiliximab, Daclizumab (Anti CD25 Monoclonal antibody), None, Other (text variable), Unknown

Nr	Variable name	Definition	Unit or Coding
T1.10 (F1.11)	Initial Immunosuppression at discharge	The immunosuppression variable will have all names as separate variables with a “Yes/No” answer option. As all immunosuppressive agents are stored separately, one has to be filled to achieve completeness (excluding Unknown). Each separate variable has a Tier 3.	Steroids oral, Cyclosporine, Azathioprine, Mycophenolate, Tacrolimus (FK-506), FTY, MNA (FK778), Sirolimus/Everolimus, Methotrexate, Cyclophosphamide, Other (text variable), Unknown
T1.11	Date of follow-up before discharge		DD-MM-YYYY
T1.12 (F1.3)	Date of Irreversible Graft Failure	For Kidney and Pancreas: requirement of permanent replacement therapy. For Heart, Lung and Liver: Date of retransplantation or Date of Death; For Small Bowel: Date of graft removal.	DD-MM-YYYY
T1.13 (F1.4)	Primary Cause of Graft Failure. It does count when National Registry uses it.	Separate field for coding system used. All coding systems are allowed.	Alphanumeric
T1.14 (F1.5)	Unified Cause of Graft Failure	For Liver and Intestine: ELTR, For Heart and Lung: ISHLT For Kidney And Pancreas: ICD-10	Alphanumeric
T1.15 (F1.6)	Date of Death		DD-MM-YYYY
T1.16 (F1.7)	Cause of Death	All coding systems are allowed.	Alphanumeric
T1.17 (F1.8)	Unified Cause of Death	For Liver and Intestine: ELTR, For Heart and Lung: ISHLT For Kidney And Pancreas: ICD-10	Alphanumeric

Tier 1 Transplantation Variables, organ specific

Nr	Variable name	Definition	Unit or Coding	Organ(s)
T1.18	Donor Warm Ischemic Time	DBD (HBD): the time from clamping till perfusion of the donor (0 till a few minutes); DCD (NHBD): time from cardiac arrest till perfusion of the donor organ. Lungs: only for DCD donors and ex vivo perfusion lungs.	Minutes, no decimal	Kidney, Pancreas, Lung, Liver, Intestine
T1.19 (T3.22)	Recipient's HLA - typing A-B-DR (1-2) antigen	Split in six variables: A1, A2, B1, B2, DR1, DR2	Alphanumeric. Stored as one string variable.	Kidney, Pancreas
T1.20	DGF (Delayed Graft Function)	Patient dialysed during first week after kidney transplantation	Yes, No, Unknown	Kidney
T1.21	Date last dialysis **Conditional**	Condition: Only when the answer on DGF is “Yes”	DD-MM-YYYY	Kidney
T1.22 (T3.35)	Insulin dependent (within time frame)	Insulin dependent after transplantation and before discharge from hospital	Yes, No, Unknown	Pancreas

Nr	Variable name	Definition	Unit or Coding	Organ(s)
T1.23	Graft Type Liver		Whole Graft, Domino, Reduced, Split	Liver

Tier 2 Transplantation Variables, common for all organs

Nr	Variable name	Definition	Unit or Coding
T2.1	Incidental tumour found in Recipient at time of transplant*		Yes, No, Coding, Text
T2.2 (F1.12)	Diabetes onset during the follow-up period	Onset of treatment for diabetes during the follow-up period. As decided by physician.	Yes, No, Unknown
T2.3 (F1.14) (T3.17)	Post-transplant Malignancy*	Time of measurement is T3.1. (PM. Completeness is difficult to check.)	Yes, No, Unknown
T2.4 (F1.15)	Kind of tumour* **Conditional**	Condition: Only when Post Transplant Malignancy is `Yes`.	De Novo, Donor Related, Recurrence of Pre Transplant Tumour, Unknown
T2.5 (F1.16)	Cranial location of tumour* **Conditional**	Condition: Only when Post Transplant Malignancy is `Yes`.	Intracranial, Extracranial
T2.6 (F1.17)	Kind of Intracranial Tumour* **Conditional**	Condition: Only when Kind of tumour is `Intracranial´	Medulloblastoma, Astrocytoma, Glioblastoma, Oligodendroglioma, Ependymoma, Meningioma, Other, Unknown
T2.7 (F1.18)	Other Kind of Intracranial Tumour* **Conditional**	Condition: Only when Kind of Intracranial Tumour is ´Other´	String
T2.8 (F1.19)	Kind of Extracranial Tumour* **Conditional**	Condition: Only when Kind of tumour is `Extracranial´	Renal Cell Carcinoma (RCC), Prostate Adenocarcinoma, Breast Cancer, Lung Cancer, Colorectal Cancer, Oesophagus Carcinoma, Pancreatic Carcinoma, Hepatocellular Carcinoma, Thyroid Carcinoma, Ovarian Cancer, Chorioncarcinoma, Sarcoma (including GIST), Malignant Melanoma, Non Melanoma Skin Cancer (Basal Cell Carcinoma, Spinocellular Carcinoma), Carcinoma in situ, Low grade Lymphoma, High grade Lymphoma, Leukaemia, Other, Unknown
T2.9 (F1.20)	Other Kind of Extracranial Tumour* **Conditional**	Condition: Only when Kind of Extracranial Tumour is ´Other´	String

Tier 2 Transplantation Variables, organ specific

Nr	Variable name	Definition	Unit or coding	Organ(s)
T2.10	2nd Warm Ischemic Time = Anastomosis Time	Time from putting the organ in the body of the recipient till opening of the arterial clamp.	Minutes, no decimal	Liver
T2.11	Type of Kidney transplant		Left, Right, Double	Kidney
T2.12	Graft Type Lung		Whole Lungs, Lobe Transplantation, Split Lungs, Tailored Lungs	Lung
T2.13	Split Type		Left lobe, Left liver, Right liver, Posterial sector	Liver
T2.14	Status at Time of transplant		Home, Hospitalized, Intensive Care	Heart, Lung
T2.15 (F2.2)	Technique for pancreas drainage		ET code list for drainage technique used	Pancreas

Tier 3 Transplantation Variables, common for all organs

Nr	Variable name	Definition	Unit or coding
T3.1	Transplant Centre ID	Centre where the patient is transplanted. Each centre has different code, names of the centre are not stored. Translation of codes is done at a National Registry level.	Alphanumeric.
T3.2	Date of hospital discharge		DD-MM-YYYY
T3.3 (F3.2)	Contributory Cause of Death		Alphanumeric
T3.4 (F3.3)	Did recipient participate in research for immuno meds		Yes, No, Unknown
T3.5 (F3.8)	Acute rejection during follow-up period		Yes, No
T3.6 (F3.9)	Treated acute rejection during follow-up period		Yes, No, Unknown
T3.7 (F3.10)	Rejection Date **Conditional**	Histological diagnosis of rejection (treated or not treated). Condition: Only when T3.5 is 'Yes'	DD-MM-YYYY
T3.8 (F3.11)	Complication	General variable indicating complications. No definition given.	Yes, No, Unknown
T3.9 (F3.12)	Graft related complications		Yes, No, Unknown
T3.10 (F3.13)	Other than graft related complications		Yes, No, Unknown
T3.11 (F3.14)	Renal complication		Yes, No, Unknown
T3.12 (F3.15)	Pulmonary complication		Yes, No, Unknown
T3.13	Biliary Tract Complication		Yes, No, Unknown

Nr	Variable name	Definition	Unit or coding
(F3.16)			
T3.14 (F3.17)	Cardiovascular complication		Yes, No, Unknown
T3.15 (F3.18)	Urogenital complications		Yes, No, Unknown
T3.16 (F3.19)	Hematological complications		Yes, No, Unknown
T3.17 (F3.21) (T2.3)	Date of Diagnosis Post Transplant Malignancy **Conditional**	Condition: Only when Post Transplant Malignancy is `Yes`.	DD-MM-YYYY

Tier 3 Transplantation Variables, organ specific

Nr	Variable name	Definition	Unit or coding	Organ(s)
T3.18	Type of last dialysis	Type of last dialysis	Haemodialysis, Peritoneal dialysis, no dialysis	Kidney
T3.19	Dialysis duration	Dialysis time in days. For second and third transplantation, total amount of all dialysis periods. One month may be counted as 30 days.	Number of days. No Dialysis = 0 Days	Kidney, Pancreas
T3.20	2nd Warm Ischemic Time	Time from putting the organ in the body of the recipient till opening of the arterial clamp (=Anastomosis Time)	Minutes, no decimal	Kidney, Pancreas, Heart, Lung, Intestine
T3.21	DCD Time until perfusion **Conditional**	Time period. DCD III: from time start withdrawal of support until perfusion. DCD II: from time start resuscitation until perfusion. DCD I: from time found dead until perfusion.	Minutes	Kidney, Lung, Liver
T3.22 (T1.19)	Recipient's HLA - typing A-B-DR (1-2) antigen	Split in six variables: A1, A2, B1, B2, DR1, DR2	Alphanumeric. Stored as one string variable.	Heart, Lung
T3.23	Cardiopulmonary bypass		Yes, No, Unknown	Lung
T3.24	CPB time		Minutes	Heart, Lung
T3.25	Intraoperative ECMO		Yes, No, Unknown	Lung
T3.26	Time On ECMO		Minutes	Lung, Liver, Intestine
T3.27	Total Cold Ischemic Time	From start of perfusion to start of anastomosis. It usually includes reperfusion time. Because this variable's definition changes across countries, it is of lesser importance than total ischemic time.	Hours and minutes	Liver, Intestine
T3.28	Were extra vessels used in the transplant		Yes, No, Unknown	Liver, Intestine

Nr	Variable name	Definition	Unit or coding	Organ(s)
	procedure			
T3.29	Total number of units transfused during surgery		Number	Liver, Intestine
T3.30	Discharge from Intensive Care Unit Date		DD-MM-YYYY	Heart, Lung
T3.31	Cross match	Compatibility testing between donor cells and those of the recipient.	Prospective, Retrospective, Not	Heart, Lung
T3.32	Cross match result	Negative if all tests are negative, positive if at least one test is positive.	Positive, Negative	Heart, Lung
T3.33 (F1.9)	Serum Creatinine at discharge		µmol/l or mg/dl	Kidney
T3.34	Diabetes onset before hospital discharge	Onset of treatment for Diabetes after transplantation and before hospital discharge	Yes, No, Unknown	Kidney
T3.35 (T1.22)	Insulin dependent	Insulin dependent diabetes after transplantation and before discharge from hospital	Yes, No, Unknown	Kidney
T3.36 (F3.44)	Protocol biopsy performed at time of follow-up		Yes, No, Unknown	Kidney, Pancreas
T3.37	Heart Transplant Type		Orthotopic, Heterotopic	Heart
T3.38	Heart Transplant Procedure Type	Describes the way the heart is connected	Bicaval, Biatrial/Lower-Shumway	Heart
T3.39	Lung Transplant Procedure Type		Single lung SLT, Sequential LTX, Bilateral lung LTX (En Bloc)	Lung
T3.40	CMV Prophylaxis		Yes, No, Unknown	Heart, Lung
T3.41	Duration mechanical ventilation	Could be intubation or oxygen mask or other	Hours	Lung
T3.42	Graft Weight		Gram	Liver
T3.43	Graft Anatomical Type		Name all segments 1 to 8, each of these eight fields can be selected separately	Liver
T3.44	Auxiliary Type		Auxiliary: one part of recipient liver remains, Non Auxiliary	Liver
T3.45	Piggy-back		Yes, No, Unknown	Liver
T3.46	Cavil replacement		Yes, No, Unknown	Liver
T3.47	Extracorporeal Bypass		Yes, No, Unknown	Liver
T3.48	Pre-transplant Portal Vein Thrombosis		Yes, No, Unknown	Liver, Intestine

Nr	Variable name	Definition	Unit or coding	Organ(s)
T3.49	Status at Time of transplant		Home without treatment, Home with treatment, Hospitalized, Intensive Care	Liver, Intestine
T3.50	Venous drainage		Portal, Systemic	Intestine
T3.51	Ileostomy type		Single, Double Pipe	Intestine
T3.52 (F3.45)	Proteinuria	This is defined for an undetermined amount of urine, hence gram/l.	gram/l	Kidney
T3.53 (F3.46)	Is growth hormone therapy used during this follow-up		Yes, No, Unknown	Kidney
T3.54 (F3.47)	BK (Polyoma) Virus Infection		Yes, No, Unknown	Kidney
T3.55 (F3.48)	CMV Infection		Yes, No, Unknown	Kidney
T3.56 (F3.49)	EBV Infection		Yes, No, Unknown	Kidney
T3.57 (F3.50)	Serum Amylase			Pancreas
T3.58 (F3.51)	Conversion from bladder to enteric drain performed		Yes, No, Unknown	Pancreas
T3.59 (F3.52)	Conversion from bladder to enteric drain date		Date	Pancreas
T3.60 (F3.53)	Anastomosis Leak		Yes, No, Unknown	Pancreas

Calculated or derived Transplantation Variables

Nr	Variable name	Definition	Unit or Coding	Organ(s)
T4.1	Age at TX	Calculated from date of birth and date of transplant; Can also be entered directly	Years, no decimal	All
T4.2	Number of Previous Transplants	Number of previous solid organ transplants, each organ transplanted count as one. Derived from T1.4.	Number	All
T4.3	Dialysis	Indicates whether recipient was on dialysis at time of transplantation. Derived from ´Date of start dialysis´.	Yes, No, Unknown	All
T4.4	Simultaneous transplantations		Yes, No	All
T4.5	Days until hospital discharge	Days from transplantation to discharge from hospital	Number	All

Nr	Variable name	Definition	Unit or Coding	Organ(s)
T4.6 (F4.3)	Graft Status	Becomes Failed when T1.12 is entered.	Functioning, Failed	All
T4.7 (F4.4)	Graft Failure Code System specific codes	Contains the values of the graft failure code used by the National Registries. These may be organ specific within a National Registry.		All
T4.8 (F4.5)	Patient Status	Patient status at date of follow-up, this item will be derived automatically from death date, but it is important to include it, for analysis purposes. Derived from ´Date of Death´	Alive, Dead	All
T4.9 (F4.6)	Cause of Death coding system specific codes	Contains the values of the Cause of Death codes used by the National Registries.		All
T4.10 (F4.7)	Serum Creatinine at discharge Unit	This variable is always coupled to a serum creatinine measurement.	µmol/l or mg/dl	Kidney

Tier 1 Follow-up Variables, common for all organs

Nr	Variable name	Definition	Unit or Coding
F1.1	Date of follow-up	All measurements in this section are coupled to this date, except where noted otherwise.	DD-MM-YYYY
F1.2	Lost To Follow-up	Only if a centre denotes a patient as lost to follow-up. No automatic setting to “lost to follow-up”.	Yes, No, Unknown
F1.3 (T1.12)	Date of Irreversible Graft Failure	For Kidney and Pancreas: requirement of permanent replacement therapy or retransplantation. For Heart, Lung and Liver: Date of retransplantation or date of death For Small Bowel: Date of graft removal retransplantation or date of death	DD-MM-YYYY
F1.4 (T1.13)	Primary Cause of Graft Failure	Separate field for coding system used. All coding systems are allowed.	Graft failure codes
F1.5 (T1.14)	Unified Cause of Graft Failure	For Liver and Intestine: ELTR, For Heart and Lung: ISHLT For Kidney And Pancreas: ICD-10	Alphanumeric
F1.6 (T1.15)	Date of Death		DD-MM-YYYY
F1.7 (T1.16)	Cause of Death	All coding systems are allowed.	Death cause code
F1.8 (T1.17)	Unified Cause of Death	For Liver and Intestine: ELTR, For Heart and Lung: ISHLT For Kidney And Pancreas: ICD-10	Alphanumeric
F1.9 (T3.33)	Serum Creatinine		µmol/l or mg/dl
F1.10 (T1.6)	Weight	Weight is registered at time of follow-up	in kg no decimal

Tier 2 Follow-up Variables, common for all organs

Nr	Variable name	Definition	Unit or coding
F2.1 (T1.10)	Immunosuppression at follow-up	The immunosuppression variable will have all names as separate variables with a “Yes/No” answer option. Entered only at the designated follow-up time. As all immunosuppressive agents are stored separately, one has to be filled to achieve completeness (excluding Unknown). Each separate variable has a Tier 3.	Steroids oral, Cyclosporine, Azathioprine, Mycophenolate, Tacrolimus (FK-506), FTY, MNA (FK778), Sirolimus/Everolimus, Methotrexate, Cyclophosphamide, Other (text variable), Unknown
F2.2 (T2.2)	Diabetes onset during the follow-up period	Onset of treatment for Diabetes during the follow-up period.	Yes, No, Unknown

Nr	Variable name	Definition	Unit or coding
F2.3	If Diabetes onset, chronic treatment	Treatment for diabetes has started with any form of anti-diabetic medication (oral or insulin) that is still used at the follow-up date.	Yes, No, Unknown
F2.4 (T2.3) (F3.21)	Post-transplant Malignancy*	Time of measurement is F3.1. (PM: Completeness is difficult to check).	Yes
F2.5 (T2.4)	Kind of tumour* **Conditional**	Condition: Only when Post Transplant Malignancy is `Yes`.	De Novo, Donor Related, Recurrence of Pre Transplant Tumour, Unknown
F2.6 (T2.5)	Cranial location of tumour* **Conditional**	Condition: Only when Post Transplant Malignancy is `Yes`.	Intracranial, Extracranial
F2.7 (T2.6)	Kind of Intracranial Tumour* **Conditional**	Condition: Only when Kind of tumour is `Intracranial´	Medulloblastoma, Astrocytoma, Glioblastoma, Oligodendroglioma, Ependymoma, Meningioma, Other, Unknown
F2.8 (T2.7)	Other Kind of Intracranial Tumour* **Conditional**	Condition: Only when Kind of Intracranial Tumour is ´Other´	String
F2.9 (T2.8)	Kind of Extracranial Tumour* **Conditional**	Condition: Only when Kind of tumour is `Extracranial´	Renal Cell Carcinoma (RCC), Prostate Adenocarcinoma, Breast Cancer, Lung Cancer, Colorectal Cancer, Oesophagus Carcinoma, Pancreatic Carcinoma, Hepatocellular Carcinoma, Thyroid Carcinoma, Ovarian Cancer, Chorioncarcinoma, Sarcoma (including GIST), Malignant Melanoma, Non Melanoma Skin Cancer (Basal Cell Carcinoma, Spinocellular Carcinoma), Carcinoma in situ, Low grade Lymphoma, High grade Lymphoma, Leukaemia, Other, Unknown
F2.10 (T2.9)	Other Kind of Extracranial Tumour* **Conditional**	Condition: Only when Kind of Extracranial Tumour is ´Other´	String
F2.11 (F3.22)	Serology of HIV*	Time of Measurement is F3.2.	Reactive, Non-reactive, Unknown
F2.12 (F3.23)	HBsAg*	Time of Measurement is F3.3.	Reactive, Non-reactive, Unknown
F2.13 (F3.24)	HCVAb*	Time of Measurement is F3.4.	Reactive, Non-reactive, Unknown

Tier 2 Follow-up Variables, organ specific (No Tier 2 variables were common for all organs)

Nr	Variable name	Definition	Unit or Coding	Organ(s)
F2.14	Dialysis		Yes, No, Unknown	Heart, Lung
F2.15 (T2.15)	Technique for pancreas drainage		ET code list for drainage technique used	Pancreas
F2.16	Bronchiolitis Obliterans Syndrome	Bronchiolitis obliterans syndrome (BOS) is the primary manifestation of chronic rejection in lung transplantation and refers to a progressive obstructive ventilatory disorder characterized by a decrease in forced expiratory volume over time after LTx. BOS is “Yes” if FEV1 < 80% of the two best post-operative FEV1-values	Yes, No, Unknown	Lung
F2.17 (F3.65)	INR		% Integer, No decimals	Liver
F2.18	Total Serum Bilirubin		mg/dl, no decimals	Liver
F2.19	Modified Karnofsky score		Number	Intestine

Tier 3 Follow-up Variables, common for all organs

Nr	Variable name	Definition	Unit or coding
F3.1	Date last seen	Date patient last seen or last known to be alive.	DD-MM-YYYY
F3.2 (T3.3)	Contributory Cause of Death		Death cause code
F3.3 (T3.4)	Did recipient participate in research for immuno med	Status at follow-up.	Yes, No, Unknown
F3.4 (T1.5)	Height	Height is registered at time of follow-up	in cm no decimal
F3.5	Pregnancy	Pregnancy at follow-up moment or occurring (and completed) since last follow-up.	Yes, No, Unknown
F3.6 (R3.18)	Patient's Employment Status at follow-up	Patient's Employment Status	Full time, part time by choice, part time due to disability, part time due to treatment, part time due to inability to find full time work, part time no reason, unknown, homemaker
F3.7	Recipient Noncompliant During this Follow-Up Period	Recipient is considered noncompliant during this Follow-Up period by physician of recipient.	Yes, No, Unknown

Nr	Variable name	Definition	Unit or coding
F3.8 (T3.5)	Acute rejection during follow-up period		Yes, No
F3.9 (T3.6)	Treated acute rejection during follow-up period		Yes, No, Unknown
F3.10 (T3.7)	Rejection Date **Conditional**	Histological diagnosis of rejection (treated or not treated)	DD-MM-YYYY
F3.11 (T3.8)	Complication		Yes, No, Unknown
F3.12 (T3.9)	Graft related complications		Yes, No, Unknown
F3.13 (T3.10)	Other than graft related complications		Yes, No, Unknown
F3.14 (T3.11)	Renal complication		Yes, No, Unknown
F3.15 (T3.12)	Pulmonary complication		Yes, No, Unknown
F3.16 (T3.13)	Biliary Tract Complication		Yes, No, Unknown
F3.17 (T3.14)	Cardiovascular complication		Yes, No, Unknown
F3.18 (T3.15)	Urogenital complications		Yes, No, Unknown
F3.19 (T3.16)	Haematological complications		Yes, No, Unknown
F3.20	If Diabetes onset, insulin dependent		Yes, No, Unknown
F3.21 (T3.17) (F1.14)	Date of Diagnosis Post Transplant Malignancy* **Conditional**	Condition: Only when Post Transplant Malignancy is `Yes`.	DD-MM-YYYY
F3.22 (F1.21)	Date Serology of HIV*	Date of last available serology for HIV	DD-MM-YYYY
F3.23 (F1.22)	Date HBsAg*	Date of last available test for HBsAg	DD-MM-YYYY
F3.24 (F1.23)	Date HCVAb*	Date of last available test for HCVAb	DD-MM-YYYY
F3.25	HBV-DNA*		Number of copies
F3.26	Date HBV-DNA*	Date of last available test for HBV-DNA	DD-MM-YYYY
F3.27	HCV-RNA*	Number of copies	Reactive, Non-reactive , Unknown
F3.28	Date*	Date of last available test for HCV-RNA	Yes, No, Unknown
F3.29	Risk factor for infection*	Risk factor for emergent diseases. Born in an endemic country, recent travel to endemic country or region, parents or sexual partner coming from endemic area.	Yes/no/unknown
F3.30	Endemic country or region of recent travel*	Specification of country or region of recent travel.	String

Nr	Variable name	Definition	Unit or coding
F3.31	HTLV (I/II) Ab*	Antibodies against Human T-Lymphotropic virus.	Reactive, Non-reactive , Unknown
F3.32	Trypanosome Cruzi Ab*	Antibodies against Tripanosoma Cruzi (causal agent of Chagas disease).	Reactive, Non-reactive , Unknown
F3.33	Plasmodium spp*	Direct test to find plasmodium spps (causal agent of malaria).	Positive, Negative, Unknown
F3.34	Other emergent diseases*		String

Tier 3 Follow-up Variables, organ specific

Nr	Variable name	Definition	Unit or coding	Organ(s)
F3.35	Signs of Antibody Mediated Rejection (AMR)		Yes, No, Unknown	Heart, Lung
F3.36	Chronic Rejection, Graft Dysfunction	Multi Factorial Graft Dysfunction	Yes, No, Unknown	Liver, Intestine
F3.37	Signs of allograft vasculopathy		Yes, No, Unknown	Heart
F3.38	Class of allograft vasculopathy		ISHLT classification	Heart
F3.39	Intervention after allograft vasculopathy (bypass, PCI, stent)		Yes, No, Unknown	Heart
F3.40	Viral Infection donor related		Yes, No, Unknown	Liver, Intestine
F3.41	Viral Infection donor transmission of HBV		Yes, No, Unknown	Liver
F3.42	Viral Infection donor transmission of HCV		Yes, No, Unknown	Liver
F3.43	Disease Recurrence		Yes, No, Unknown	Kidney, Liver, Intestine
F3.44 (T3.36)	Protocol biopsy performed at time of follow-up		Yes, No, Unknown	Kidney, Pancreas
F3.45 (T3.52)	Proteinuria		gram/l	Kidney
F3.46 (T3.53)	Is growth hormone therapy used during this follow-up		Yes, No, Unknown	Kidney
F3.47 (T3.54)	BK (Polyoma) Virus Infection		Yes, No, Unknown	Kidney
F3.48 (T3.55)	CMV Infection		Yes, No, Unknown	Kidney
F3.49 (T3.56)	EBV Infection		Yes, No, Unknown	Kidney
F3.50 (T3.57)	Serum Amylase			Pancreas
F3.51 (T3.58)	Conversion from bladder to enteric drain performed		Yes, No, Unknown	Pancreas
F3.52 (T3.59)	Conversion from bladder to enteric drain date		Date	Pancreas
F3.53 (T3.60)	Anastomosis Leak		Yes, No, Unknown	Pancreas

Nr	Variable name	Definition	Unit or coding	Organ(s)
F3.54	Statin treatment		Yes, No, Unknown	Heart, Lung
F3.55	LDL			Heart, Lung
F3.56	HDL			Heart, Lung
F3.57	Permanent Pacemaker		Yes, No, Unknown	Heart, Lung
F3.58	NYHA class	NYHA class 1-4	Number	Heart
F3.59	BOS stage		ISHLT classification	Lung
F3.60	Bronchial Stricture		Yes, No, Unknown	Lung
F3.61	Bronchial Stricture: If yes, Stent?		Yes, No, Unknown	Lung
F3.62	FEV1		Number	Lung
F3.63	PostTx: bronchopleural fistula		Yes, No, Unknown	Lung
F3.64	PostTx: Airway dehiscence		Yes, No, Unknown	Lung
F3.65 (F2.4)	INR		% Integer, No decimals	Intestine
F3.66	SGOT/AST	Either SGOT/AST or SGPT/ALT has to be entered: taken together they rate as tier 1.	U/l	Liver, Intestine
F3.67	SGPT/ALT	Either SGOT/AST or SGPT/ALT has to be entered: taken together they rate as tier 1.	U/l	Liver, Intestine
F3.68	Alkaline Phosphate			Liver, Intestine
F3.69	If Vascular Thrombosis, Hepatic portal vein thrombosis		Yes, No, Unknown	Liver
F3.70	A-fetoproteine **Conditional**	Condition: Only for HCC patients		Liver, Intestine
F3.71	IV fluid Dependence		Yes, No, Unknown	Intestine
F3.72	TPN Dependent		Yes, No, Unknown	Intestine
F3.73	Full function			Intestine
F3.74	Tube Feeding		Yes, No, Unknown	Intestine
F3.75	Viral Hepatitis: De novo		Yes, No, Unknown	Liver
F3.76	Hepatitis B (HBV): Recurrent	HBV recurrent from previous disease	Yes, No, Unknown	Liver
F3.77	HCV recurrent	HCV recurrent from previous disease	Yes, No, Unknown	Liver
F3.78	HIV recurrent	HIV recurrent from previous disease	Yes, No, Unknown	Liver

Calculated or derived follow-up Variables

Nr	Variable name	Definition	Unit or coding	Organ(s)
F4.1	Before or after discharge	Calculated "Yes/No" variable that indicates whether the follow-up data are pertaining to the period after transplantation and before discharge from the hospital	Yes, No	All
F4.2	Follow-up moment	This 'Follow-up moment' variable is generated automatically from 'Date of follow-up', to facilitate analysis in selecting follow-up periods. The value '3 month' will be given for an exact follow-up time between 2 and 4 months after transplantation. The value '6 month' will be given for an exact follow-up time between 5 and 7 months after transplantation. The value '1 year' will be given for an exact follow-up time between 10 and 14 months after transplantation. And so on. If more than one follow-up visit falls within these intervals, the closest follow-up time is chosen.	3 month 6 month 1 year 2 years 3 years 4 years … (continued until 60 years) These are string choices	All
F4.3 (T4.6)	Graft Status	Deterioration of organ function, so that permanent replacement therapy is required.	Functioning, Failed	All
F4.4 (T4.7)	Graft Failure Code System specific codes	Contains the values of the graft failure code used by the National Registries. These may be organ specific within a National Registry.		All
F4.5 (T4.8)	Patient Status	Patient status at date of last follow-up, this item will be derived automatically from 'Date of death'	Alive, Dead	All
F4.6 (T4.9)	Cause of Death coding system specific codes	Contains the values of the Cause of Death codes used by the National Registries.		All
F4.7 (T4.10)	Serum Creatinine Unit	This variable is always coupled to a serum creatinine measurement.	µmol/l or mg/dl	All
F4.8	Death with a functioning graft	This item can be derived from graft failure item and death item.	Yes, No, Unknown	Heart, Lung, Liver, Intestine

3.4 Non-standard risk donors

3.4.1 Introduction

During the last decade the profile of deceased organ donors has changed considerably. Not only the average donor age has increased but also donors with greater co-morbidity are offered and accepted, for transplantation, thereby potentially increasing the donor related risks of transplantation. This development might have an influence both on short and long term transplant results. When non-standard risk donors are used for transplantation, the associated risk is not only limited to a possible influence on the outcome after

transplantation due to a poor graft function, but does also include the potential for the transmission of a disease such as an infection or a tumour.

Donor related recipient morbidity and mortality are not very common in the daily reality of organ transplantation in each country, but the information gathered can provide valuable information if it is shared with other European countries. Having a sufficient number of cases will help to raise awareness about the risks regarding certain types of donors and their implications for future transplantation results in terms of safety.

The objective of this project and the part that corresponds to the safety WP is fully consistent with the recently adopted *European Directive on quality and safety of organ transplantation (Directive 2010/53/EU)*.

In these terms, at the beginnings of the project, it was decided to consider all donors that meet at least one of the following conditions as a non-standard risk donor:

1. **Acute intoxication as direct cause of death;**
2. **Present/past history of neoplasia;**
3. **Positive serology for**
   - HIV
   - HCV
   - HBV
4. **Risk factors for viral infectious diseases (window period);**
5. **Emergent infectious diseases or risk factors for emerging infectious diseases.**

Taking into account safety and post-transplant outcomes it is necessary to include not only variables of the donors who represent a certain risk, but also those coming from recipients (pre- and post-transplant), which may have an influence on future developments (in terms of certain infections and / or tumours that worsen their prognosis with immunosuppressant). The combination of donor and recipient information is necessary to help clarifying whether the presence of a disease after transplantation is in fact related to the characteristics of the donor and therefore the safety of the donation and transplantation process.

3.4.2 Recommended variables and definitions

The variables, developed by WP6, have been agreed upon with the other EFRETOS consortium partners and the experts of the different organs groups provided by WP4.

The variables selected are based on different sources:
- the *Annex* of the *Directive 2010/53/EU;*
- the common practice of the consortium partners (and therefore the assessment made in their countries);
- the literature review (see Deliverable 3).

The variables are separated into two sets:

- a set of donor variables to be collected in case a non-standard risk donor is used for transplantation;
- a set of recipient variables to be collected pre- and post-transplant, related to certain infections (caused by viruses such as HCV, HBV, HIV or in case a recipient meets criteria of newly emergent diseases) or malignancies in recipients that may influence the safety of the process and/or the results of transplantation in terms of morbidity and survival.

For practical purposes, the variables of donors and recipients related to each issue are shown together. The number in each cell corresponds to the tier classification agreed upon by the consortium and experts (Tier 1: mandatory when entering the registry, Tier 2: mandatory, but to be adapted by the national registry within a

specific number of years after first joining the European Registry, Tier 3: all optional data including the variables of special interest for scientific purposes).

Acute intoxication as direct cause of death

DEFINITIONS

Donors with acute intoxication as a direct cause of death: any acute intoxication, even it is not the cause of death of the donor may compromise the function of a donated organ and invalidate it for transplantation. The purpose of this variable is not to assess organs affected, but to detect potential general risk for recipients when the levels of a toxic substance in the donor were lethal.

Toxic substance involved: Menu to be displayed with the most frequent toxic substances found in the literature as direct cause of brain dead donors (more detailed in Deliverable 3).

VARIABLES

Recommended variables are displayed in tables 1 and 2.

Table 1: Recommended variables related to donors with acute intoxication as direct cause of death

Donor	Type of variable	All organs
Cause of death: acute intoxication	Include intoxication in the menu of causes of death	1
Toxic substance involved	Menu to be displayed *	3

**See table 2*

Table 2: List of toxic substances involved in brain dead donors, to be included in menu to be displayed

Toxic substance involved	
Amanita Phalloides	Hydrocarburs
Barbiturics	Isoniacid
Benzodiazepines	Lead
Carbon Monoxide	Methanol
Chloroquines	Neuroleptic
Cocaine	Organophosphorade pesticides
Cyanur	Paracetamol
Dextropropoxylen	Rodenticides (dicumarin)
Ecstasy	Theophylline
Ethanol	Tricyclic antidepressants
Ethylenglycol	Other: specify (free text)
Unknown	

Past/Present history of neoplasia

DEFINITIONS

Malignant tumour: includes every malignant tumour diagnosed in the donor, even if there is no tumour free interval prior to donation. This includes all incidental tumours found before or after the transplantation. The variable “moment of tumour diagnosis” has been included to differentiate the normal circumstances (tumour known before the implantation of an organ) from those situations in which the organ was transplanted before the tumour had been diagnosed. The latter might happen if a transplant already took place before the results of the histopathological analysis of a mass because of the bad clinical status of the recipient.

Malignant tumour of the recipient: refers to any malignant tumour diagnosed before the inclusion of the patient on the waiting list, during the waiting time, or tumours diagnosed in the follow-up.

Kind of tumour: classification will be provided by WP6, based on the *Council of Europe Guidelines on assessment of donors with neoplasia* and, on the *WHO classification* for intracranial tumours. We consider this classification easier to manage than the one derived from the International Codification of Diseases.

Tumour free time: period of time in which the neoplasia is considered cured (0 is considered a current process).

Note: Several entries should be allowed for these variables (in the donor and in the recipient) in case more than one tumour has been diagnosed.

VARIABLES

Recommended variables are displayed in tables 3 - 5.

Table 3: Recommended variables related to donors with a past/present history of neoplasia.

DONOR VARIABLES

DONOR	Type of variable	All organs
Tumour		
Malignant tumours	Yes, No, Unknown (all donors)	1
Moment of diagnosis	Menu: • Previously known • Incidentally found before transplantation • Incidentally found after transplantation ***Organ specific***	2
Kind of tumour / type of tumour	Menu (classification developed by WP6)	2
Tumour free time	Years	3
Tumour grading	Depending on the type of tumour	3
Tumour staging	Depending on the type of tumour	3

Table 4: Recommended variables related to donors with a past/present history of neoplasia.

RECIPIENT BASELINE VARIABLES

RECIPIENT PRE-TRANSPLANT All recipients	Type of variable	All organs
Malignant tumours	Yes, No, Unknown	3
Time since malignancy diagnosis and time listing	Years	3
Kind of tumour / type of tumour	Menu (classification developed by WP6) *	3

**See table 6.*

Table 5: Recommended variables related to donors with a past/present history of neoplasia.

TRANSPLANTATION and FOLLOW-UP VARIABLES

TRANSPLANTATION AND FOLLOW-UP	Type of variable	All organs
Post-transplant malignancy	Yes	2
Post-transplant malignancy	Menu with: • De novo • Recurrence of pre-transplant tumour • Donor derived • Unknown	3
Kind of tumour / type of tumour	Menu (classification developed by WP6)*	2
Date of diagnosis	Date	3

**See table 6.*

Table 6 includes the classification to be displayed for the variable: Kind of tumour/type of tumour (see more details in Deliverable 3).

Table 6: List of tumours to be included in menu to be displayed under the variable "Kind of tumour"

Kind of tumour: Intracranial / extracranial		
Intracranial (Tier 2)		Extracranial (Tier 2)
Medulloblastoma Astrocytoma Glyoblastoma Oligodendroglioma Ependymoma Meningioma Other Unknown	Free text for every type of intracranial tumour (Tier 3)	Renal Cell Carcinoma (RCC) Prostate Adenocarcinoma Breast Cancer Lung Cancer Colorectal Cancer Oesophagus Carcinoma Pancreatic Carcinoma Hepatocellular Carcinoma Thyroid Carcinoma Ovarian Cancer Chorioncarcinoma Sarcoma (including GIST) Malignant Melanoma Non Melanoma Skin Cancer (Basal Cell Carcinoma, Spinocellular Carcinoma) Carcinoma *in situ* Low grade Lymphoma High grade Lymphoma Leukaemia Other: (Please specify)_____ Unknown

Positive serology for HIV, HCV, HBV

DEFINITIONS

HIV Ab (I//II): antibodies against Human Immunodeficiency Virus subtype 1 or 2;
HBs Ag: surface antigen of hepatitis B virus;
HBs Ab: antibodies against Hepatitis B virus surface molecule;
HBV DNA: qualitative and/or number of copies of HBV virus tested by polymerase chain reaction (PCR);
HBc Ab: antibodies against Hepatitis B Virus core molecule;
HCVAb: antibodies against hepatitis C virus;
HCVRNA: qualitative and /or number of copies of HCV tested by PCR.

VARIABLES
Recommended variables are displayed in tables 7 – 9.

Table 7: Recommended variables related to donor positive serology for HIV, HCV, HBV.

DONOR VARIABLES

DONOR	Type of variable	All organs
HIV Ab (I/II)	Reactive, Non-Reactive, Unknown	2
HBs Ag	Reactive, Non-Reactive, Unknown	2
HBs Ab	Reactive, Non-Reactive, Unknown	2
HBV DNA	Reactive, Non-Reactive, Unknown Number of copies	3
HBc Ab	Reactive, Non-Reactive, Unknown	2
VHCAb	Reactive, Non-Reactive, Unknown	2
HCV RNA	Reactive, Non-Reactive, Unknown Number of copies	3

Table 8: Recommended variables related to donor positive serology for HIV, HCV, HBV

RECIPIENT BASELINE VARIABLES

RECIPIENT PRE-TX	Type of variable	All organs
HIV Ab	Reactive, Non-Reactive, Unknown	2
HBsAg	Reactive, Non-Reactive, Unknown	2
HBsAb	Reactive, Non-Reactive, Unknown	2
HBc Ab	Reactive, Non-Reactive, Unknown	2
HBV-DNA	Reactive, Non-Reactive, Unknown Number of copies	3
HCV Ab	Reactive, Non-Reactive, Unknown	2
HCV-RNA	Reactive, Non-Reactive, Unknown Number of copies	3

Variables shown in table 8 should be collected in the recipient already prior to the transplantation. Only with these data it is possible to distinguish new seropositivity after transplantation for a specific disease from already pre-existing findings. This will allow differentiating the effects in terms of morbidity and survival of seropositivity in the donor from those in the recipient on outcome after transplantation.

Note: the serology of the recipient pre-transplant corresponds to the last available serology during the period in the waiting list (ideally the day of the transplant).

Table 9: Recommended variables related to donor positive serology for HIV, HCV, HBV

TRANSPLANTATION and FOLLOW-UP VARIABLES.

RECIPIENT FOLLOW-UP	Type of variable	All organs
Serology of HIV	Reactive, Non-Reactive, Unknown	3
Date	Date of last available serology for HIV	3
HBsAg	Reactive, Non-Reactive, Unknown	3
Date	Date of last available test for HBsAg	3
HBV-DNA	Reactive, Non-Reactive, Unknown Number of copies	3
Date	Date of last available test for HBV-DNA	3
HCVAb	Reactive, Non-Reactive, Unknown	3
Date	Date of last available test for HCVAb	3
HCV-RNA	Reactive, Non-Reactive, Unknown Number of copies	3
Date	Date of last available test for HCV-RNA	3

Note: the serology of the recipient during the follow-up corresponds to the last available serology

Risk factors for viral infectious diseases (window period)

DEFINITIONS

There is international consensus about the increased risk of transmission of a viral infectious disease (HBV, HCV; HIV) when using donors with specific risk behaviours. However there are differences in the criteria constituting risk behaviours. All partners and experts of the EFRETOS project agreed on the following criteria for risk behaviour for the purpose of the future European Registry:

- Drug users (intravenous, intramuscular or subcutaneous) in the previous 2 years.
- Risk sexual behaviour (multiple sexual partners) in the previous 6-12 months.

In case at least one of these criteria is fulfilled, the corresponding variables have to be collected.

Other situations that may suppose a risk for viral infectious diseases are those that cause false negative results in the screening, as hemodilution diagnosed at the moment of death with no previous blood sample available and no possibility to wait 24 hours to repeat determination. Transfusion of a large number of units of blood or the infusion of crystalloids and/or colloids to the potential donor prior to perform serological tests may cause, as a result of hemodilution, false negative results in the screening for viral infections. An example of a hemodilution decision algorithm is as follows:

HEMODILUTION ALGORITHM EXAMPLE

Plasma volume (PV) = donor's weight (kg) / 0.025
Blood volume (VS) = donor's weight (kg) / 0.015

A. Total volume of blood transfused / 48h

Volume of: RBCs / 48h ... ... ml
whole blood / 48h ... ... ml
Reconstituted blood ... ... ml

TOTAL: A = ... ml

B. Total volume of colloid infused / 48h

Volume of: dextran ... ... ml
plasma ... ... ml
Platelets ... ... ml
Albumin ... ... ml
hetastarch ... ... ml
other ... ... ml
... ... ml

TOTAL: B = ... ml

C. Total volume of crystalloid infused / 1h

Volume of saline solution ... ... ml
dextrose solution ... ... ml
Ringer lactate ... ... ml
other ... ... ml
... ... ml
... ... ml

TOTAL: C = ... ml

Determination of the potential Haemodilution

1. Is B+C> VP? YES/NO

2. Is A+B+C> VS? YES/NO

Comment:
If the answer to either question 1 or 2 is YES, there exist Hemodilution

Food and drug Administration. (Guidance for Industry. Screening and testing of donors of human tissue intended for transplantation available at www.fda.gov)

VARIABLES
Recommended variables are displayed in table 10.

Table 10: Recommended variables related to donors with risk factors for viral infectious diseases.

PITFALLS IN SEROLOGIC SCREENING. DONOR	Type of variable	All organs
Risk factor for infection (iv drug user)	Reactive, Non-Reactive, Unknown	2
Risk factor for infection (risky sexual behaviour)	Reactive, Non-Reactive, Unknown	3
Hemodilution	Reactive, Non-Reactive, Unknown	3

Emergent Diseases Special Cases

The risk of acquiring infectious diseases by people and thus by potential donors are different depending on the geographical areas they come from. Therefore it is important to know the origin of the donor and some risk factors related to the possible transmission of these infections (sexual partners, mother to child transmission...). This will allow measures to prevent the transmission of these diseases in case of positive tests or when a potential donor meets one of the risk factors for these diseases. The information of these pathologies in Europe is scarce but the experience will be useful if some countries share data in a registry.

DEFINITIONS

HTLV (I/II) Ab: antibodies against Human T-Lymphotropic virus;
Trypanosome Cruzi Ab: antibodies against Tripanosoma Cruzi (causal agent of Chagas disease);
Plasmodium spp test: direct test to find Plasmodium spps (causal agent of Malaria).

VARIABLES
Recommended variables are displayed in tables 11 – 13.

Table 11: Recommended variables related to emergent infectious diseases.

DONOR VARIABLES

DONOR	Coding	All organs
SPECIAL CASES (EMERGENT DISEASES)		
Risk factor for infection (born in an endemic country, recent travel to endemic country or region, parents or sexual partner coming from endemic area):	Reactive, Non-Reactive, Unknown	3
Country	Free text	3
HTLV (I/II) Ab	Reactive, Non-Reactive, Unknown	3
Trypanosome Cruzi Ab	Reactive, Non-Reactive, Unknown	3
Plasmodium spp (test)	Positive, Negative, Unknown	3
Other: specify	Free text	3

Table 12: Recommended variables related to emergent infectious diseases.

RECIPIENT BASELINE VARIABLES

RECIPIENT PRE-TRANSPLANT	Type of variable	All organs
SPECIAL CASES (EMERGENT DISEASES)		
Risk factor for infection (born in an endemic country, recent travel to endemic country or region, parents or sexual partner coming from endemic area):	Reactive, Non-Reactive, Unknown	3
Country	Free text	3
HTLV (I/II) Ab	Reactive, Non-Reactive, Unknown	3
Tripanosoma Cruzi serology	Reactive, Non-Reactive, Unknown	3

Plasmodium spp	Positive, Negative, Unknown	3
Other: specify	Free text	3

Table 13: Recommended variables related to emergent infectious diseases.

TRANSPLANTATION and FOLLOW-UP VARIABLES

RECIPIENT FOLLOW-UP	Type of variable	All organs
SPECIAL CASES (EMERGENT DISEASES)		
Risk factor for infection (born in an endemic country, recent travel to endemic country or region, parents or sexual partner coming from endemic area):	Yes, No, Unknown	3
Country	Free text	3
HTLV (I/II) Ab	Reactive, Non-Reactive, Unknown	3
Tripanosoma Cruzi serology	Reactive, Non-Reactive, Unknown	3
Plasmodium spp	Positive, Negative, Unknown	3
Other: specify	Free text	3

3.4.3 Conclusions

Part I of Deliverable 10 in the EFRETOS project has produced a list of variables and definitions to be incorporated into the European Registry to follow. The list of variables is based on current data collections, literature review and consensus among EFRETOS partners and ESOT expert groups in WP 4. Some of these variables have been classified as Tier 1 and 2, meaning that national registries should incorporate these variables to their current data collection if they are not already collecting them. Benefits derived from a standardized and systematic data collection on all these safety aspects will for sure contribute to gain knowledge in this complex and evolving area in the European setting.

4 Methods

4.1 Introduction

This chapter describes the methods that can be used to display and summarize data in a European Registry of registries. Methods of analysis that allow characteristics of donors and recipients to be compared will be discussed as well as techniques for summarizing and comparing outcomes following transplantation. Some of these methods are illustrated in the next chapter, based on data from a pilot study to validate the concept of a European Registry.

4.2 Common definition of methodology

4.2.1 Methods for summarizing data

Statistical methods that are likely to be used in summarizing data from the European Registry and in more detailed analyses of factors that may be associated with outcomes are summarized.

There are various methods available for analysing transplant outcome data, ranging from simple descriptive methods, such as summary statistics, to more complex techniques such as multi-level regression models. Outcomes following transplantation are considered to include, but are not limited to the following:

- patient survival – time to death, or whether or not the patient is still alive a given number of days after transplant;
- graft survival – time to failure of graft, or whether or not the graft is still functioning a given number of days after transplant;
- transplant survival – time to the earlier of graft failure or patient death, or whether or not the patient is alive with a functioning graft a given number of days after transplant;
- serum creatinine – the serum creatinine level following transplant. This acts as a measure of graft function for kidney transplants;
- delayed graft function – whether or not the graft functions immediately after transplant, precise definition will be given in the final data dictionary.

The techniques used for describing and summarizing variables of interests depend largely on the outcome being analysed and the intended use to which the results of the analyses will be put. The techniques used may include any of those identified in the following section.

4.2.2 Descriptive analyses

This analysis is undertaken to produce quantities that summarize the outcome of interest.

Graphical techniques
Statistical techniques often lead to results that are presented in a graphical format. Examples include estimates of the probability that an individual survives beyond any given time, which is often referred to as Kaplan-Meier survival estimates. These may be used to show, for example, the percentage of grafts that are still functioning at various times after transplant. Pie charts may also be used to show how percentages differ between a number of categories, and may be used, for example, to display information on causes of graft failure and the contribution of each cause to the total number of failed grafts. Bar charts may be used to compare the values of summary statistics between groups, and might be used to depict differences in numbers being transplanted over a number of years, for example.

Numerical summaries
Examples include a median graft survival time, which gives the time beyond which 50% of grafts are functioning, or the percentage of grafts that function for at least a year after transplant. The summary quantities are often provided with a confidence interval that gives a measure of precision that depends on the number of individuals or transplants included in the analyses. Other examples include the mean or median recipient age, which may be quoted with a range to indicate the spread of values.

Descriptive statistics may be supplemented by an assessment of the extent of evidence in the data against a pre-specified hypothesis. This may be used, for example, to test whether there is any evidence against the hypothesis that there is no difference in graft failure rates between patients who receive organs from live donors and those who receive organs from deceased donors.

4.2.3 Statistical modelling

Statistical models are used to quantify the effect of characteristics of transplant recipient, donor and other factors on the outcomes being analysed. They are also used to assess the effect of one factor on the outcome when the effect of other confounding factors has been adjusted for.

There are different kinds of regression models, and the type of model used depends on the type of outcome being analysed.

Linear regression models
Linear regression is used to analyse outcomes that are continuous measures. An example of such an outcome is the serum creatinine level of a patient after transplant. However, most analyses of transplant outcomes tend not to involve such continuous measures and this method is therefore not often used.

Logistic regression models
Logistic regression is used to analyse outcomes that can only take two possible values, which denote the presence or absence of a characteristic in each individual. An example of such an outcome is whether the graft is still functioning or not a year after transplant. In this case a logistic model would be used to determine what effect the factors have on the chance that the graft of a given patient will function for at least one year.

Survival time regression models
Survival analysis is undertaken when the outcome of interest is the length of time that elapses before an endpoint is reached. The models in survival analyses show what influence factors have on the time it takes for the endpoint to be reached. Relevant endpoints for transplant patients can be the failure of a graft or the death of a patient. The Cox regression model for the effect that variables have on the hazard of an event, such as transplant failure, is particularly widely used.

4.3 Publication of summary data

4.3.1 The level of analysis

One aspect of the European Registry on which agreement is needed is the ”level” of analyses to be provided as output from the European Registry. Data will be provided to the European Registry on individual transplant recipients, and so the registry data will be at the “transplant level”. Consideration was given to whether the European Registry should include information on the centre or region in which the patient is treated. However, it was agreed that analyses at the centre level, or the regional level, are best carried out by a national registry. It was therefore agreed that the data in the European Registry should not include the name of the transplant centre in which a patient is treated, or the region, or any identifier for a centre or region. It would not then be possible for any centre specific analyses to be carried out by the European Registry. However, it is important that there be a link between patient level data in the Registry and that held

by the national registry. For example, this would enable queries about a patient's record in the European Registry to be dealt with by the corresponding national registry. Accordingly, it is proposed that a patient level and a transplant level identifier be included in the European Registry. The corresponding national registry will then hold the key that enables the record in the European Registry to be linked to a particular patient. The data in the European Registry do not contain then any data from which details about a specific patient can be identified.

4.3.2 Data to be published

Following the survey of current practice, a number of recommendations are made for the initial publication of summary data from the European Registry.

It is proposed that the main vehicle for publication of results be a web site. This would be refreshed on a regular basis so that it remains up to date, although probably not more than once a year.

It is further proposed to start with a relatively small set of output data and then build on this as resources allow. We also propose that initially only unadjusted data is presented, and that this be accompanied by suitable warnings on the consequent limitations.

It is therefore proposed that the following information is provided by the European Registry in the first instance, separately for each of the countries who contribute national data and for each donor type:

- Number of transplants recorded for each organ in each calendar year;
- Adult (age≥18) patient survival rates at 1, 3, 5 years following transplantation, for each organ;
- Adult (age≥18) graft survival rates (i.e. graft survival censored for death of the patient) at 1, 3, 5 years following transplantation, for each organ;
- Adult (age≥18) transplant survival rates (i.e. graft survival not censored for patient death) at 1, 3, 5 years following transplantation, for each organ.
- Paediatric (age<18) survival rates at 1, 3, 5 years following transplantation, for each organ;
- Paediatric (age<18) graft survival rates (i.e. graft survival censored for death of the patient) at 1, 3, 5 years following transplantation, for each organ;
- Paediatric (age<18) transplant survival rates (i.e. graft survival not censored for patient death) at 1, 3, 5 years following transplantation, for each organ.

Survival curves (Kaplan-Meier estimates) for patient, graft and transplant survival may also be presented for each country.

In due course, arrangements might be made for individuals to download from the web site patient level data containing key variables. This facility is available from the UNOS (United Network for Organ Sharing in the United States), for example.

4.3.3 Additional analyses

Data that will allow more detailed analyses of information contained in the European Registry may be requested. Such analyses may include comparisons of graft and patient survival times for specific factors, such as recipient age group, or more complex multivariate survival analyses that incorporate adjustment for a number of factors. Indeed, any assessment of the extent of variation between countries in survival rates requires a proper degree of risk adjustment if the results are to stand up to scrutiny. Whether or not data are made available to applicants will be decided by a European Registry Review Committee that is set up to oversee the function of the European Registry.

5 Governance and Administration

The following chapter addresses the topics of governance and administration of the future pan-European Registry of registries. It builds on and refers to the conclusions of the previous project Deliverables D4 and D8.

First the underlying principles for governance are given, followed by the recommended future functions and services of the registry, the aspect of ownership of the data, issues concerning access to the data and sovereignty of Member States.

Next the administration of the proposed European Registry is described, going into topics such as the responsibilities of the Management Board, the Review Committee and the Registry Central Staff, its intended functions, as well as its organizational structure.

The chapter also includes a discussion on the relationship between the European Registry and existing international follow-up registries currently established within the European Union (EU) and ends with a more detailed description of anticipated tasks of the Management Board, the Review Committee, the Registry Central Staff and the data contributors.

5.1 Introduction

The European Registry will serve a variety of stakeholders including national competent authorities, national transplant registries, transplant centres and individual professionals, patients and donor (families), partly with different interests. It is essential for every stakeholder that the European Registry respects the interests of other participants. All stakeholders however will expect from the European Registry that its data are reliable, actual and its analyses are scientifically sound. Because of the nature of the data, another prerequisite is that the data are handled in compliance with national and European data protection and data safety regulations. And finally in many EU Member States data are currently collected by national transplant registries governed by established groups that include clinicians who act as scientific Review Committees. Creating a dynamic and for all parties satisfying interaction between these existing national registries and their review committees and the new governance body of the European Registry will be the most difficult hurdle to negotiate.

In most EU Member States data collection on post-transplant results is currently not made obligatory by the national authorities. The EFRETOS survey highlighted that several EU Member States currently do not even have a national transplant registry. As the EU Directive on quality and safety of organ donation and transplantation (Directive 2010/53/EC) does not make data collection of transplant results obligatory, the success of a future European Registry will largely depend on the ability of the Competent Authorities of the EU Member States develop and provide appropriate incentives to encourage transplant communities to submit data to national transplant registries.

By communicating clearly to the EU Member States as well as to the EU, which services the new European Registry will offer, and by explaining the benefits of cooperation for the EU as well as for its Member States, a business case can be made for investing EU goodwill and money in implementing the recommendations of the EFRETOS project and thus setting up a European Registry. An important argument for this can also be found in the conclusion of the pilot described in Deliverable 4 in which five countries submitted their national registry data. Of these five countries, that can be seen as highly motivated and with long established transplant activities, already significant difficulties were observed in merging their data to a consistent register.

As a consequence of the findings of the pilot study, it can be expected that it will take a considerable amount of time for the European Registry to obtain a smooth data collection process and yield sufficient quality of its

data (see Deliverable 12). On the other hand with a larger European Registry with high quality data, answers to questions of clinical importance can be found with greater certainty.

Especially during this initial period - but to be continued later on - it is essential to monitor quality levels of the data delivered by the different cooperating national registries. A proposal for a minimal quality standard for the delivered data is described in Deliverable 12. The minimal quality standard can serve two purposes: first it could be used as a threshold for national data to be included in data analysis and secondly it can serve as an internal gauging tool for national data quality.

An important goal of the new European Registry will be to provide stakeholders such as national authorities, transplant centres and individual professionals with answers to requests for information in a timely fashion.

A major challenge of designing a European Registry will be to adequately address privacy protection and data safety issues. Clear policies on ownership of data and on the publishing of information based on data from the European Registry should be developed and agreed upon by the cooperating national registries.

5.2 Governance - underlying principles

The governance of the new European Registry intends to respect and safeguard individual privacy as well as the sovereignty of each Member State, to identify and act upon national quality and safety issues related to the field of organ transplantation, and most importantly will strive for a harmonization with the existing national governance policies.

Every national registry within Europe can join the new European Registry of registries. As a prerequisite for joining the European Registry a letter of support from the Ministry of Health or the responsible Competent Authority has to be provided by the national registry to the governance body of the European Registry. The EFRETOS consortium would even suggest allowing access to the European Registry for countries from outside Europe at a later stage, as long as the candidate country adheres to the rules and principles of the European Registry.

The Registry intends to uphold three main principles, namely transparency, openness and not-for-profit status.

1. Transparency
   a. Governance structure;
   b. Data ownership;
   c. Data quality;
2. Openness
   a. Every European country may enter data;
   b. Adherence to rules;
3. Not-for-profit status.

These basic principles will be part of the Articles of Association of the European Registry that will have to be set up as one of the first steps of the future European Registry based on the results of the EFRETOS project.

5.3 Use of the European Registry of registries, data ownership and access

5.3.1 General principles

The main purpose of the establishment of a European Registry is to gain and increase knowledge in the field of solid organ transplantation. Increasing knowledge will ultimately lead to a reduced risk for patients with end-stage organ failure undergoing transplantation. For this purpose donor, peri-transplant and recipient factors in relation to the outcome of transplantation will be studied. The information gained can help to improve patient selection and donor organ allocation policies.

The European Registry shall not be used for organ allocation. Notable, as the European Registry is to become a registry on outcome of transplantation, information on wait listed patients who did not receive a transplant are not included. This delineation of the patient groups and the fact that data are only delivered at certain time intervals and not immediately updated furthermore precludes the European Registry to be used in the day-to-day process of organ allocation. In addition it is not the aim of the European Registry to identify differences in quality of patient care between individual transplant programs or to detect exceptional performance of professionals; both tasks are the responsibility of the respective EU Member states.

In order to fulfil its purpose the European Registry should be set up to provide certain services. These are: to provide access to inhabitants of the EU to an actual overview of the activities and profiles of national registries within EU Member States, including information on active transplant programs, annual number of transplants performed within each Member State and some basic demographic statistics; and to set up an information request service for data extracts and data analyses.

An important factor for Competent Authorities to consider for cooperating with the new European Registry will depend on safeguards that EFRETOS can give on who has access to data, and for what purpose data will be used and what type of analyses will be conducted. Therefore, data access and data release has to be governed by transparent policies that have to be developed involving all partners actively contributing to the European Registry.

5.3.2 Categories of data requests and their handling

In the day-to-day practice standardized reports have to be created and interpreted, incoming requests have to be evaluated and reacted upon and adherence to the policies has to be monitored. Of course data may only be released if the quality of data is appropriate to address the request according to the quality levels described in Deliverable 12. These general procedures will safeguard against any traces of unauthorized usage of national data and prevent wrong interpretation due to inadequate quality of the data.

Most EU Member States apply a model where access to data is strictly controlled by especially established review committees, this in contrast to the USA where complete data sets can be requested via a liberal standard request procedure.

Data usage is a sensitive issue for any registry dealing with sensitive data such as outcome of transplants. As mentioned previously the future European Registry should build on the fact that most countries already have committees in place that govern the data release for their national registry. However, if each and every data release from the European Registry has to be approved separately by each of these national review committees, the European Registry will have no momentum and is likely to be regarded by its future users (i.e. the stakeholders) as an unattractive and user unfriendly institute, which hardly serves any purpose.

Therefore general policies of the European Registry on data usage need to be developed. These policies will be based on the Articles of Association of the European Registry (see section 2) laying down legal and functional limits of data release and will be developed by the governing body of the European Registry involving national stakeholders of all contributing countries.

It is crucial that this governing body of the European Registry defines a set of data that can be used for data reports and data requests, and can be released without the additional need for authorization. Whether these data mirror the Tier 1 data (Deliverable 7) has to be decided by the future governing body of the European Registry.

For data requests going beyond these standard reports and analyses, authorization has to be given by a committee of experts. This committee is responsible for assessing whether or not data requests are complying with approved policies and general principles of the European Registry.

Details on the organizational structure of European Registry including the governing body (Management Board) and the expert committee (Review Committee) are described in section 4 of this document.

National registries will be able to access their own national data. For all other types of requests the following table is proposed:

Categories of data requests		Data release to
A	Standardized reports and related data requests that do not require specific authorization	All stakeholders
B	Data requests that require specific authorization	Authorized stakeholders

The definition of these two categories and any modification of the definitions later on is the responsibility of the future governing body of the European Registry.

Finally, what follows are some basic rules of engagement that need further elaboration in the future Articles of Association of the European Registry, and the contracts between the national registries and the European Registry (see section 2). The European Registry delivers original data if the data request is approved. The European Registry can offer data analysis if reimbursed. The source of data, released by the European Registry should always be given. If data analysis is reviewed and thereafter approved, this can be mentioned in the article. If users of the European Registry choose to perform and present analyses without subsequent approval, this should then explicitly be stated by the European Registry's disclaimer. If data analysis is considered to be of low quality by the expert committee and is published anyway this might have influence on future evaluation of data requests by this group.

5.4 Organizational structure and distribution of responsibilities within the European Registry

There are several possibilities for designing a governance model. Internationally well-established is the model where an international group of elected scientists form the management for a limited duration of time. Another model is that a National Authority establishes and manages a registry or governs an organization that is assigned to set up and sustain the European Registry.

In this paragraph, a three layered governance structure is proposed. These are the Management Board, the Review Committee and the Central Staff (figure 1). In addition a proposal is given for their composition which is based on models currently in place in well-established transplant registries as well as on the current situation in several EU Member States.

For the governance structure of the new European Registry it is proposed that major stakeholders such as delegates from the participating national and multinational registries providing data to the European Registry as well as/or delegates from the Competent Authorities should constitute the Management Board of the new European Registry.

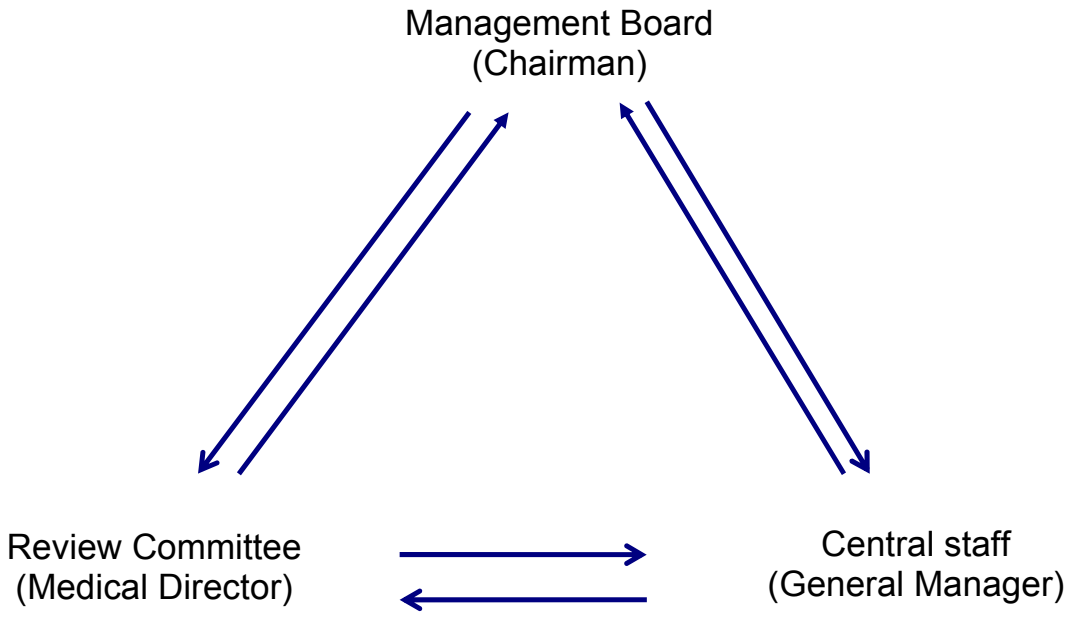


Figure 1. Governance structure

The European Registry is directed by the Management Board and Review Committee. The General Manager of the European Registry supported by the Registry Central Staff will be responsible for data collection, cleaning, storage and the production of routine reports complying with category A.

The Management Board is responsible for policies regarding request handling and data release, the definition of the data access types and other policies regarding data safety and security. Such policies should be in accordance with medical and ethical principles. The Management Board is also responsible for the performance of the Review Committee.

The Review Committee will be responsible for assessing the data requests and for judging the quality of publications that used the Registry data and for workload prioritization.

5.4.1 Management Board

The Management Board acts as governing body for the European Registry organization. It is responsible for developing and sustaining a framework of policies that ensures that the registry can function in compliance with the existing legislative, scientific and ethical conditions.

Tasks and responsibilities of the Management Board

The Management Board will develop policies for managing a registry including criteria, policies, and standards to which the European Registry must conform. Policies for data field development, patient data privacy, data definitions, data collection protocols, data use protocols, data distribution protocols, data analysis; country enrolment, data protection, data validity and integrity have to be set up. Of special importance will be the policies on data requests and their handling as described in section 3.2.

The Management Board is responsible for the direction of all activities executed by the Review Committee and the Central Staff of the European Registry.

The Management Board will agree upon proposals for European Registry adaptations, determine priorities and cost effectiveness.

In summary, the Management Board is responsible for the policies that are directed at developing and controlling the execution of:

- data collection / data definition;
- data protection/safety;
- quality standards;
- data ownership/usage
  - (maybe in the framework of basic principles laid down in “Articles of association/Charter of the European Registry”).

In addition the Management Board has a control function that is focused at the

- performance of the Review Committee;
- authorization of budget proposals put forward by the Central Staff;
- authorization of strategic development policies put forward by the Central Staff.

Members of the Management Board

In order to be able to fulfil the above mentioned tasks, the Management Board will consist of members appointed by national Competent Authorities or delegated bodies responsible for registry questions of the participating countries. All national or supranational registries delivering data to the European registries shall also send a representative to the Management Board. These representatives have to be (re-)appointed at least every three years by the respective authority and/or registry.

Important to note is that only representatives of countries and organizations that supply data to the future European Registry can exercise voting rights in the Management Board. The number of votes per country will be limited to one vote per country independent of the number of representatives sent by this country to the Management Board. Arguments for setting up this construction are that these groups are major stakeholders, as well as the custodians of the national data (see section 3).

The start-up period of the European Registry (see section 5) is characterized by the need to develop detailed policies in the areas described above while at the same time no country has delivered data to the European Registry yet. During this period the Management Board will be open to all countries intending to join the European Registry including but not limited to the current members of the EFRETOS consortium. After a transition period to be defined by the Management Board only representatives from countries and organizations actually supplying data will have voting rights as described above.

Sending observers to the Management Board is possible for national and international transplant societies, for patient organizations and for multinational organ transplant registries (not providing data). These observers will have no voting rights. Countries willing to join the European Registry after the start-up period may send observers (appointed by the Competent Authority and/or by the national registry) to the Management Board.

Policies will have to be developed by the Management Board defining and managing the number of representatives per country and for identifying which organizations can send observers to the Management Board. This will include regulations on how long a country intending to join the European Registry may act as an observer without delivering data.

The Registry Management Board’s chairman is elected among the European Registry Management Board members and will take this position for a limited duration of time.

COMPOSITION OF THE MANAGEMENT BOARD	
Definite delegates from	**Possible** delegates from
• Competent authorities or delegated bodies responsible for registry questions. • National and supranational registries (If not yet covered). • Only if supplying data!	• Representatives from national transplant societies. • Representatives from countries willing to join the European Registry (limited period of time). • Multinational registries with cooperation. • Patient organizations.
Policy needed for • Number of representatives per country.	Policy needed for • Identification of organizations allowed sending representatives. • Number of delegates.
Voting rights	Observers • None of the above mentioned have voting rights.

5.4.2 Review Committee

Tasks and responsibilities of the Review Committee

Within the mandate of the Management Board the Review Committee will review and evaluate proposals for European Registry adaptations, determine priorities in relation to available resources and make recommendations to the Management Board regarding approval of such proposals.

Further the Review Committee is expected to oversee the implementation of adaptations and monitor their on-going progress, participation rates, and cost benefit ratio, to conduct regular evaluations regarding the benefits of the European Registry, and to direct and oversee all activities performed by the Registry Central Staff.

One of the key tasks of the Review Committee will be the evaluation of data requests going beyond standard reports and analyses. It is the responsibility of the Committee to assess whether or not these data requests should be met (see 3.2). In case data requests are considered to be in conflict with approved policies from the Management Board and general principles of the European Registry, data release is only possible after additional involvement of the Management Board.

External users can ask for their analyses of the data provided by the registry to be reviewed prior to publication. If approved by the Review Committee, this can be mentioned in the article. If data analysis is considered to be of low quality by the Review Committee and is published anyway this has to be taken into account when evaluating future data requests by of the same group (see 3.2).

The Review Committee will comment on analyses of the data provided by the Central Staff for the Annual Report of the European Registry and will contribute to the interpretation of the data presented.

In summary the Review Committee will have the following tasks:

- evaluation of non-standard information requests;
- prioritization of tasks of the Central Staff;
- guiding the Central Staff in the production of Annual Reports;
- cooperation with the Central Staff
    - control (content wise) of performance of Central Staff;
- development of proposals for policies that should be developed regarding data collection / analysis etc.
- publication review / policy.

Members of the Review Committee

The profile of its members is intended to be of medical scientific nature. Therefore it is suggested that members of the Review Committee shall be proposed by the transplant community. The selection of the members of the Review Committee among these proposed candidates is done in the Management Board. If possible the number of experts shall be limited to one per country. Every type of (solid) transplantable organ should be represented; the total number of experts should be limited to ten plus a Medical Director. The Medical Director is elected by and among the members of the Review Committee. He holds a position in the Management Board and is the independent chairman of the Review Committee. If necessary the Review Committee can make use of external experts to address specific questions.

The term of membership is three years with 50% of the members ending their term every eighteen months. Of the initial members 50% have to leave already after eighteen months, they will be selected by lottery. Members can be re-elected once.

The Review Committee is supported by the General Manager as well as statistical and technical experts of the Central Staff of the European Registry as advisors.

COMPOSITION OF THE REVIEW COMMITTEE

- Medical Director is head of Review Committee;
- (Medical) experts from the transplant field – elected
- Advisors:
    - General Manager of Central Staff;
    - (Bio)statistician(s) and technical experts from Central Staff;
    - External experts to address specific questions.

Interaction between Management Board and Review Committee

Tasks of both the Management Board and the Review Committee will have to be established. It can be envisaged that initially the Management Board will take all decisions concerning data collection items, data analyses and requests. In a later phase after it has been established which data can be accessed by whom without authorization and which data need authorization, the Review Committee will become more independent. Any change in definition of the two types of data (see 3.2) will need to be approved by the Management Board.

The Medical Director holds a position in the Management Board thereby guaranteeing the close cooperation and interaction between these two bodies.

5.4.3 Central Staff

Tasks and responsibilities of the Central Staff

The Central Staff will be responsible for data hosting, data collection, monitoring of the quality of the data and for data analysis. The Central Staff will be responsible for the implementation of all agreed policies and operating procedures. The Central Staff will also have responsibility for the financial and human resource requirements, as well as for communications.

On top of that the Central Staff will be responsible for adhering to European data protection and safety rules, to preparing proposals for new policies for the Management Board based on input from Review Committee as well as from external initiatives. Controlling data quality according to policies approved by the Management Board is another responsibility. Regarding data requests the Central Staff is responsible for forwarding requests needing approval by the Review Committee (s. 3.2), and for preparing the Annual Report together with the Review Committee.

The central staff of the European Registry is led by a General Manager who will - as a professional - also be involved in the daily work. To the outside he will act as an ambassador.

Composition of the Central Staff of the European Registry

Biostatisticians, data managers, IT specialists (development and infrastructure) should be working for the European Registry. The functions for human resource management, finance & accounting and i.e. facility management should be present, but not necessarily under responsibility of the European Registry; i.e. outsourcing of these functions - or parts of these functions - is seen as a realistic option. To what degree IT tasks can be outsourced has to be decided based on daily practice.

It is anticipated that the Central Staff will be embedded in either an Organ Exchange Organization (OEO) or an academic institution. Considerable advantages are expected to be realized if the European Registry is to be hosted by an existing organization that has experience in organ donation, allocation and transplantation.

5.5 Required resources for the European Registry of Registries

A European Registry can only function under specific conditions. National registries should see the benefits for their patients of committing themselves to join forces with other national registries. After such commitment has been established, a European Registry should be established involving setting up the organization, hiring the required staff, developing and implementing the policies and procedures, organizing processes, developing the software and installing the hardware. The services should be available, affordable and meet the requirements of the stakeholders requesting data for release and or analysis.

In the development of a European Registry different phases can be identified. During the *start-up period* policies have to be developed, personnel to be hired, investments to be made and processes to be organized. During the so called "*early" running period*, high flexibility is needed to accommodate a greater diversity in data formats entering the registry as well as in data quality. This will require a higher initial workload from the side of data management and IT requiring higher staffing levels in these areas. In the *longer term period* - after approximately 4-5 years - the "definite" lower staff levels can be sustained, equipment and other investments to be depreciated and replaced systematically in time.

5.6 Relation to other international European registries

Several scientific international transplant follow-up registries have proven to be a powerful driver of improving knowledge, like the European Liver Transplant Registry (ELTR) and the International Society for Heart and Lung Transplantation Registry (ISHLT).

A future European Registry should aim at developing a close relationship with these well-established registries. It might be 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.

Given the purely scientific nature of these organ specific registries, it is highly likely that the focus of future cooperation will lie in the enabling of comprehensive international studies, provided that such studies would comply with policies agreed upon by the European Registry's Management Board.

If cooperation with one of these international transplant follow-up registries is established, observers from these registries could join the Management Board as described above (4.1.2).

5.7 Addendum

5.7.1 Detailed task description of the Review Committee

Data collection

Decide on initial cohort. Options are: to either perform a backfill of the European Registry or to start with data collection for transplants performed as of entering the registry. We recommend that there will be a degree of backfilling so that the European Registry more quickly becomes a useful resource.

Decide on refresh dates. Feasible options for updating the European Registry are: either an annually data upload (ISHLT model) or twice a year (ELTR model).

Decide on a reminder scheme. If a contributor did not submit data within X time to the European Registry a reminder will be sent once and repeated after Y time.

Decide on the data delivery model. Updates of follow-up data can be submitted to the European Registry as follows: only records with a changed item are sent or the total national registry is submitted (ISHLT model).

Decide on data format of the mandatory data set.

Access to data

Decide on how the collected data are made available to professionals and the public in the framework of policies developed by the Management Board. Options are: via online quarterly data reports, via annually refreshed data slides, and via interactive queries.

Additionally, all contributors may submit queries to the European Registry to obtain specific data sets or data analyses needed for a research project or manuscript. Such requests would be made using a data request form.

Decide on level of access for contributors, for instance a country that delivers data to the Registry will always have full access to their own data.

Decide on level of access for non-contributors in the framework of policies developed by the Management Board.

Request for data

Decide on models for handling requests for data and analyses from the European Registry. We recommend that requests are sent in via a data request form, with priority given to requests which are from contributors and which are directly related to immediate patient care, and where routine data requests are handled promptly.

Decide on exact format of delivered data sets.

Decide on requests for specialized data or complex analyses, i.e. requests that are time consuming. A fee for the collection and/or analysis of such data may be involved.

Decide on publication policy.

Data management

Decide on business rules to be implemented in the data management procedures. Decide on how to handle violations against these rules, for instance a violation will initiate a correspondence between the Central Staff and the contributors. A protocol for this interaction will need to be drafted and response time of the contributors will be monitored.

Data quality

Decide on a standardized approach with regard to the assessment of data quality indicators. For instance it might be decided that country X is excluded from all reports if the data completeness has remained below x% for a stated period of time.

Decide on duration of this initial phase of complete record submission.

Decide on audit policy.

Data field development

Decide on content and definition of the data items in the three datasets according to new insights.

Decide on record identification.

5.7.2 Detailed task description of the Central staff

Performs all tasks related to the registry from data collection to data distribution.

Data collection

According to a pre-defined account management policy data collection from the participating countries will be executed. This includes keeping track of incoming data, sending out reminders and establishing communication pathways for ensuring data quality.

Data management

Query data items that fail validation checks or that do not meet appropriate quality management indices and act upon feedback from contributors on data discrepancies.

Data analysis

Following the European Registry policy, standard and special requests for data analysis will be handled.

Data distribution

A registry web site will be built. An annual report will be produced and disseminated via this web site; these will include case mix adjusted country specific outcome data. An interactive report building package will be

made available; this will include the creation of Kaplan-Meier curves. A yearly update of a slide kit will be posted on the European Registry web site. All these options will be publicly accessible. Data retrieval of the original data set will be restricted to the own country.

5.8 Estimated budget for setting up and sustaining a European Registry

5.8.1 Functional and structural assumptions used for the cost calculation

Based on the surveys performed within the EFRETOS project, as well as on the current practice within the national transplant follow-up registries of the UK (NHSBT), France (ABM), the Netherlands (NOTR) and Eurotransplant, an estimate can be made on the required resources and manpower necessary for setting up and sustaining a future European Registry of registries. For this calculation several assumptions are made:

The EFRETOS registry will:

- be hosted by a contracted well-established organization experienced in running a registry for evaluation the outcome of organ transplants;
- sustain a staffing level and running costs that is appropriate in relation to the number of participating national registries;
- outsource as many non-essential registry functions as possible in order to keep the staffing levels under responsibility of the European Registry minimal.

The functional, legal and technical requirements of the European Registry are described in detail in Deliverable 14. Based on this document the following technical assumptions concerning the set-up are made:

The European Registry will include:

- web service enabling importing of data from other registries;
- web based application for data entry, data cleaning, data storage, and data removal;
- storage in a central relational database management system (Oracle, SQL-server or other) with high security level (authorization);
- Export-functionality to registries;
- business intelligence software;
- online analysis tools;
- web site for general information and dissemination.

5.8.2 Cost estimate European Registry

As described in section 5 of this document different phases can be distinguished in the evolution of the European Registry. These phases will have an impact on the costs. During the first year or "*start-up-period"*, personnel has to be hired, policies have to be developed, processes to be organized, hardware investments have to be made. Most importantly the core applications of the registry the functional specifications have to be set up based on these the applications have to be built and tested. During the "*early running period"* (year 1-5) the work of the registry has to be organized in such a way that high flexibility is possible to allow the entry of data into the registry in spite of a diversity in data formats and data quality. This will result in a higher initial workload for data management and ICT requiring higher staffing levels in these areas during this period of time. In the "*longer term period"* – after approximately 5 years – the "definite" staff levels can be sustained.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Personnel						
Central Staff						
General Manager	€ 100.000	€ 100.000	€ 100.000	€ 100.000	€ 100.000	€ 100.000
ICT support for hardware and software	€ 120.000	€ 120.000	€ 120.000	€ 120.000	€ 120.000	€ 60.000
Data entry / data management	€ 80.000	€ 80.000	€ 80.000	€ 80.000	€ 80.000	€ 40.000
(Bio-)statisticians	€ 100.000	€ 100.000	€ 100.000	€ 100.000	€ 100.000	€ 100.000
Support Staff (shared services)						
Secretary, human resources, finance, communications	€ 50.000	€ 50.000	€ 50.000	€ 50.000	€ 50.000	€ 50.000
Total Personnel costs	€ 450.000	€ 450.000	€ 450.000	€ 450.000	€ 450.000	€ 350.000
ICT infrastructure costs						
Initial development of the IT system (functional specifications, development and testing)	€ 300.000	270.000-	-	-	-	-
Hardware acquisition and maintenance	€ 100.000	€ 50.000	€ 50.000	€ 50.000	€ 50.000	€ 50.000
Software licenses (data base and data analysis)	€ 80.000	€ 60.000	€ 60.000	€ 60.000	€ 60.000	€ 60.000
Other costs						
Expenses for Management Board and Review Committee (including remuneration of Medical Director)	€ 45.000	€ 45.000	€ 45.000	€ 45.000	€ 45.000	€ 45.000
Travel costs Central Staff	€ 5.000	€ 5.000	€ 5.000	€ 5.000	€ 5.000	€ 5.000
Annual costs	**€ 980.000**	**€ 880.000**	**€ 610.000**	**€ 610.000**	**€ 610.000**	**€ 510.000**

6 Functional requirements

6.1 Registry functionality

What follows is a general scheme for the European Registry functionality. Detailed specifications will be described by the future Management Board and Review Committee of the European Registry.

All countries in Europe can participate in the new European Registry once they are authorized by their national government or Competent Authority to deliver data to the European Registry.

Data submission
Countries can submit data to the European Registry by uploading their data into the central data using the registry systems designed for this purpose.

Data format
Countries should deliver data on the registration of transplanted patients with the information contained in the mandatory set according to a pre-defined format.

Types of data sets
All EU countries can submit data to the European Registry on a voluntary basis, but countries that have agreed to participate in the registry are required to deliver data contained in the minimal set. After the initial phase these participating countries should deliver data contained in the basic set. Countries can voluntary deliver data contained in the expanded set.

Data submission time points
Follow-up data should be delivered according to a pre-defined data collection scheme. The Central Staff will take care of a corresponding data reminder scheme to support data delivery.

Record identification
According to the European Union directive regulating collection and storage of personal data (EU 95/4/EC) data should be non-identifiable outside the transplant centre. The best solution for matching new follow-up data to existing registrations of the same recipient and to avoid double listings a unique identifying number will be assigned to each registered patient, donor and transplant. In addition the country specific identifiers will be stored confidentially and securely in order to allow a trace back from the data in the European Registry to the contributor.

Interaction with editorial tables
Sharing national transplant data with the European Registry comes with the obligation to deliver high quality data. Upon the uploading/data entry phase the submitted data will be screened according to pre-defined business rules. Discrepancies arising from these checks will be forwarded to the data contributor using editorial tables. The corrected data will then be resubmitted to the registry and the process of data checking is restarted till the data quality meets up with the requirements. Participating countries that fail to correspond in a timely fashion on these editorial tables may be removed from the registry reports.

Data base handling
The uploaded data bases will be stored into a central data base with pre-defined data fields. An interactive data base structure will be built. An extensive description of the formats for the three data sets will be provided.

European Registry data base
The data is entered and maintained in a central data base with internet access. Each country is represented in this data base and representatives from a country can view, modify, obtain reports and download their own data. In addition, all countries can obtain general overviews of the complete European Registry.

6.2 Current status in the EU Member States (EFRETOS partners)

A survey was sent to sixteen countries participating in the EFRETOS Management Board. This paragraph provides a complete overview of their responses.

6.2.1 Assigned organization

Do you have a national organization responsible for collecting follow-up data?

Country	Response	Name of the organization
Austria	Y	OEDTR
Belgium	N	
Croatia	N	
Denmark	-	
Finland	-	
France	Y	ABM
Germany	Y	Aqua institute
Iceland	-	
Italy	Y	CNT
Luxembourg	N	
Netherlands	Y	NTS
Norway	-	
Slovenia	N	
Spain	Y	ONT
Sweden	-	
United Kingdom	Y	NHSBT

The specific tasks of these organizations are described in the table below. Notice that Belgium, Croatia, Luxembourg and Slovenia do not have a national organization responsible for collecting follow-up data, but these countries participate in a voluntary registry managed by Eurotransplant. Austria has a scientific registry for kidney follow-up data that cooperates closely with Eurotransplant; data for the other organs are directly managed by Eurotransplant.

What are the specific tasks of this organization?

Country	Data collection	Reporting of outcome data	Auditing of centres
Austria	Y	Y	
Belgium	Y	Y	
Croatia	Y	Y	
Denmark	-		
Finland	-		
France	Y	Y	Y
Germany	Y	Y	Y
Iceland	-		
Italy	Y	Y	Y
Luxembourg	Y	Y	
Netherlands	Y	Y	Y
Norway	-		
Slovenia	-		
Spain	Y	Y	Y
Sweden	-		
United Kingdom	Y	Y	Y

Additional comments:
Italy: The Transplant law prescribes to collect data through a national information system, and in 2002 the Minister of Health entrusted CNT with the task of monitoring transplant outcomes through data collection. Audits are carried out periodically on all centres by a national commission set up by CNT*UK*: Tasks include comprehensive data collection on donors, patients registered for transplant, transplant procedures and follow-up information. NHSBT does very limited data collection itself, but instead processes and stores data collected by staff in transplant units. Post-transplant outcome data reported at a national level and also by centre, with and without risk adjustment. Early post-transplant outcomes are monitored using CUSUM methods, centres are compared using several statistical methods. This auditing is data driven; NHSBT does not conduct clinical audit of services provided by centres.

What type of staff work at this organization?

Country	Data managers	Data analysts	Software developers	Data entry person
Austria	Y	Y	Y	Y
Belgium	Y	Y	Y	Y
Croatia	Y	Y	Y	Y
Denmark				
Finland				
France	Y	Y	Y	Y
Germany	Y	Y	Y	Y
Iceland				
Italy	Y	Y	Y	
Luxembourg	Y	Y	Y	Y
Netherlands	Y	Y	Y	N
Norway				
Slovenia	Y	Y	Y	Y
Spain	Y	Y		Y
Sweden				
United Kingdom	Y	Y	Y	Y

Additional comments:
Italy: Staff is organized in different departments: a medical department, an IT department, a service department (including a publicity campaign office and a training office, plus administrative services). The IT department includes data manager, data analyst, software developers, and software development analysts.

UK: In addition to the personnel mentioned in the table the following staff is present: data entry staff, data support officers, data base data base officers, scientific support officers, data services managers, software developers/programmers, systems analysts, data base administrators, systems administrators, helpdesk staff, software testers, project managers, duty officers (24/7 office for offering organs), marketing, campaigns and publications staff, web developers, donor transplant coordinators and team leaders/managers, statisticians, a medical director, human resources, finance, office services and corporate services.

6.2.2 National Registry

Do you have a registry that contains all organ transplant registrations?

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

Does the national registry have a registry review board (i.e. a committee that controls the use of the registry?

Country	Response
Austria	Y
Belgium	Y
Croatia	Y
Denmark	
Finland	
France	Y
Germany	Y
Iceland	
Italy	N
Luxembourg	
Netherlands	Y
Norway	
Slovenia	Y
Spain	Y
Sweden	
United Kingdom	Y

Additional comments:
Italy, UK, ET have boards for each organ, the Netherlands has just one committee.

How is this registry review committee organized (e.g. organ specific delegates, chosen delegates, legal ethical experts, representatives of the ministry)?

Country	Organ specific delegates	Clinicians	Legal/ethical experts	Statisticians	Representatives of the ministry
Austria	Y	Y		Y	N
Belgium	Y	Y		Y	N
Croatia	Y	Y		Y	N
Denmark					
Finland					
France		Y		Y	N
Germany	Y	Y		Y	N
Iceland					
Italy					
Luxembourg		Y		Y	N
Netherlands	N	Y		N	Y
Norway					
Slovenia	Y	Y		Y	
Spain	Y	Y		N	Y
Sweden					
United Kingdom	Y	Y		Y	N

Additional comments:
UK: There are boards for each organ group – kidney/pancreas, liver/small bowel, cardiothoracic, ocular. The liver and cardiothoracic groups include a clinical representative from each unit and a statistician. Due to the larger number of renal units, their board includes the chairs of the kidney and pancreas advisory groups, a scientific advisor, nephrologist, UK renal registry representative and statistician. Similarly, the ocular board includes the chair of the ocular tissue advisory group, around six clinical representatives and a statistician.
Spain: Organ specific delegates (transplant team representatives) and representatives of the Ministry (ONT)

What are the tasks of this committee?

Country	Reviewing and approving/rejecting applications for national or international data	Advising on the prioritization of projects conducted	Specification of variables
Austria	Y		Y
Belgium	Y		Y
Croatia	Y		Y
Denmark			
Finland			
France	N	N	Y
Germany	Y		Y
Iceland			
Italy			
Luxembourg			Y
Netherlands	Y	Y	Y
Norway			
Slovenia	Y		Y
Spain	Y		Y
Sweden			
United Kingdom	Y	Y	

Additional comments:
France: There is an internal (internal to the Agence de la Biomédecine) review board. Its tasks are:
- technical improvement of the registry
- forecast of future needs and evolutions

It is not really about controlling the use of the registry.

When did the national registry start?

Country	Year start registry	Year first transplant in registry
Austria	1967	1971
Belgium	1967	1963
Croatia	2008	2006
Denmark		
Finland		
France	1959	1959
Germany	1967	1967
Iceland		
Italy	2001	2002
Luxembourg	1967	1980
Netherlands	2002	1966
Norway		
Slovenia	2000	
Spain	1998 (liver)	1984 (liver)
Sweden		
United Kingdom	1985	1962

6.2.3 Follow-up data request procedure

How do you request for follow-up data? (multiple options are possible)

Country	Mail/fax	E-e-mail	By automatic e-mail	By automatic e-mail, generated by a schedule	Triggered by log-in procedure with a schedule	Other
Austria	Y	Y			Y	
Belgium	Y	Y			Y	
Croatia	Y	Y			Y	
Denmark						
Finland						
France	Y	Y			Y	
Germany	Y	Y			Y	
Iceland						
Italy	Y	Y			Y	
Luxembourg	Y	Y			Y	
Netherlands					Y	File upload
Norway						
Slovenia	Y	Y			Y	

Spain		Y		Y	Y	
Sweden						
United Kingdom	Y					electronic forms put in users electronic work area.

Additional comment:
UK: Also paid data collectors are sent to some hospitals to collect data.

Is it mandatory for centres to report follow-up data to the national registry?

Country	Voluntary	Mandatory
Austria	Y	
Belgium	Y	
Croatia	Y	
Denmark		
Finland		
France		Y
Germany		Y
Iceland		
Italy		Y
Luxembourg	Y	
Netherlands		Y
Norway		
Slovenia	Y	
Spain		Y
Sweden		
United Kingdom	Y	

Additional comments:
France: The collection of FU data is required by the bioethics law, August 6, 2004

UK: voluntary.
There is no legal requirement for centres to report follow-up data, but there is a strong desire from the transplant community to have comprehensive data and so centres are chased up if they do not supply data. The collection of follow-up data is required by some commissioners of organ transplantation.

Spain: For reference centres, graft and patient survival data are mandatory; the remaining variables are voluntary at this moment.

Do you have data collection targets (e.g. 80% of follow-up forms should be returned within two months of their due date)?

Country	Response
Austria	N
Belgium	N
Croatia	N
Denmark	
Finland	
France	N
Germany	N
Iceland	

Italy	Y
Luxembourg	N
Netherlands	Y
Norway	
Slovenia	N
Spain	N
Sweden	
United Kingdom	Y

Additional Comments:
Italy: If percentage of supplied follow-up is under 80%, it will be highlighted in the annual report of the outcome assessment.

UK:
- **98%** of transplant record forms received within 3 months of transplant;
- **75 %** of 3 month forms received within 4 months of transplant;
- **98 %** of 12 month forms received within 4 months of first transplant anniversary; **97 %** of annual forms received within 6 months of each transplant anniversary.

Spain: Still in progress

The Netherlands: Aim to receive 90% of the data within 1 year after transplantation.

6.2.4 Data delivery

How are follow-up data delivered?

Country	Paper questionnaires	On site by study nurses	Online data entry by centres	Local follow-up system with data upload	Free delivery in all kinds of formats and modes
Austria	Y		Y		Y
Belgium	Y		Y		Y
Croatia	Y		Y		Y
Denmark					
Finland					
France			Y		
Germany	Y		Y		Y
Iceland					
Italy			Y		
Luxembourg	Y		Y		Y
Netherlands				Y	
Norway					
Slovenia	Y		Y		Y
Spain			Y	Y	
Sweden					
United Kingdom	Y	Y	Y	Y	

When are data delivered?

Country	Upon request at appointed fixed time points	Upon request for specific projects	Continuous without request no fixed time points
Austria	Y	Y	Y
Belgium	Y	Y	Y
Croatia	Y	Y	Y
Denmark			
Finland			
France	Y		
Germany	Y	Y	Y
Iceland			
Italy	Y		Y
Luxembourg	Y	Y	Y
Netherlands			Y
Norway			
Slovenia	Y	Y	Y
Spain	Y annual		
Sweden			
United Kingdom	Y		Y

Additional comments:
UK: continuous without request no fixed time points – Yes, for the data upload of pre-defined dataset from local systems only.

6.2.5 Data management

What kind of actions do you take to improve the quality of the data (e.g. by data cleaning)?

Country	Manual data management	Automatic data management	No actions
Austria	Y	Y	
Belgium	Y	Y	
Croatia	Y	Y	
Denmark			
Finland			
France	Y	Y	
Germany	Y	Y	
Iceland			
Italy		Y	
Luxembourg	Y	Y	
Netherlands	Y	Y	
Norway			
Slovenia	Y	Y	
Spain	Y	Y	
Sweden			
United Kingdom	Y		

At what time points do you perform data quality controls?

Country	Uploading/data entry and saving phase	Analysis phase	No actions
Austria	Y	Y	
Belgium	Y	Y	
Croatia	Y	Y	
Denmark			
Finland			
France		Y	
Germany	Y	Y	
Iceland			
Italy	Y	Y	
Luxembourg	Y	Y	
Netherlands	Y	Y	
Norway			
Slovenia	Y	Y	
Spain	Y	Y	
Sweden			
United Kingdom	Y	Y	

Do you make use of quality indicators that induce reminders for follow-up?

Country	Response
Austria	N
Belgium	N
Croatia	N
Denmark	
Finland	
France	N
Germany	N
Iceland	
Italy	Y
Luxembourg	N
Netherlands	N
Norway	
Slovenia	N
Spain	N
Sweden	
United Kingdom	N

Additional comments:
ET: Quality indicators are only used for the trial data bases.

Italy: An online system shows a flag for each transplant without a due follow-up.

The Netherlands: If an item is missing then whole record is not uploaded.

6.2.6 Registry data

Do you have a fixed format for the variables stored in the registry?

Country	Response
Austria	Y
Belgium	Y
Croatia	Y
Denmark	
Finland	
France	Y
Germany	Y
Iceland	
Italy	Y
Luxembourg	Y
Netherlands	Y
Norway	
Slovenia	Y
Spain	Y
Sweden	
United Kingdom	Y

Please give your standard format for each of the variables in the EFRETOS pilot study

	Italy	France	Austria, Belgium, Croatia, Germany, Luxembourg, Netherlands, Slovenia	Spain	UK
Age recipient	Date of birth dd/mm/yyy	Date of birth dd.mm.yyy	Date of birth dd/mm/yyyy	Date of birth dd/mm/yyyy	Date of birth dd/mm/yyyy
Gender recipient	F/M	F/M	Male/Female	Male/female	MALE/FEMALE/NOT REPORTED/UNKNOWN
Age donor	Date of birth dd/mm/yyy	Date of birth dd.mm.yyy	Date of birth dd/mm/yyyy	Date of birth dd/mm/yyyy	Date of birth dd/mm/yyyy
Gender donor	F/M	F/M	Male/Female	Male/female	MALE/FEMALE/NOT REPORTED/UNKNOWN
Primary disease recipient	ICD-10 / SNOMED	ABM internal thesaurus	ICD-10	ICD-10/ SNOMED	NHSBT list
Donor type	Cad/Liv	décédé/vivant	ET list	BD (Ki) NHBD (Ki) LD (Ki) Cadaveric (Li) Living (Li) Domino (Li)	NHSBT list
HLA mismatch	HLA mismatch per locus	HLA mismatch per locus	HLA mismatch per locus	HLA mismatch per locus	HLA mismatch per locus

Ischemic time	number (minutes)	HH:MM	number in hours and in minutes	Number in minutes	Number in minutes
Date of transplant	dd/mm/yyyy	dd.mm.yyy	dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy
Date of graft failure	dd/mm/yyyy	dd.mm.yyy	dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy
Date of death	dd/mm/yyyy	dd.mm.yyy	dd/mm/yyyy	dd/mm/yyyy	dd/mm/yyyy

NHSBT list of primary disease

CHRONIC RENAL FAILURE, AETIOLOGY UNCERTAIN
GLOMERULONEPHRITIS, HISTOLOGICALLY NOT EXAMINED
SEVERE NEPHROTIC SYNDROME WITH FOCAL SCLEROSIS
IGA NEPHROPATHY
DENSE DEPOSIT DISEASE
MEMBRANOUS NEPHROPATHY
MEMBRANO-PROLIFERATIVE GLOMERULONEPHRITIS
RAPIDLY PROGRESSIVE GN WITHOUT SYSTEMIC DISEASE
FOCAL SEGMENTAL GLOMERULOSCLEROSIS WITH NEPHROTIC SYNDROME IN ADULTS
GLOMERULONEPHRITIS, HISTOLOGICALLY EXAMINED
PYELONEPHRITIS/INTERSTITIAL NEPHRITIS - CAUSE NOT SPECIFIED
PYELONEPHRITIS/INTERSTITIAL NEPHRITIS - ASSOCIATED WITH NEUROGENIC BLADDER
PYELONEPHRITIS/INTERSTITIAL NEPHRITIS - CON OBS UROPATHY WITH/WITHOUT V-U REFLUX
PYELONEPHRITIS/INTERSTITIAL NEPHRITIS - ACQUIRED OBSTRUCTIVE UROPATHY
PYELONEPHRITIS/INTERSTITIAL NEPHRITIS - V-U REFLUX WITHOUT OBSTRUCTION
PYELONEPHRITIS/INTERSTITIAL NEPHRITIS – UROLITHIASIS
PYELONEPHRITIS/INTERSTITIAL NEPHRITIS - OTHER CAUSE
TUBULO INTERSTITIAL NEPHRITIS - (NOT PYELONEPHRITIS)
NEPHROPATHY DUE TO ANALGESIC DRUGS
NEPHROPATHY DUE TO CIS-PLATINUM
NEPHROPATHY DUE TO CYCLOSPORIN A
LEAD INDUCED NEPHROPATHY (INTERSTITIAL)
NEPHROPATHY CAUSED BY OTHER SPECIFIC DRUG
CYSTIC KIDNEY DISEASE-TYPE UNSPECIFIED
POLYCYSTIC KIDNEYS, ADULT TYPE (DOMINANT TYPE)
POLYCYSTIC KIDNEYS, INFANTILE (RECESSIVE)
MEDULLARY CYSTIC DISEASE, INC NEPHRONOPHTHISIS
CYSTIC KIDNEY DISEASE - OTHER SPECIFIED TYPE
HEREDITARY/FAMILIAL NEPHROPATHY-TYPE UNSPECIFIED

HEREDITARY NEPHRITIS WITH NERVE DEAFNESS (ALPORTS SYNDROME)
CYSTINOSIS
PRIMARY OXALOSIS
FABRY'S DISEASE
HEREDITARY NEPHROPATHY-OTHER
CONGENITAL RENAL HYPOPLASIA - TYPE UNSPECIFIED
OLIGOMEGANEPHRONIC HYPOPLASIA
SEGMENTAL RENAL HYPOPLASIA
CONGENITAL RENAL DYSPLASIA +/- URINARY TRACT MALFORMATION
SYNDROME OF AGENESIS OF ABDOMINAL MUSCLES
RENAL VASCULAR DISEASE-TYPE UNSPECIFIED
RENAL VASCULAR DISEASE-MALIGNANT HYPERTENSION
RENAL VASCULAR DISEASE-HYPERTENSION
RENAL VASCULAR DISEASE-POLYARTERITIS
WEGENER'S GRANULOMATOSIS
ISCHEMIC RENAL DISEASE/CHOLESTEROL EMBOLISM
GLOMERULONEPHRITIS RELATED TO LIVER CIRRHOSIS
CRYOGLOBULINEMIC GLOMERULONEPHRITIS
RENAL VASCULAR DISEASE-CLASSIFIED
DIABETES-INSULIN DEPENDENT (TYPE I)
DIABETES-NON-INSULIN DEPENDENT (TYPE II)
MYELOMATOSIS/LIGHT CHAIN DEPOSIT DISEASE
AMYLOID
LUPUS ERYTHEMATOSUS
HENOCH-SCHONLEIN PURPURA
GOODPASTURE'S SYNDROME
SYSTEMIC SCLEROSIS (SCLERODERMA)
HAEMOLYTIC URAEMIC SYNDROME (INC MOSCHOWITZ SYNDROME)
MULTI-SYSTEM DISEASE – OTHER
CORTICAL OR TUBULAR NECROSIS
TUBERCULOSIS
GOUT
NEPHROCALCINOSIS AND HYPERCALCAEMIC NEPHROPATHY
BALKAN NEPHROPATHY
KIDNEY TUMOUR
TRAUMATIC OR SURGICAL LOSS OF KIDNEY
OTHER DISEASE
UNKNOWN

NHSBT list of donor type

Deceased heart beating
Non-heart beating
Living related
Living unrelated
Domino
Donor type unspecified
Donor type unknown
Non-heart beating - cornea/valve only
Living - relationship unspecified
Living unrelated - pooled
Living unrelated - altruistic
Not reported

ET list of donor type

Heart-beating
Non-heart beating, unclassified
Non-heart beating, type I
Non-heart beating, type II
Non-heart beating, type III
Non-heart beating, type IV
Domino
Living, Father, Blood related
Living, Mother, Blood related
Living, Son / Daughter, Blood related
Living, Spouse / Partner, Not Blood Related
Living, Blood related: NOS
Living, Not blood related: NOS
Living, Brother / Sister, Blood related
Living, Grand Father / - Mother, Blood related
Living, Grand Son / - Daughter, Blood Related
Living, Nephew / Niece, Blood Related
Living, Uncle / Aunt, Blood related
Living, Not related
Living, Not blood Related Family
Living, Friend, Not blood related
Living, Anonymous donor, Not blood related
Living, Cousin, Blood related
Living, Father in law / Mother in law, Not blood related
Living, Brother in law / Sister in law, Not blood related
Living, Son in law / Daughter in law, Not blood related

How do you register the follow-up data? Multiple options are possible

Country	At organ level	At transplant level	At patient level
Austria	Y	Y	Y
Belgium	Y	Y	Y
Croatia	Y	Y	Y
Denmark			
Finland			
France	NA	NA	NA
Germany	Y	Y	Y
Iceland			
Italy	Y	Y	
Luxembourg	Y	Y	Y
Netherlands	Y	Y	Y
Norway			
Slovenia	Y	Y	Y
Spain	Y		Y
Sweden			
United Kingdom	Y		Y

In case you receive an organ from another OEO, do you register the donor number from the other OEO or only your own donor registration number?

Country	Donor number own organization	Donor number other OEO
Austria	Y	N
Belgium	Y	N
Croatia	Y	N
Denmark		
Finland		
France	Y	N
Germany	Y	N
Iceland		
Italy	Y	N
Luxembourg	Y	N
Netherlands	Y	N
Norway		
Slovenia	Y	N
Spain	Y	N
Sweden		
United Kingdom	Y	N

In case an organ from your own OEO is used for transplantation in another OEO, do you register the recipient/transplant number from the other OEO?

Country	Transplant/recipient number own organization	Transplant/recipient number other OEO
Austria	Y	N
Belgium	Y	N
Croatia	Y	N
Denmark		
Finland		
France	Y	N
Germany	Y	N
Iceland		
Italy	Y	N
Luxembourg	Y	N
Netherlands	Y	N
Norway		
Slovenia	Y	N
Spain	Y	N
Sweden		
United Kingdom	Y	N

If one of the patients on your waiting list is transplanted outside your country/organization, do you keep track of this patient?

Country	Response
Austria	
Belgium	
Croatia	
Denmark	
Finland	
France	N
Germany	
Iceland	
Italy	Y
Luxembourg	
Netherlands	
Norway	
Slovenia	
Spain	N
Sweden	
United Kingdom	Y

Additional comments:
Italy: In the registry a field “exit from list for transplant in other country” is present and the destination country is specified. Data are recorded in a separated registry.
UK: only if they return to the UK for follow-up.
Spain: Clinical records are kept at the hospital but information on these cases is not included in the registry so far.
ET: Only if they return to an ET country.

Do you have a system to identify double registration on the waiting list across OEOs?

Country	Response
Austria	N
Belgium	N
Croatia	N
Denmark	
Finland	
France	N
Germany	N
Iceland	
Italy	N
Luxembourg	N
Netherlands	N
Norway	
Slovenia	N
Spain	N
Sweden	
United Kingdom	N

Do you have a system to identify double registration of a transplant across OEOs?

Country	Response
Austria	N
Belgium	N
Croatia	N
Denmark	
Finland	
France	N
Germany	N
Iceland	
Italy	N
Luxembourg	N
Netherlands	N
Norway	
Slovenia	N
Spain	N
Sweden	
United Kingdom	N

Do you have a separate analysis data base?

Country	Response
Austria	Y
Belgium	Y
Croatia	Y
Denmark	
Finland	
France	N
Germany	Y
Iceland	
Italy	N
Luxembourg	Y
Netherlands	N
Norway	
Slovenia	Y
Spain	Y
Sweden	
United Kingdom	Y

How often do you refresh your separate analysis data base?

Country	Response
Austria	Weekly
Belgium	Weekly
Croatia	Weekly
Denmark	
Finland	
France	-
Germany	Weekly
Iceland	
Italy	
Luxembourg	Weekly
Netherlands	?
Norway	
Slovenia	Weekly
Spain	Different
Sweden	
United Kingdom	Daily

Additional comments:
Spain: Once a year (liver), Remaining of registries, refreshing occurs at demand, anytime is needed (updating is online).

6.2.7 Analysis

What kind of quality indicators do you use?

Country	None, all data delivered are taken up in the analysis	Only centres that fulfil specific criteria are taken up in the analysis	Only data that fulfil specific criteria are taken up in the analysis
Austria	Y		
Belgium	Y		
Croatia	Y		
Denmark			
Finland			
France	Y		
Germany	Y		
Iceland			
Italy			Y
Luxembourg	Y		
Netherlands			Y
Norway			
Slovenia	Y		
Spain			Y
Sweden			
United Kingdom	Y		

Additional comments:
Italy: Only transplants with at least one follow-up data set are used in the analysis.
Spain: Only patients with consistent data in the variables analysed are utilized.

Level of access to the registry data (multiple options are possible)

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

Slovenia	Y		Y			
Spain		Y	Y			Y
Sweden						
United Kingdom	Y		Y			

Additional comments:
UK and ET: A centre has full access to all data in the registry, on request (e.g. for specific projects), but only if approved by review board.
UK: A centre can view aggregate data on the number of donor and transplants at their centre and across the UK, split down by various characteristics, but cannot view other centres' data.
Spain: A centre has full access to all data in the registry, on request (e.g. for specific projects) after approval by the scientific committee.

6.2.8 Data dissemination

How are data from the registry disseminated (multiple options are possible)?

Country	Annual report on paper	Annual report as pdf online	Annual report as interactive tables online	Kaplan-Meier curves online	Slide kits	Data extracts
Austria	Y	Y		Y	Y	Y
Belgium	Y	Y		Y	Y	Y
Croatia	Y	Y		Y	Y	Y
Denmark						
Finland						
France	Y	Y				
Germany	Y	Y		Y	Y	Y
Iceland						
Italy		Y				
Luxembourg	Y	Y		Y	Y	Y
Netherlands	Y	Y		Y	Y	Y
Norway						
Slovenia	Y	Y		Y	Y	Y
Spain		Y			Y	
Sweden						
United Kingdom	Y	Y	Y	Y	Y	Y

6.2.9 Conclusions of the survey

The survey showed some important similarities but also substantial differences concerning the functional requirements between the participating countries. These findings have to be taken into account when setting up the future European Registry. Several aspects are already reflected in the proposed governance structure of the European registry, others have to be addressed when developing the functional specifications of the future European Registry.

The main findings can be summarized as follows:

Coverage of the national registries

- None of the responding countries currently has a registry on outcome after intestine transplantation. In all countries, except in Spain, data on outcome of all other solid organ transplantations is collected in a centralized registry.

Data delivery by transplant centres and quality control

- Only in France, Germany, Italy, The Netherlands and Spain the reporting of follow-up data to the national registry is mandatory.
- All countries use several different models for requesting follow-up data/communication with the transplant centres concerning data delivery. Remarkable is that regular mail/ fax is still used in all countries.
- The existing national registries offer their centres a high level of service and flexibility by allowing at least 3 different ways of data delivering, except in the Netherlands where data can only be submitted via a system of data upload.
- All registries have fixed data formats for the registry variables. The formats of 11 variables were compared across the participating countries, except for dates, the formats were not uniform.

All responding countries perform audits in their transplant centres as a part of their quality assessment except in the Eurotransplant countries.

Data handling by the national registries

- None of the registries in Europe collects the donor number and/or transplant number of another OEO. In addition, a double registration of a wait listed or transplanted patient across the OEOs is not checked by any country.
- All countries, except France, Italy and the Netherlands have a separate analysis data base.

Data requests and review committees

- All responding countries, except Italy have an international/national review committee installed.
- The organization of the review committee is quite similar across Europe. The Netherlands has just one review committee, but in all the other countries, organ specific review committees are installed. In all existing review committees clinicians are present, and legal/ethical experts are absent. Except for Spain and the Netherlands, all countries have statisticians taken part in the review committee, and vice versa, representatives of the ministry do not participate in the review committee except in Spain and the Netherlands.
- In all countries except in France the review committee has the task of reviewing.
- Annual reports both on paper and as a pdf are prepared by all the countries. Eurotransplant, the Netherlands and the UK offer the additional service of providing Kaplan-Meier survival curves on-line, while only in the UK, centres have the option of extracting annual report data via interactive tables.

7 Technical requirements

7.1 Technical requirements

7.1.1 Basic assumptions

Following the functional specifications, the overall assumptions of the registry are:

- All data are stored in a centralized data base.
- Data will be send from national registries to the data base by uploading standardized files.
- All uploaded data will be available for analysis through on-line analysis tools and download of defined files.

7.1.2 Functional design

The technical requirements depend on the functional specifications of the new European Registry as defined in chapter 6.

- Relational data base management system to store the data with the possibility to define business rules in the data base will be created.
- Online computerized up-load facilities for the participating countries will be installed. This function will be a hand started online facility to upload a file in one of the specified formats of the new European Registry (CSV, Excel or XML).
- All uploaded data will be checked on consistency, data correctness and completeness as defined in the chapter on quality assurance. Results of the uploading will be reported to the delivering party by online reports. Only files with complete correct data will be used for merging into the European Registry's data base.
- All uploaded files will be stored by country per uploaded file.
- Newly delivered and correct data will be merged per country in a cumulative file per country.
- All data from all countries will be merged into the data base, the new European Registry data base.
- For analysis the data will be exported to the analysis data base, the new European Registry analysis data base.
- To produce analysis reports business intelligence and statistical systems will be installed.
- The following analysis functions will be available per participating country:
  - downloading data out of the European Registry data base allowed for this particular participating country as an excel file and as a comma separated value file;
  - on-line patient and graft survival graphs with the possibility for comparison with the whole new European Registry data base;
  - Online interactive table generating tools.

Availability of the system

The system has to be available 24/7 with an optimal uptime by installing a fail over system. For regular maintenance a down time with a maximum of two hours, four times a year is acceptable.

Open source

For development of the software the open source Java programming language can be used. It is preferential that open source development tools are used. If an open source relational data base management system can meet all the requirements this system has to be used.

7.1.3 The new European Registry

Schematic overview of the European Registry

- Uploaded data will be stored in a table per country.
- Each successful upload in the country table will be uploaded to the European Registry relational data base. This data base will be the final European Registry data base containing all uploaded data from all countries in the defined format.
- For the ease of (statistical) analysis the European Registry analysis data base will be installed. This data base will be refreshed and updated on regular basis from the European Registry relational data base.

7.1.4 Data flow

Uploading of data from a registry to the European Registry

All data have to be uploaded by a simple tool with the possibility to upload Comma Separated Value (CSV) files, excel files and Extended Markup Language (XML) files. After a successful technical upload has been achieved, the first check of the quality of the data will be performed. The response will be sent by e-mail to the user containing as attachment an excel file with the results of the upload. If no errors were encountered the file will be released for merging into cumulative country file. In case one or more errors were detected the uploaded file will be marked as not usable for merging into the European Registry.
All uploaded files will be specified with an uploaded date/time timestamp and the account information of the uploading user.

7.1.5 Merging the registries into the new European Registry

Merging into the cumulative country table

A successfully uploaded file will be merged into the country cumulative table. All defined checks will be performed. If no errors occurred the file will be merged into the cumulative country table and released for uploading into the European Registry data base. In case one or more errors were encountered, the merging will not be performed, the file will be marked as not usable and an e-mail will be sent to the user who uploaded the file. This e-mail contains an excel file with the errors encountered. In the case of erroneous data the data in the uploaded file will not be merged into the country cumulative file.
During the start-up of a country it is - for a limited interim period - possible that the data do not comply completely with the definitions of the data sets. The data will be imported in the country file and will be converted in the uploading process to the European Registry data base.

The European Registry data base

The central European Registry data base is **the** final data base containing all uploaded data from the participating countries. Each successful upload in a country table will have a consecutive upload to the European Registry data base. All data in the European Registry data base will comply with the specifications of the registry. The data base is a relational data base and will be used for all kind of data management purposes and producing of standard reports.

The European Registry analysis data base

To have easy access to the European Registry data for analysis, downloading and reporting an analysis data base has to be defined. The technical structure will be tailored to the use of business intelligence and statistical software. The analysis data base will be updated and refreshed periodically out of the European Registry data base, at least once a week.
For optimal authorization of access to the data base, the system must have an extensive authorization tooling.
The European Registry analysis data base will be used for generating interactive flexible standard reports.

7.1.6 Analysis and reporting software

Business Intelligence software

For standard reports that can be downloaded and special reports with dynamic queries and downloads of rough data Business Intelligence (BI) software has to be installed. The user interface has to be intuitive and very user friendly. The same BI-software has to fulfil the needs for the central European Registry office to produce special reports on request.

Software for statistics

To produce statistical analysis a standard statistical software application has to be installed, as there are SAS , SPSS or R. For simple analysis standard software as excel has to be installed.

Tailor made software

For the user interface, to send requests to the central office for non-standard reports and downloads software should be developed according to prevailing technical standards. This counts too for the production of specialized reports not available in BI.

Survival graphs

Software has to be developed to produce online survival graphs conform the functional specifications.

Other software and or tools

For data management standard tools have to be installed.

7.1.7 Hosting the new European Registry

The IT infrastructure should be installed in accordance with prevailing standards and for the future. Open standards have to be used.

7.1.8 Hardware and operating system European Registry

The technical infrastructure will consist of data base servers, one for production and one as fail over. For the software and communication two identical application servers, one production and one fail over. The fail over servers will be used for development, testing and acceptation.

The data base server must have a capacity for:
1. Storing all data
2. Analysis of the data and reporting

As operating system an open source system like Linux will be installed both on the data base as the application servers.

For other standard applications as statistical software one or two servers has to be installed.

All servers can be different physical servers but they can also be implemented as virtual severs in a server park.

7.1.9 Internet server and secure network

For secure communication with internet and secure communication of the users with the data base a separate redundant internet web server has to be installed. The network has to be a secure network according to common standards in IT.

7.1.10 Data base and application server

Data base

The data base system has to be a Relational Data base Management System (RDBMS) that is widely used as a world standard in his kind. The performance has to be high with large amount of data, also during the processing of statistical analysis. The system must have an excellent track record and a belief in continuity for the next twenty years. The expected growth of data requires flexible and easy scalability.
The data base system should provide comprehensive functionality for authorization for user access to data at different levels.
To monitor access to the data base, the system must offer enhanced logging and journaling facilities with easy to use reporting tools.

Application server

For communication with the internet server and the data base and for the developed applications an application server has to be implemented. The application server has to be a world standard with a high performance and showing a high belief in continuity.

7.1.11 Software for website including member site

Communication with the community and the general public will be achieved via a web site with a public and with a secure part (member site). For this purpose an open source content management system will be used. The web site will be installed on an open source web server. For communication between the collaborating countries and the hosting party, a secure part (member site) will be implemented including a work space.

7.1.12 Security plus maintenance tools

Standard security and maintenance tools have to be installed. For authorization of users to access the European Registry a comprehensive tool with reporting facilities has to be available.

7.1.13 Software development

The software for the front end has to be developed in an open source language like JAVA, using a development tool which is consistent with the installed RDBMS. For data base manipulation a specific language has to be used, also consistent with the RDBMS. If necessary in the front end, Java script can be used. All development has to be performed confirm international good IT-practice.
A consistent Development, Test, Acceptance, Production (DTAP) street has to be established. An issue tracking system has to be used.

7.1.14 Requirements for the hosting party

The hosting party must have a standard supplier quality accreditation, e.g. ISO-9000-3 and comply with (the national implementation of) the standard for information security management in health ISO-27799:2008.
The organization must be a financial sound and stable business, with clean audits of annual accounts and have a good status and reputation with the services required.
To provide maintenance and support, and for developing future enhancements and delivering continuous improvement a sufficient number of staff with the required expertise has to be available. For the provided services the organization must have an on-going/continual service improvement and development program.

Help desk and support

Help desk and support hours have to be 8:00 am tot 5:30 pm CET.
The help desk manages accounts by a standard authorization procedure, where authorization will be granted per functional entity.
For incident reporting, support and requests a standardized registration, tracking and monitoring system has to be used.

Systems Operations

For optimal system operation:

1. Hardware, software (including operating systems and monitoring software) has to be installed, configured, tested and monitored. It is necessary to provide and manage connectivity.
2. System availability above 99.99% has to be ensured by:
   - Monitoring all hardware, software, servers, data bases and network operations.
   - Monitoring data base growth and updating the data base system when thresholds are being approached.
   - Applying security and anti-virus protection
3. Regular back-ups have to be performed daily, weekly and monthly. All back-ups will be held off site in a secure, protected location.
4. An automatic recovery procedure in the event of a system failure has to be available. Annual disaster recovery tests have to be performed.
5. Internet redundancy has to be provided.
6. Multiple handling processes to resolve data or system problems have to be made available.

7.2 Current status in the Member States (EFRETOS partners)

7.2.1 Follow-up system for data entry

Who enters the follow-up data?

Country	Centres/ external users	Central by the own organization based on paper questionnaires
Austria	Y	Y
Belgium	Y	Y
Croatia	Y	Y
Denmark		
Finland		
France	Y	N
Germany	Y	Y
Iceland		
Italy	Y	N
Luxembourg		
Netherlands	Y	N
Norway		
Slovenia	Y	Y
Spain	Y	N
Sweden		
United Kingdom	Y	Y

Additional Comments:
UK: also use electronic transfer from user systems.
ET: We have a data exchange with CTS and ÖBIG. The data we receive from these registries are uploaded in our Datamart.

Do you use data entry screens? If yes, give details

Country	Response	Per organ	Per transplant	Per recipient	Per time point
Austria	Y	Y	Y	Y	Y
Belgium	Y	Y	Y	Y	Y
Croatia	Y	Y	Y	Y	Y
Denmark					
Finland					
France	Y	?	?	?	?
Germany	Y	Y	Y	Y	Y
Iceland					
Italy	Y				
Luxembourg	Y	Y	Y	Y	Y
Netherlands	N				

Norway					
Slovenia	Y	Y	Y	Y	Y
Spain	Y	Y	Y	Y	Y
Sweden					
United Kingdom	Y	Y	N	Y	Y

Do you upload files from other systems?

Country	Response	Specify
Austria	N	
Belgium	N	
Croatia	N	
Denmark		
Finland		
France	N	
Germany	N	
Iceland		
Italy	N	
Luxembourg	N	
Netherlands	Y	Excel
Norway		
Slovenia	N	
Spain	Y	
Sweden		
United Kingdom	N	CSV,XML

If you offer your users schedules for collection of follow-up data, please describe the process. (paper / electronic by e-mail / electronic work lists and so on)

Country	Response
Austria	Y
Belgium	Y
Croatia	Y
Denmark	
Finland	
France	N
Germany	Y
Iceland	
Italy	Y
Luxembourg	Y
Netherlands	Y

Norway	
Slovenia	Y
Spain	N
Sweden	
United Kingdom	Y

Additional comments:
Italy: only data entry screens.
UK: paper forms posted out when due for completion of electronic forms put in electronic work areas with transplant units*:* electronic by e-mail.
ET: offers on-line work lists.
The Netherlands: offers online work lists.

7.2.2 Data storage

How do you store your follow-up data?

Country	Relational data base	File system	XML	Object data base
Austria	Y			
Belgium	Y			
Croatia	Y			
Denmark				
Finland				
France	Y			
Germany	Y			
Iceland				
Italy	Y			
Luxembourg	Y			
Netherlands	Y			
Norway				
Slovenia	Y			
Spain	Other organs	liver		
Sweden				
United Kingdom	Y			

7.2.3 Architecture

Hardware architecture used in follow-up data collection

Which data base server do you have?

Country	Hardware	Operating system
Austria	HP	HP-UX
Belgium	HP	HP-UX
Croatia	HP	HP-UX
Denmark		
Finland		
France	HP	Linux Red Hat 5
Germany	HP	HP-UX
Iceland		
Italy	IBM P5 520	AIX ver 5.2.0
Luxembourg	HP	HP-UX
Netherlands	HP	HP-UX
Norway		
Slovenia	HP	HP-UX
Spain	HP	HP
Sweden		
United Kingdom	Sun v490, two node cluster	Solaris 10

Which applications server do you use?

Country	Hardware	Operating system
Austria	Dell	Linux
Belgium	Dell	Linux
Croatia	Dell	Linux
Denmark		
Finland		
France	Intel Xenon	Linux
Germany	Dell	Linux
Iceland		
Italy	IBM X3650	Windows server 2003 SP2
Luxembourg	Dell	Linux
Netherlands	Dell	Linux
Norway		
Slovenia	Dell	Linux

Spain	HP 8640 Itanium II (4 cells)	Windows 2008 R2Server
Sweden		
United Kingdom	Sun v245	Solaris 10

Software architecture used in follow-up data collection

Country	Data base	Application server	Software development language
Austria	Oracle 11G	Oracle application Server	Java, PL/SQL
Belgium	Oracle 11G	Oracle application Server	Java, PL/SQL
Croatia	Oracle 11G	Oracle application Server	Java, PL/SQL
Denmark			
Finland			
France	Oracle 10G	Oracle	Java, JSP, PL/SQL
Germany	Oracle 11G	Oracle application Server	Java, PL/SQL
Iceland			
Italy	Oracle 9.2.0.5 64bit	Web server system: IIS ver. 6	ASP 2.0 with HTML and Java Script .
Luxembourg	Oracle 11G	Oracle application Server	Java, PL/SQL
Netherlands	Oracle 11G	Oracle application Server	Java, PL/SQL
Norway			
Slovenia	Oracle 11G	Oracle application Server	Java, PL/SQL
Spain	Oracle 10.2 g	Oracle application Server	Apache 2 -J2EE Runtime 1.6
Sweden			
United Kingdom	Oracle 10.2	Oracle AS10g	PLSQL, Java, Oracle SQL navigator

Is your follow-up data collection system a system separated from your system for day-to-day business for organ allocation?

Country	Response
Austria	N
Belgium	N
Croatia	N
Denmark	
Finland	
France	N
Germany	N
Iceland	

Italy	N
Luxembourg	N
Netherlands	N
Norway	
Slovenia	N
Spain	Y
Sweden	
United Kingdom	N

Additional comments:
ET: this is an integral part of the day to day business

Does your follow-up system have interfaces with other systems within your organization?

Country	Response
Austria	Y
Belgium	Y
Croatia	Y
Denmark	
Finland	
France	N
Germany	Y
Iceland	
Italy	N
Luxembourg	Y
Netherlands	Y
Norway	
Slovenia	Y
Spain	Y, except for liver
Sweden	
United Kingdom	N

Please describe the architecture for the software development

Country	response
Austria	JDeveloper, ADF (10.1.2, 10.1.3, 11), JHeadstart, Designer, PL/SQL
Belgium	JDeveloper, ADF (10.1.2, 10.1.3, 11), JHeadstart, Designer, PL/SQL
Croatia	JDeveloper, ADF (10.1.2, 10.1.3, 11), JHeadstart, Designer, PL/SQL
Denmark	
Finland	
France	JDeveloper, PL/SQL/Developer
Germany	JDeveloper, ADF (10.1.2, 10.1.3, 11), JHeadstart, Designer, PL/SQL
Iceland	
Italy	ASP 2.0 with HTML and Java Script for clients

Luxembourg	JDeveloper, ADF (10.1.2, 10.1.3, 11), JHeadstart, Designer, PL/SQL
Netherlands	JDeveloper, ADF (10.1.2, 10.1.3, 11), JHeadstart, Designer, PL/SQL
Norway	
Slovenia	JDeveloper, ADF (10.1.2, 10.1.3, 11), JHeadstart, Designer, PL/SQL
Spain	J2 EE, Eclipse, Struts
Sweden	
United Kingdom	PL/SQL, Java, Oracle SQL navigator

Business rules; where are the business rules of the follow-up system located

Country	In data entry screens	In data base (as second layer)	In the web service	In the file upload
Austria	Y	Y		
Belgium	Y	Y		
Croatia	Y	Y		
Denmark				
Finland				
France		Y		
Germany	Y	Y		
Iceland				
Italy	Y	Y		
Luxembourg	Y	Y		
Netherlands		Y		Y
Norway				
Slovenia	Y	Y		
Spain		Y		
Sweden				
United Kingdom		Y		

If you use a separate environment for analysis purposes, please describe the technical architecture (servers, data base, tools, etc.)

Country	Server	Data base	Tools
Austria		Oracle 11G, data ware house	Business Objects
Belgium		Oracle 11G, data ware house	Business Objects
Croatia			
Denmark			
Finland			
France	- No separate envir.		
Germany		Oracle 11G, data ware house	Business Objects
Iceland			

Italy			ERP, Business Objects 5.0
Luxembourg		Oracle 11G, data ware house	Business Objects
Netherlands		Oracle 11G, data ware house	Business Objects
Norway			
Slovenia		Oracle 11G, data ware house	Business Objects
Spain			Business Intelligence Microstrategy 9.2, SPSS
Sweden			
United Kingdom	Separate	Separate	SAS

Additional comments:
ET: from the follow-up in the Data Ware House the last follow-up data are extracted and copied to the Datamart, which is also an Oracle 11G data base. All of the most recent follow-up data received from CTS and ÖBIG are copied into the Datamart.

If you offer your users online analysis tools, please describe the technical architecture

Country	Response
Austria	Online survival graphs, developed in JSP
Belgium	Online survival graphs, developed in JSP
Croatia	Online survival graphs, developed in JSP
Denmark	
Finland	
France	NA
Germany	Online survival graphs, developed in JSP
Iceland	
Italy	Only online reports on Tx and donation
Luxembourg	Online survival graphs, developed in JSP
Netherlands	Online survival graphs, developed in JSP
Norway	
Slovenia	Online survival graphs, developed in JSP
Spain	No
Sweden	
United Kingdom	No

Are there national standards/regulations on information security management in health, based on ISO 27799:2008

Country	Response	Name
Austria	Y	ISO 27799:2008
Belgium	Y	ISO 27799:2008
Croatia	Y	ISO 27799:2008
Denmark		
Finland		
France	N	
Germany	Y	ISO 27799:2008
Iceland		
Italy	Y	Certificazione qualita ISO 9001, CMMI livello 3, Sicurezza CED ISO 27001
Luxembourg		ISO 27799:2008
Netherlands	Y	NEN 7510 will be adapted in conformity to ISO 27799:2008
Norway		
Slovenia	y	ISO 27799:2008
Spain	y	ISO 27001, ISO 27002 and Spanish National Safety Scheme
Sweden		
United Kingdom	y	2009 UK Mandatory Cabinet Office requirement for IG, Caldicot, Suffolk Matrix, UK Legislation (Data Protection Act)

Are all registry related IT tasks subcontracted of performed internally?

Country	Subcontracted	Internally
Austria		Y
Belgium		Y
Croatia		Y
Denmark		
Finland		
France		Y
Germany		Y
Iceland		
Italy	Y	
Luxembourg		Y
Netherlands		Y
Norway		
Slovenia		Y
Spain		y
Sweden		
United Kingdom	Y	Y

8 Legal and Ethical requirements

8.1 Introduction

The aim of this work package is to delineate the legal framework of national and European data protection legislation with regard to the establishment of a pan European register for the follow-up of transplantation outcome data.

Public access to documents as well as privacy, integrity and data protection have been recognized as fundamental rights as well on the European level as in national legislation. Data protection principles aim to establish conditions under which it is legitimate and lawful to process personal data.

Particular attention needs to be paid to the collection and processing of special categories of data such as the data concerning health that require special protection. In this context it is necessary to determine the legal and ethical balance between the obligatory protection of the individual rights with respect to their personal data and the necessity to evaluate transplantation outcome for quality and safety aspects in order to improve transplantation in general but also regarding the individual post-transplant care of the recipients.

8.2 European framework

European Convention on Human Rights

With the adoption of the Convention for the Protection of Human Rights and Fundamental Freedoms (usually referred to as the European Convention on Human Rights (ECHR)) by the Council of Europe in 1950, the respect for private life was established[2]
Article 8 of the European Convention stipulates that:

- *everyone has the right to respect for his private and family life, his home and his correspondence;*
- *there shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedom of others.*

The European Court of Human Rights has confirmed in a number of decisions that the right to private life also protects health related data of an individual.
All Council of Europe member states are party to the Convention[3].

Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data (Convention No.108)[4]

In this Convention the protection of personal data has been guaranteed for the first time as a separate right granted to an individual. It also regulates the trans-border flow of personal data.
The right to protection of personal data was laid down in Article 8:
1. Everyone has the right to the protection of personal data concerning him or her.

[2] Convention for the Protection of Human Rights and Fundamental Freedoms; ETS No. 005, 3 September 1953. http://conventions.coe.int/treaty/en/Treaties/Html/005.htm
[3] See Chart of signatures and ratifications (http://conventions.coe.int)
[4] COE Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data, ETS No. 108, 28 January 1981. http://conventions.coe.int/treaty/en/treaties/html/108.htm

2. Such data must be processed fairly for specified purposes and on the basis of the consent of the person concerned or some other legitimate basis laid down by law. Everyone has the right of access to data which has been collected concerning him or her, and the right to have it rectified.
3. Compliance with these rules shall be subject to control by an independent authority.

Nearly all Council of Europe Member States have ratified the Convention and have implemented its principles into their national legislation. These principles concern in particular fair and lawful collection and automatic processing of data, storage for specified legitimate purposes; the quality of the data; their accuracy; the confidentiality of sensitive data; information of the data subject; and his/her right of access and rectification. The Convention provided the legal framework for the EU Data Protection Directive 95/46.

Council of Europe Recommendation (97) on the protection of medical data

In February 1997 the Council of Europe's Committee of Ministers adopted a Recommendation on the Protection of Medical Data[5]. This document, which also applies to genetic data, protects personally identifiable information, limits the access to health data and sets standards for the use of medical data in scientific research.

Convention on Human Rights and Biomedicine

The Convention[6] lays down a series of principles and prohibitions concerning bioethics, medical research, consent, rights to private life and information, organ transplantation, etc. The aim of the Convention is to guarantee everyone's rights and fundamental freedoms and, in particular, their integrity and security of the dignity and identity of human beings in this sphere.
Article 10 guarantees the right to respect for medical confidentiality, thereby reaffirming the principle introduced in Article 8 of the European Convention on Human Rights en reiterated in the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data. Restrictions to the respect of privacy are possible for one of the reasons and under the conditions provided for under Article 26.1. The possible exceptions listed by this article are aimed at protecting collective interests (public safety, prevention of crime, and the protection of public health) or the rights and freedom of others. The Convention is only binding for countries that have ratified it[7].

Directive 95/46/ EC of the European Parliament and the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data

Directive 95/45 EC is the central piece of legislation on the protection of personal data in Europe. Due to its importance it will be dealt with separately in section 8.3.

Directive 2010/53/EU on standards of quality and safety on human organs intended for transplantations[8] and the Action Plan on Organ Donation and Transplantation (2009-2015) of the European Commission[9]

Last summer the Directive on standards of quality and safety on human organs intended for transplantations entered into force. It has to be adopted into national law within a timeframe of two years. Article 16 of this Directive deals with the protection of personal data with special regard to organ donation and transplantation.

[5] The European Parliament and the Council of the European Union, Recommendation R(97)5, on the Protection of Medical Data, 1997.
[6] Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine, ETS No. 164 of 1 December 1999.
[7] For signatures and ratifications see: http://conventions.coe.int
[8] Directive 2010/53 EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantations (OJ L243, 16/09/10)
[9] Communication from the Commission of 8 December 2008 - Action plan on Organ Donation and Transplantation (2009-2015): Strengthened Cooperation between Member States COM(2008) 819 – Not published in the Official Journal

It stipulates the importance of strict confidentiality rules and security measures, in accordance with Directive 95/46, for the protection of donor's and recipients' personal data.

The Action Plan sets out to complement this legal framework with a compilation of information in the form of registers facilitating the evaluation of post-transplant results (priority action 9). These registers shall help to develop good medical practice in organ donation and transplantation. According to the Action Plan promoting EU-wide registers with common definition of terms and methodology could help in the evaluation of post-transplant results.

8.3 Directive 95/46

Principles and definitions

The Data Protection Directive 95/46[10] regulates the processing of all personal data within the European Union. It was adopted on 24 October 1995 and has two main objectives:

- to achieve a harmonized minimum level of data protection throughout the EU;
- to allow for the free movement of personal data within the EU.

It regulates both automatic and manual processing of all personal data of *identified* or *identifiable* natural persons. A person is identifiable if the person's identity can be established reasonably, without disproportionate effort[11].

The Directive applies to personal information which must be processed in accordance with the following basic principles and standards[12]:

- *Legitimacy*: personal data may only be processed if the data subject has unambiguously given his consent or processing is necessary in specific situations as mentioned in article 7 of the Directive;
- *Quality*: personal data must be processed fairly and lawfully and collected for specified, explicit and legitimate purposes and may not be further processed in a way incompatible with those purposes;
- *Transparency*: the data subject must be given information regarding data processing relating to himself;
- *Proportionality*: personal data must be adequate, relevant and not excessive in relation to the purposes for which they are collected and further processed;
- Confidentiality and security: technical and organizational measures to ensure confidentiality and security must be taken with regard to the processing of data;
- *Surveillance*: supervision of processing by the national supervising authority must be ensured.

The Directive 95/46 EU applies to the *processing* of *personal data* by a *data controller.*
Key definitions:

- *Processing:* "any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organization, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination blocking, erasure or destruction".[13]
- *Personal data:* "any information relating to an identified or identifiable natural person (data subject), in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity".[14]
- *Data controller*: "a person who, alone or jointly with others, determines the purposes and means of the processing of personal data".[15]

[10] **Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (OJ L281, 23/11/95)**
[11] L.B. Sauerwein and J.J. Linneman (2001) „Guidelines for personal data Processors", Ministry of Justice, The Hague, pp 13.
[12] See Summeries of EU legislation, factsheet on Directive 95/46EC, (http://europa.eu/legislation_summaries/information_society/l14012_en.htm
[13] Article 2(b) of Directive 95/54EC
[14] Article 2(a) of Directive 95/54EC
[15] Article 2(d) of Directive 95/54EC

Personal data can only be processed for specified explicit and legitimate purposes and may not be processed further in a way incompatible with those purposes.

The processing of special categories of data

According to Article 8 special categories of data such as data concerning health underlie particular protection.

The Directive contains provisions on the processing of special categories of data. These categories are defined in Article 8 as: "personal data, revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life".

The processing of these specific personal data is prohibited unless:
- explicit consent is given by the data subject;
- processing is required by national employment law;
- processing is necessary to protect the vital interest of the data subject or a third party and the data subject is physically or legally incapable of consenting;
- processing is carried out in the course of its legitimate activities with appropriate guarantees by a foundation, association or any other non-profit seeking body with a political, philosophical, religious or trade-union aim;
- the data has manifestly been made public by the data subject
- Or the data is necessary for legal proceedings.

Implementation in EU Member States

To date all EU Member States have implemented this Directive into national law.

8.4 Legislation Croatia

Due to the fact that Croatia is still in the process of becoming an official member of the European Union and has been a member of Eurotransplant since 2007, a survey was conducted of the Croatian legislation on privacy and data protection.

8.4.1 Legal grounds

The personal data protection is a constitutional right. Article 37[16] of the Constitution of the Republic of Croatia states that:
"Everyone shall be guaranteed the safety and secrecy of personal data. Without consent from the person concerned, personal data may be collected, processed and used under conditions specified by law.
Protection of data and supervision of the work of information systems in the State shall be regulated by law.
The use of personal data contrary to the purpose of their collection shall be prohibited".

Croatia adopted the Act on Personal Data Protection[17]. This Act regulates the protection of personal data regarding natural persons and the supervision of collecting, processing and use of personal data. The Act has also been harmonized in all relevant provisions with the Directive 95/46 EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

Next to the Act on personal data protection there are two other legal acts regulating the personal data protection domain:
1. Regulation on the manner of keeping the records of personal data filing systems and the pertinent records form (Official Gazette No 105/04);

[16] See The Constitution of the Republic of Croatia, Official Gazette No. 41/01 (http://www.constitution.org/cons/croatia.htm)
[17] Act on Personal Data Protection, Zagreb, 18 June 2003, Official Gazette No. 103/03 (http://www.ceecprivacy.org/doc/law_croatia.pdf)

2. Regulation on the procedure for storage and special measures relating to the technical protection of special categories of personal data (Official Gazette No 139/04).

In April 2005 Croatia has ratified the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data (Convention 108) and Additional Protocol to the Convention regarding Supervisory Authorities and Trans border Data Flows.

8.4.2 Purpose of personal data collecting

Personal data may be collected for a purpose known to the data subject, explicitly stated and in accordance with the law, and may be subsequently processed only for the purposes it has been collected for or for a purpose in line with the purpose it has been collected for.
Personal data must be relevant for the accomplishment of the established purpose and must be accurate, complete and up-to-date[18].

Personal data may be collected and subsequently processed[19]:

- with the consent of the data subject only for which a data subject has given his/her consent;
- in cases determined by law;
- for the purpose of protecting the life or physical integrity of the data subject or another person in cases when the data subject is physically of legally unable to give his/her consent;
- if personal data processing is necessary for a data controller to carry out tasks of public interest;
- to comply with legal obligations of a data controller;
- for the purposes of signing and fulfilling of contract clauses, in which a data subject is a party;
- if the data subject has personally disclosed his/her data.

8.4.3 Basic rights of data subjects

1. Right to withdraw a given consent;
2. Right to access information on personal data;
3. Right to correct inaccurate or incomplete data, to prevent a disclosure of such data or to erase data;
4. Right to be removed from the marketing list;
5. Right to complain;
6. Right to the compensation for damages.

Personal data of natural persons can be transferred across the Croatian border to other countries of international organizations on the basis of an international agreement, a law or some other legal act or a written consent of the data subject according to Article 13 of the Act on personal data protection. Personal data can easily be transferred to those states and international organizations which have an adequate level of personal data protection.

[18] Article 6 of Act on Personal Data Protection
[19] Article 7 of Act on Personal Data Protection

8.5 Data collection and publication

Overview data collection EFRETOS Member States

Based on the results of the surveys, an outline of the current status of post-transplant follow-up data obtained in each EFRETOS Member State will be presented.

Legal basis for data collection

The legal basis for the collection of medical data can be found in specific regulations in the national transplantation acts predominantly in combination with the consent of the data subject. The EFRETOS survey is designed in order to find out on what legal basis personal post-transplant follow-up data may be collected and whether there are legal constraints or a mandatory data collection foreseen e.g. in the national transplantation acts.

Purpose for which data is collected

It is essential to delineate the exact data set that it 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 data collection in the desired extend and the foreseen purpose is either permitted by law or covered by explicit consent of the individual patient.

Data subjects rights

The EU Data Protection Directive lays down the minimum set of rights of the individual regarding the processing of personal identifying data. Individuals should be fully informed on the possible use of information about them and the extent to which this information may be shared. Based on the implementation into national law data subject rights may nevertheless vary since Member States can always pass stricter regulations than set up in the Directive.

Disclosure of data

Not all data need the same level of protection. Medical data sets that contain personal information can be subject to different degrees of security measures:

Identified: These data sets contain personal identifiers from which individuals can be distinguished.
Coded: Identifiable information is substituted by a code of randomly assigned numbers and/or letters.
Anonymized: All personal identifiers or codes are removed.

For all procedures performed in the European Registry, protocols and written policies must be developed in which the requirements and the authorizations will be laid down. These requirements have to be in compliance with the national legislation of the country where the European Registry will reside.

Legislation host country of the registry

Depending on where the European 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 the national provisions.

European Registration Number

Due to the European wide mobility of patients it needs to be ensured that data related to the individual is not collected more than once and thus affecting the evaluation. For this purpose it would be recommendable to assign a unique European Registration Number to each person whose data is collected for the Registry.

Liability for unauthorized or incorrect data processing

The Directive 95/46 EU provides in Article 24 that Member States shall adopt measures to ensure the full implementation of the Directive and shall particularly lay down sanctions to be imposed in case of infringement of the provisions. Since the Directive has been implemented by all EU Member States the sanctions put forward by national law are relevant according to the distinction above.

Financial aspects, legal enforcement of data collection and incentives

The collection of quality data and its evaluation and analysis is very time consuming and cost intensive. As already stipulated in the Action Plan a European Registry that allows the evaluation of post-transplant results needs to be supported by the national legal framework. In order to ensure a comprehensive data collection on a national level the most preferable option is to implement a mandatory collection of a defined set of post-transplant follow-up data for the purpose of thorough evaluation in order to define and continually improve good medical practice. Member States should take the opportunity of implementing the Directive on quality and safety to amend their national legislation on transplantation.

If a mandatory data collection is not installed in a legal framework other possibilities have to be considered. Patients, physicians and transplant centres need to be convinced of the added value of such a European Registry and reimbursement of the expenses need to be ensured.

8.6 Survey on national legislation

The aim of the survey was to collect information on the legal framework regarding data protection and privacy from the EFRETOS Member States and Croatia in relation to the collection of follow-up transplantation data. As far as international exchanges of data between registries exist their protection is determined by national and European legislation. Some countries may have specific regulations regarding organ transplantation.

8.6.1 National legislation on mandatory reporting by centres of outcome data

Current status in the EU Member States (EFRETOS partners)
A survey on all legal aspects was conducted and sent to the EFRETOS partners. Hereunder a brief analysis of the survey is given which lays the foundation for the final recommendations on the legal aspects of data collection and establishment of a European Registry.

Legal obligation behind the systematic of collection on post-transplant follow-up data

Country	response
Austria	N
Belgium	N
Croatia	N
Denmark	
Finland	
France	Y
Germany	Y
Iceland	

Italy	N
Luxembourg	N
Netherlands	Y
Norway	
Slovenia	N
Spain	N
Sweden	
United Kingdom	N

The data collection on national level is the fundamental basis for the European Registry of registries. Regrettably only 3 out of 11 countries have a mandatory data collection in their legal framework.

Way in which the data is stored in the national registries

Country	Identifiable	Coded	Anonymized
Austria	Y		
Belgium	Y		
Croatia	Y		
Denmark			
Finland			
France	Y		
Germany	Y		
Iceland			
Italy	Y		
Luxembourg	Y		
Netherlands	Y		
Norway			
Slovenia			
Spain		Y	
Sweden			
United Kingdom	Y		

Additional comments:
ET and UK: All information can be linked back to identifiable patient characteristics – name, date of birth etc., but anonymous recipient ID is used for virtually all purposes.
The necessity of codifying or anonymizing depends on the national data protection legislation.
Germany: The data collection by the Aqua Institute (D) is based on coded data.

Countries in which the transplantation act contains provisions on data protection

Country	Response
Austria	N
Belgium	N
Croatia	N
Denmark	
Finland	
France	Y
Germany	Y
Iceland	
Italy	N
Luxembourg	N

Netherlands	N
Norway	
Slovenia	
Spain	N
Sweden	
United Kingdom	N

Through the reactions on the survey it became clear that the relevant legal provisions for data protection in the context of organ donation and transplantation are not exclusively regulated in the national transplantation acts but in particular in the broader data protection law as well as various other legal provisions. Thus usually there are no exemptions foreseen for medical research and epidemiology. The fragmentation of legal provisions relevant for data protection in the context of organ donation and transplantation complicate an analysis of the legal requirements.
Preferably the national legislator should take the opportunity of implementing the Directive on quality and safety to facilitate changes in the transplantation acts This would be an opportunity to incorporate all provisions regarding data protection in the context of transplantation in the respective transplantation act and thus lay the legal grounds for national and European wide registries for the systematic collection of post-transplant follow-up data recording the defined requirement throughout the EFRETOS project. Such tailor-made legislation could furthermore facilitate the necessary exemptions for medical research and epidemiology.

8.6.2 National legislation on data protection

Purpose of data collection in national registry

The data collection of post-transplant results serves various purposes such as the development and monitoring of organ allocation schemes, national and centre specific survival rates. On-going research and audit into short term and long term outcomes following transplantation, including complications and co morbidities.

Due to the necessity to safeguard the anonymity between donor and recipient the correlation between the relevant data underlies by specific restrictions.

8.6.3 Survey of national legislation on data presentation

Use and disclosure of data

The data is published in aggregated form in annual reports and scientific publications. Most countries allow for cooperation with the international registries such as CTS, ISHLT, ELTR and supply data to those registries in an anonymized way.

All the participating countries that have a registry have drawn up a data protection policy. These policies include measures to safeguard the integrity of the data and of its processing. The majority of EFRETOS Member States have defined procedures in order to deal with access requests.

Transfer of Personal Data to Third (Non-EU, Non-EFTA) countries

Third countries are all countries outside the European Union, with the exception of the countries of the European Economic Area (EEA). The countries of the EEA (Norway, Liechtenstein and Iceland) have undertaken to implement the Directive in their own legislation. The main rule is that personal data may only be transferred to third countries if that country provides an adequate level of protection. To determine whether a country provides an adequate level of protection on should check whether the European

Commission on basis of Article 26 of Directive 95/46 has passed a ruling concerning the level of protection in the country concerned. The Commission has so far recognized Switzerland, Canada, Argentina, Guernsey, Australia, Jersey, Isle of Man and the United States (Transfer of Air Passenger Name Record Data and Safe Harbour) as providing adequate protection. In the absence of an adequacy finding a data transfer may still take place if one of the derogations listed in Article 26 (1) of the Directive applies or if the controller adduces that adequate safeguards are in place through the use of standard contractual clauses ex Article 26 (2) approved by the Commission.

The derogations summed up in Article 26 (1) are:

- the data subject has given his consent;
- the transfer is necessary for the performance of a contract between the data subject and the controller;
- the transfer is necessary for the conclusion of performance of a contract in the interest of the data subject between the controller and a third party;
- the transfer is necessary or legally required on important public interest ground, or for the establishment, exercise or defence of legal claims;
- the transfer is necessary in order to protect the vital interest of the data subject;
- the transfer is made from a register which according to laws and legislation is intended to provide information to the public and which is open to consultation either by the public in general or by any person who can demonstrate legitimate interest, to the extent that the conditions laid down in law for consultation are fulfilled in the particular case.

European Code of Conduct for the Exchange of Medical Data

A European Code of Conduct ought to incorporate the principles for the European exchange of personal medical data. The Code of Conduct may be used as one of the pillars on which the European Registry will be based. The Code of Conduct promotes data protection and confidentiality frameworks and it prevents that person identifiable information is transmitted.

Goal of a European Code of Conduct is the promotion of scientific research in the transplant medicine and the tracking and tracing of transplanted organs in the case of undesirable events like viral contamination.

The European Code of Conduct could be based on the following documents:

- Declaration of Istanbul;
- European legislation (Directive 95/46 EC);
- Protocol for a Research database developed by the Centre for International Blood and Marrow Transplant Research;
- UN Guidelines concerning personal data files;
- The International Code of Conduct for the Exchange of Medical Data.

8.7 Model informed consent form

The national legal requirements for a consent form allowing the use of sensitive medical patient data for evaluation and research purposes may vary.
Hence, below the key elements for the content of an informed consent form are enumerated by which patient follow-up data for the European Registry can be obtained in case there is no other legitimation for the collection and usage of identifiable personal follow-up data.

- Information on content and purpose of data collection;
- Information on disclosure of data and to what extent it may be shared;
- Information about the benefits for research and development in transplantation medicine;
- Clarification that participation and consent are on a voluntary basis (unless there is a legal obligation), written clearly in terms understood by the person involved;
- Clarification that lack of consent will not result in any disadvantages regarding the medical treatment;

- Clarification that consent can be withdrawn at any time;
- Specific provision for obtaining written authorization for representatives of incompetent persons;
- Verification of identity of person involved by the health professional co-signing the consent form.

In order to facilitate the first explanatory requirements the European Registry should draw up a patient information leaflet that should be available in all languages of the participating countries giving the required information in order to obtain informed consent.

8.8 Recommendations

8.8.1 Measures (or regulations) on national level

The data collection on the national level is the fundamental basis for the European Registry of registries.

It needs to be ensured that data collection in the desired extend and for the foreseen purpose is either permitted by law or covered by expressed informed consent of the individual patient.

In order to ensure a comprehensive data collection on a national level the most preferable option is to implement a mandatory collection of a defined set of post-transplant follow-up data for the purpose of evaluation, research and analysis in order to define and continually improve good medical practice.

The national legislator should take the opportunity of implementing the Directive on quality and safety to facilitate changes in the national transplantation act and incorporate all provisions regarding data protection in the context of transplantation in the transplantation act in question.

The national legislator has to establish a stable balance between data protection legislation and freedom of research. Data protection must give room for exemptions for medical research and epidemiology.

Notwithstanding the protection of confidentiality of the identity of donors and recipients national provisions should allow for correlation of donor data and recipient data.

It should be ensured that clear and transparent procedures for dealing with requests to access data are established.

8.8.2 Measures on international level for the instalment of a European Registry of registries

A European Registry would require the assignment of a unique European identification number for each recipient which needs to be facilitated on national level.

Depending on where the European 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 data in accordance with the national provisions.

Patients, physicians and transplant centres need to be convinced of the benefits of the European Registry.

A patient information leaflet has to be designed that should be available in all languages of the participating countries giving the required information in order to obtain informed consent of the recipient.

On the European level it should be ensured that clear and transparent procedures for dealing with requests to access data are established.

8.8.3 Conclusion

Data collection needs to be standardized.

Data collection needs to be put on a legal basis:
- in order to have mechanisms to enforce data collection or to install other incentives;
- in order to achieve the right balance between data protection and freedom of research;
- in order to protect sensitive patient data;
- in order to be able to present the results.

Lack of legal authorization for data collection can be compensated by informed consent of the patient

Member States should take the opportunity of implementing the organ Directive to amend their national legislation on transplantation and donation accordingly.

8.8.4 ANNEX A

International Code of Conduct for the Exchange of Personal Medical Data

This International Code of Conduct for the Exchange of Personal Medical Data is adopted by the Members of the Transplantation Society, an international forum for the worldwide advancement of the organ transplantation

Background
International exchange of data regarding organ donation and transplantation is important to further progress in scientific research. This includes evaluation of existing technology and quality assurance based on these data. The results of this research improve transplant results and are therefore important for all patients. These results can also play a role in a broader context as the results allow the detection of potential threats to public health.

In many parts of the world, data are gathered from transplant results. Good registration of the results is an important basic requirement if we want to improve our knowledge. It also helps to prevent organ trafficking and trade[20]. Based on compound data, more reliable and better supported conclusions can be drawn from which all patients will benefit. Given the international nature of science, it is vital to exchange data between different countries. Data could ultimately be used worldwide to benefit medical scientific research.

Because data refer to individual patients, it is important to take great care to protect the privacy of these individuals when information is used for scientific research. Many countries already have regulations in place to protect the privacy of personal data within their own borders.

A professional working method and the reliability of the persons and organizations involved in transplant medicine, ask for transparency on the issue of the exchange of personal medical data[21]. It is for the benefit of all to know how doctors and scientists handle personal medical data when exchanging it electronically. The following international Code of Conduct is a justification to society about of the working methods used. Each

[20] Code of conduct on trafficking

[21] For the purpose of this Code of Conduct, 'personal medical data' shall mean medical data available in the patient's medical records.

person or transplant organization that is involved in exchanging personal medical data should therefore endorse this code.

Purpose of the international Code of Conduct

The purpose of this Code of Conduct is to ensure the quality of data and the privacy of the individual in the international exchange of information in both transplant areas where this trans-border data flow is needed:

1. to promote scientific research in transplant medicine and
2. to enable tracking and tracing of transplanted organs in the case of undesirable events like viral contamination.

The purpose can be achieved through an optimal international exchange of personal medical data. This exchange should at the same time be subject to the most appropriate safeguards.

The essential principles to be used to achieve the purpose of this Code of Conduct have been identified. These principles contain a framework for patients, governments and organizations in transplant medicine on how to deal with the international exchange of personal medical data for scientific medical research. The essential principles are represented in this international Code of Conduct. Those who wish to exchange and use personal medical data for scientific medical research shall therefore endorse and apply this code.

Working method

The development of this international Code of Conduct involved an examination of the relevant regulations, including the UN Guidelines for the regulation of computerized personal data files, the Australian National Privacy Principles, the Safe Harbor Privacy Principles used in the US, the OECD guidelines on the protection of privacy and trans border flows of personal data and EU Directive 95/46/EC on standard contractual clauses for the transfer of personal data to third countries. The international Code of Conduct also took note of the “Protocol for a Research Database for Hematopoietic Stem Cell Transplantation and Marrow Toxic Injuries”.

Explanatory Memorandum

related to paragraphs 3, 5 and 6 of the

International Code of Conduct for the Exchange of Personal Medical Data

3. *We exchange personal medical data only to make tasks possible for which the doctor involved, or the medical transplant organization recording, transmitting, receiving or processing the personal medical data is authorized.*
   Example: an organization collects medical data on patients to allow organs to be allocated optimally. These data may not be used to examine which health insurer has the most patients waiting for a donor.

5. *We only exchange personal medical data to another country or organization if that country or organization has legislation in place or otherwise offers a mechanism to ensure an appropriate level of protection to patients.*
   An appropriate level of protection is ensured if the following principles are met:
   a. *Rights of patients*: patients have a right to access to their own medical data. They are also entitled to corrections if the medical data processed about them prove to be incorrect.
   b. *Specificity*: personal medical data must be processed with a specific purpose and may only be used and transmitted if doing so is compatible with the purpose of transmission.
   c. *Quality and proportionality*: the personal medical data must be precise and kept up to date where necessary. The personal medical data must also be suitable and relevant in terms of the goal for which it is transmitted or processed. So there will be not more data exchanged than necessary for a specific goal.
   d. *Transparency*: information shall be provided to patients or next of kin for the purpose for which the personal medical data are processed and they may also be informed of the person or organization responsible for this processing. All information required to ensure that personal medical data are handled fairly shall also be provided.

e. *Security*: the person, organization or national authority responsible for processing the medical data must take technical and organizational security measures appropriate to the risks associated with processing (fraud, data destruction, computer viruses). Those under the authority of the person responsible may process personal medical data only on the instructions of that person.
f. *Appropriate degree of compliance*: patients, next of kin of donors, doctors as well as scientists shall be aware, or be made aware, of their rights and obligations. Compliance with the principles of personal medical data protection depends on the possibility of imposing effective sanctions on violations of those principles. The possibility of direct control by supervisory authorities, auditors or other controllers is also relevant.
g. *Assistance*: patients shall be able to assert their rights quickly and effectively, without prohibitive expenses being incurred in doing so. It shall be made possible for complaints to be handled independently.
h. *Suitable compensation*: if damage has incurred as a result of violations of the principles of data protection, damage shall be compensated in a suitable manner according to the applicable law.

6. *It should only be possible to identify the patient behind the recorded personal medical data in cases where the public safety overrides the private interests of an individual patient*.

This means that in certain cases, it shall be possible to determine the identity of a patient or donor to be able to trace patients who may be in medical danger. For example, if medical scientific research indicates that a particular method of transplant surgery may have certain life-threatening side effects or, for example, if it is suspected that the development of a disease in a patient is associated with a previous organ transplant. In that case, it may make sense to inform other patients who were recipients of an organ from this donor.

9 Quality assurance

Quality assurance refers to a program for the systematic monitoring and evaluation of the various aspects of a project, service, or facility to ensure that standards of quality are being met. Quality assurance cannot absolutely guarantee the production of quality products, unfortunately, but makes this more likely.
Quality assurance of data can be defined as the state of completeness, validity, consistency, timeliness and accuracy that makes data appropriate for a specific use.
There are a number of theoretical frameworks for understanding data quality. A systems theoretical approach influenced by American pragmatism expands the definition of data quality to include information quality, and emphasizes the inclusiveness of the fundamental dimensions of accuracy and precision on the basis of the theory of science[1]. One framework seeks to integrate the product perspective (conformance to specifications) and the service perspective (meeting consumers' expectations)[2]. Another framework is based in semiotics to evaluate the quality of the form, meaning and use of the data[3]. One highly theoretical approach analyses the ontological nature of information systems to define data quality rigorously[4].
A considerable amount of data quality research involves investigating and describing various categories of desirable attributes (or dimensions) of data. These lists commonly include accuracy, correctness, currency, completeness and relevance. Nearly 200 such terms have been identified and there is little agreement in their nature (are these concepts, goals or criteria?), their definitions or measures[5].
Generally speaking, a data quality assurance program is an explicit combination of organization, methodologies, and activities that exist for the purpose of reaching and maintaining high levels of data quality. In particular when we come to clinical databases, their usefulness depends strongly on the quality of the collected data. If the data quality is poor, the results of studies using the database are likely to be biased and unreliable. Data quality assurance should start with deciding in advance the uses to which the data base is going to be put, developing an explicitly defined minimum data set, and setting up a user friendly interface. The quality of the collected data can be assessed by computer validation, during which computerized range and consistency checks are based on information within the data base itself. Also, note validation can be used, which implies a comparison of the original data base against medical records. Eventually, audits can and should be performed to guarantee the reliability of the data and accuracy of the conclusions drawn by this data. That is the perspective from which we started our work.

9.1 Survey of registry quality systems

To define a quality system for the European Registry, the first step is to get an overview of performance indicators used in existing registries. For this purpose, a survey has been sent to all EFRETOS associated partners and collaborating partners analysing the systems presently adopted by the different organizations. The questionnaire included 29 questions (14 functional questions and 15 quality questions), centred on some data quality assurance aspects covering both data collection and data analysis. Mostly closed answers on a Yes/No basis have been inserted in order to facilitate data analysis after collection of inputs. The questionnaire has been sent to the coordinator, to all associated and collaborating partners (21 countries in all). Ten partners (covering 20 countries) have returned the questionnaire. These countries are: Austria, Belgium, Croatia, the Czech Republic, Denmark, Finland, France, Germany, Iceland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom. The results of this survey represent the basis for addressing the problem of data quality assurance of transplant outcomes in the proper light and have been compared with existing literature on quality assurance for other international clinical registries such as The Scientific Registry on Transplant Recipients (www.SRTR.org), and the European Liver Transplant Registry (www.ELTR.org)

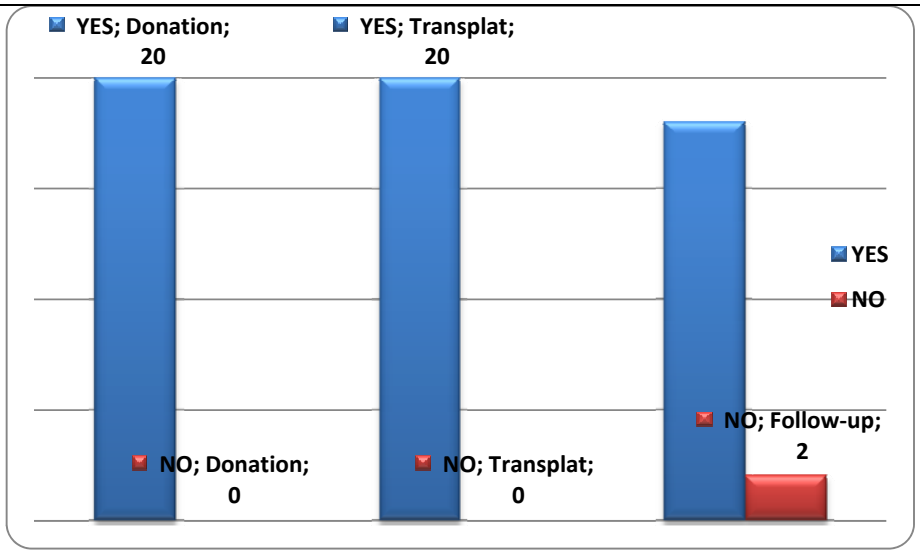
Table 1 shows all questions (functional and quality questions) included in the survey and indicates the total number of answers:

Table 1.

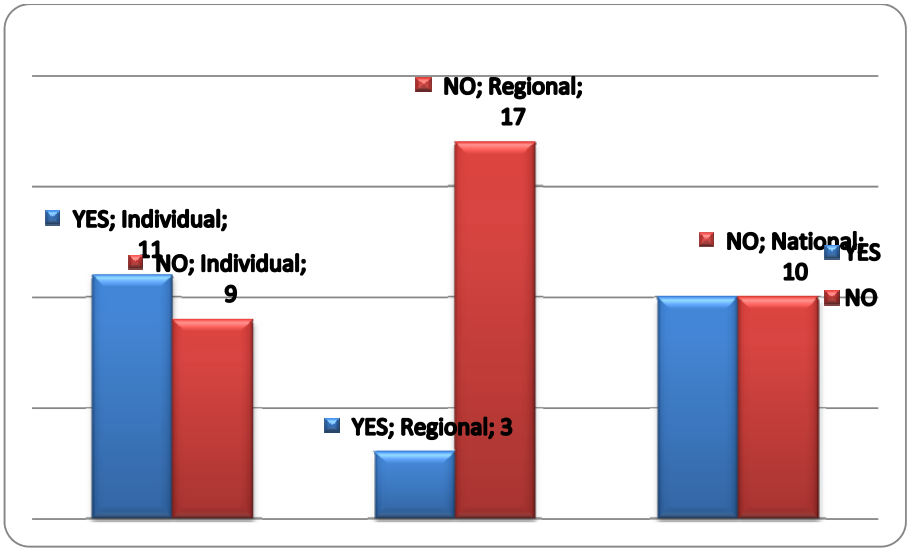
FUNCTIONAL QUESTIONS	YES	NO
Q.1.1 Do you collect data on the donation process?	20	0
Q.1.2 Do you collect data on the transplant process?	20	0
Q.1.3 Do you collect data on the follow-up of transplant recipients?	18	2
Q.2 Does the Registry hold patients identifiable information?	19	1
Q.3.1 At which level are donation data being collected? Individual donation unit	11	9
Q.3.2 At which level are donation data being collected? Regional Registry	3	17
Q.3.3 At which level are donation data being collected? National Registry	10	10
Q.4.1 At which level are transplant data being collected? Individual donation unit	11	9
Q.4.2 At which level are transplant data being collected? Regional Registry	3	17
Q.4.3 At which level are transplant data being collected? National Registry	9	11
Q.5 Is it mandatory by National Authorities to collect post-transplant outcome data?	11	9
Q.6 Are the data contributors financially reimbursed?	3	17
Q.7 Is there a National Authority towards which outcome data have to be reported?	10	10
Q.8 Are the outcome data used by National Authorities for monitoring?	9	11
Q.9 Are the outcome data used for publications?	20	0
Q.10 At what time points are data collected (every 6 months, annually, other)?	*	*
Q.11.1 Is it compulsory to register data? Donor data	20	0
Q.11.2 Is it compulsory to register data? Recipient data	19	1
Q.11.3 Is it compulsory to register data? Transplant procedure data	19	1
Q.11.4 Is it compulsory to register data? Post-transplant outcome data	11	9
Q.12 Who is entitled to access data base?	*	*
Q.13 Who is entitled to use the data?	*	*
Q.14 Is there a system in place for obtaining follow-up data when it is due?	18	2
QUALITY QUESTIONS		
Q.15 Do you perform a check on the data format at time of upload or data entry?	19	1
Q.16 Do you perform a check on internal consistency at time of upload or data entry?	19	1
Q.17 Do you perform a check on duplicate records?	20	0
Q.18 Do you perform a check on accuracy?	20	0
Q.19 Do you perform a check on reliability?	17	2
Q.20 Is there a check on completeness of data set?	18	2
Q.21 Is there a check on completeness of the outcome data?	18	2
Q.22 Is there a check on completeness of covariate information?	18	2
Q.23 Is there a check for systematic omissions?	17	3
Q.24 Do you use quality indicators for data contributors?	9	11
Q.25 Do you require minimal standards of quality for your data contributors?	9	11
Q.26 Are all consecutive transplants delivered by the data contributors?	19	1
Q.27 Do you perform periodically audits at the transplant centres?	4	16
Q.28 What types of audits take place?	*	*
Q.29 Do you verify data that were previously supplied during these audits?	4	0

* Free text answer.

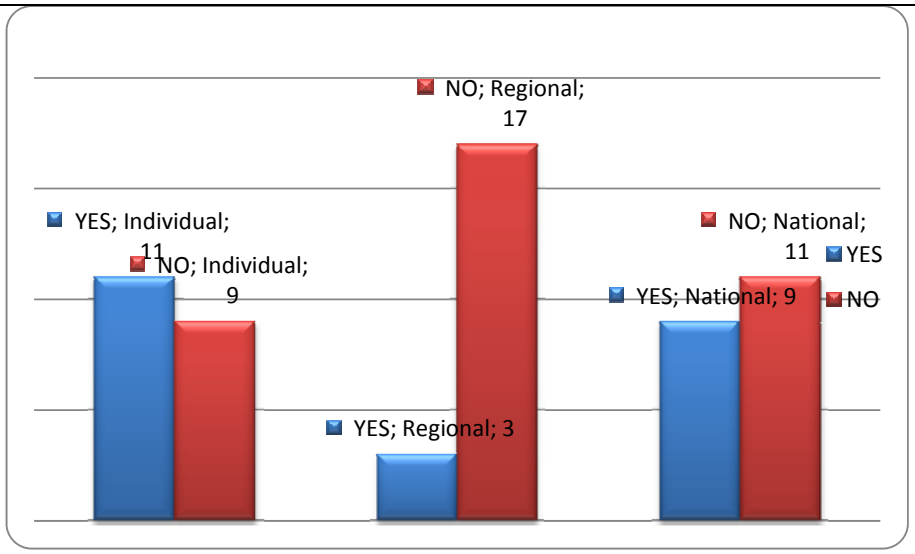
The following graphs show the responses to questions Q1, Q3, Q4 and Q11.



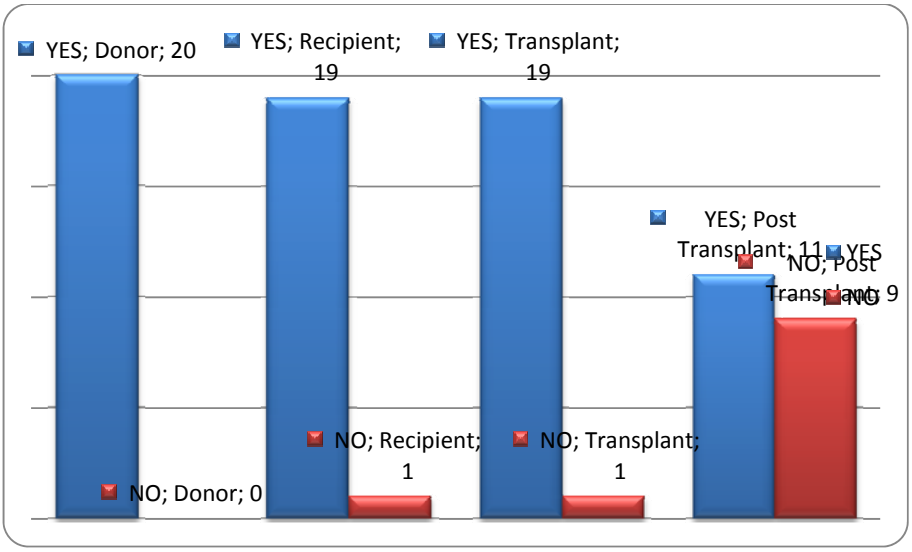
Q.1 Do you collect data on the donation/transplantation/follow-up process?



Q.3 At which level are donation data being collected?



Q.4 At which level are transplant data being collected?



Q.11 Is it compulsory to register data?

Depicted below are the responses to the questions Q10, Q12, Q13 and Q28.

Q10. At what time points are data collected (every 6 months, annually, other)?

- Annually (3 partners)
- On-going through website collection (2 partners)
- Immediately after transplantation; after 3, 12 months after transplantation and every 12 months (5 partners)

Q12. Who is entitled to access data base?

- It depends on the user level: hospital (access to data from the own hospital), regional and interregional (data of their own region), national (all data);
- National transplant coordinator centre workers; transplant coordinators;
- Medical personnel dealing with procurement and transplantation;
- Personnel using data on their line of work;
- A limited number of national centre staff has access to the raw data from all centres. No one else can access the data base directly;
- Centre own data. Everyone summarized demographics. Outcome data collected by BQS in Germany are not accessible at all. Any outcome data collected by ET for any of the ET countries are only made available to the transplant centres themselves and as overall national outcome to the transplantation community.

Q13. Who is entitled to use the data?

- It depends on the user level: hospital (access to data from the own hospital), regional and interregional (data of their own region), national (all data);
- All persons who obtain agreement from transplant centres or from national centre can use the data for a specific study;
- Ministry of Health;
- Each transplant centre can request their own data is sent back to them. Requests for data from multiple transplant centres are assessed by a group of clinicians involved in that type of transplantation who may or may not give approval for the data to be released;
- Centre own data. Everyone summarized demographics. Requests for specific outcome data: protocol has to pass the ET organ Advisory Committees.

Q28. What types of audits take place?

- 4 Countries perform periodically audits at the transplant centres;
- All these countries perform on site audits with external commission.

The average level of quality among ten partners seems to be satisfying. Nevertheless the following issues should be highlighted:

- Donation and transplant data are collected in a heterogeneous way and not all countries collect these data at national level;
- Collecting post-transplant outcome data is mandatory only for 55% of the countries;
- Data contributors are financially reimbursed only in 15% of the countries;
- Minimal standards of quality for data contributors are required only by 45% of the countries;
- Quality indicators are used only by less than 50% of the countries;
- Periodically audits at the transplant centres are performed only by 20% of the countries.

On the basis of this survey, it can be concluded that although the average level of quality is good, not all of the reviewed countries have an acceptable quality system in place. Hence, it is very important to present some recommendations (see chapter 2) in order to gradually implement a robust quality assurance system in those countries.

9.2 Quality assurance system

Generally speaking, *data quality* is of fundamental importance in every data base, but when we deal with clinical data bases this importance increases enormously. Indeed for clinical data bases data collection and subsequent data analysis might have a direct influence on patient health. In particular for transplant data bases collecting data to asses transplant outcome; it is important to have high quality data because

if data quality is poor, results will be biased and conclusions including comparison of transplant outcomes will not be reliable.

For assuring high data quality the entire process of managing data has to be optimized during all the different phases involved: Data Delivery, Data Collection, Data Validation, Data Storage, Data Analysis.

The Quality Assurance Data System has been implemented trying to address all these needs and to avoid error propagation among the different phases.

The whole quality system process can be divided in the above mentioned five important steps:

8.11.1. Data definition;
8.11.2. File definition for gathering data;
8.11.3. Data quality controls;
8.11.4. Definition of quality indicators & certification levels;
8.11.5. Audits.

High quality standards during these five steps assure control of data quality during the entire process of data managing, in particular during delivery, collection and validation phases.

Steps 1 and 2, i.e. “Data definition” and “File definition” are related to the data *delivery phase*. In this phase a detailed data definition is important. An overview of all variables is needed and in addition a complete description of their properties, like field type and string length, is essential. This also includes a definition of the requirements (“File definition”) in order to assure a standard according to which all variables have to be supplied.

Step 3, i.e. “Data quality control”, is directly linked to the *data collection phase*. In this phase data are imported into the registry and during the importing process different control measures take place described later in this document. These control measures are of fundamental importance in order to assure the data quality and allow also a subsequent data validation by defining indicators and levels of certification.

Step 4 and 5, i.e.“Quality indicators” and “Audits”, are related to the *data validation phase.* In this phase, after all quality controls have been performed, it is possible to assess data quality and hence assign a level of certification to the different contributors. The validation phase can be completed with audits that allow a cross check on data supplied from each contributors.

9.2.1 Data definition

The first and the most important step is the definition of a “standard” for data to be collected.
“Standard” means to define in detail:

- Variables to be collected (mandatory data set);
- File type for the delivery of the variables (e.g. xls, csv, text delimited and so on);
- Type of each variable (e.g. numeric, date, string, list etc.);
- Format of some variables (e.g. date format “01/01/2010” or “01-01-2010” etc.);
- Range of validity for numeric variables (e.g. age 0-100);
- List of items for “Code List Variables” (e.g. Yes/No);
- Business rules (e.g. date of birth cannot be earlier than date of transplant).

Once these standards are defined in detail, the probability of errors during data delivery will be highly reduced.

9.2.2 File definition for gathering data

The second step is to translate the requirements of point 8.11.1. on data into a "standard file structure" that will be used by all partners for delivering data in the pre-defined standardized format.

For the EFRETOS project, a standard file structure was created for all mandatory variables using information from the WP4 Deliverable. As previously agreed data were classified into four files, which represent four different moments in the transplantation process:

- RECIPIENT PRE-TRANSPLANTATION
- TRANSPLANTATION AND FOLLOW-UP UNTIL TRANSPLANTATION DISCHARGE
- FOLLOW-UP AFTER TRANSPLANTATION DISCHARGE
- DONOR

Addressing the specific characteristics of organ:
- Kidney
- Pancreas
- Heart
- Lung
- Liver
- Intestine

For each combination of moments in the transplantation process and organs a different data delivery file consisting of a number of selected variables (i.e. all Tier 1 and Tier 2 data) in a standardized order, type, format and coding had to be developed. In this project 24 files with all requirements were defined (see Annex).

A more detailed view of each of these files shows a common part composed by:

- Name of the file and the type of organ in the first row (e.g. KIDNEY-DONOR, HEART-PATIENT_PRE_TRANSPLANTATION-QUALITY etc.)

- Information on the fields in the second row as follow :

Variable description	Variable name	Field type	Unit	Alternative unit	Code list	Lowest value	Highest value	Length or format of variable	All business rules	Comments

Variable description	Describe type of information for each variable.
Variable name	Name to simply identify different variables.
Field type	**Z** = Date, **N** = Numerical, **F** = Free Text, **D** = Code list (such as Y/N).
Unit	Measurement unit (e.g. age in years).
Alternative unit	Alternative measurement unit
Code list	It is a list of defined items or a list of defined codes. This is important to avoid free text and the related high probability of error in filling fields. These lists are reported in the Annex.
Lowest value	Lowest allowed value for a numerical variable.
Highest value	Highest allowed value for a numerical variable.
Length or format of variable	"Length" is the length of a numerical variable x,y where x is the number of integer digits and y is the number of decimal digits; "Format" shows how a string has to be composed or which format a "data variable" has to have (e.g. DD-MM-YYYY)

All business rules	In this field all conditions that must be met by the variables are reported (e.g. check that "Birth date" is not greater than date of data filling, or check a field which has to be filled also in particular conditions and etc.).
Comments	Comments and Notes.

After the first two rows, the file contains all the variables of Tier 1 and Tier 2 which are different for each organ as stated in Deliverable 7. The Tier 1 variables are highlighted in orange colour, while the Tier 2 variables are highlighted in dark-yellow colour.

The above defined requirements for each of the 24 files are of fundamental importance in order to be able to perform a check on quality of data delivered by all partners.

According to the requirements stated in each of the 24 "standard file structure" all data have to be supplied, in order to have a satisfying data quality.

9.2.3 Data quality controls

Once all requirements and constraints for variables and for files are defined, it is very important to control the Data quality by automatic procedures during data collection.

Assuming the data are delivered by rows (one row for each patient) in csv or excel file type, it is important to check data in two different phases to assure a high data quality:

- ✓ **During file uploading**
- ✓ **After file uploading**

Checks during the uploading phase

During the uploading phase, the followings checks have to be performed:

1) Check on "*File type*" : we expect a csv or an excel file.

2) Check on "*Number of fields*": The number of delivered separate data fields must match with the expected number of data fields. For example for the Heart-Donor file, 28 mandatory variables are expected in 28 columns.

3) Check on "*Variables name and position"* in the first row of the data set. For example for Heart-Donor file the following sequence of fields (variables) is expected:

Variable name	Field type
Donor_ID	Free text
Donor_gender	Code list
Donor_blood_group	Code list
Donor_height	Numerical
Donor_weight	Numerical
Donor_age	Numerical
Donor_cause_death_code_system	Code list
Donor_cause_eeath_codes	Code list
Unified_donor_cause_death	Free text
Acute_intox	Code list
Donor_type	Code list
Perfusion_fluid	Code list
Anti-CMV	Code list
Anti-EBV	Code list
HIV_Ab	Code list
HBs_Ag	Code list
HBs_Ab	Code list
HBc_Ab	Code list
HCV_Ab	Code list
Drug_user	Code list
Cigarette_Use	Numerical
Donor_tumour	Code list
Moment_diagnosis_tumour	Code list
Kind_tumour	Code list
Kind_intracranial_tumour	Code list
Kind_intracranial_tumour_other	Code list
Kind_extracranial_tumour	Code list
Kind_extracranial_tumour_other	Code list

Table 2

For this purpose the first row of the file has to be extracted and analysed to check the compliance with the above described expected sequence and naming.

5) Check on "*Field type*" for each field.
For each field a defined format as shown in table 2 (second column) is expected.
For example for "Donor ID", an integer number has to be delivered, for "Donor's gender" a text from a code list and so on.

6) Check on *"Field format"* where appropriate.
For example for "Donor's height", a 3 digits integer number with 0 decimals is expected; for "Donor age in years at organ donation" a 3 digits integer with 1 decimal is expected etc.

7) Check on *"Field coding"* when required.
For some fields there are a fixed number of values as for example for "Donor's blood group", in this case we expect only one of 4 different text values : "A","B","0" and "AB". For "Donor's gender" we expect "F" or "M" , for "Donor type" we expect "DCD", "DBD", "Living" and so on. During the uploading process a check for internal consistency should take place (verification of coding by built-in business rules). Inconsistencies detected during this internal check should be reported to contributors for corrections (e.g. if *"gender" is reported as "Male" and "Female" instead of "M" and "F"*).

8) Check on "Range" for numerical variables.
For example, in the fields "Donor's height" and "Donor's weight" positive number less than 2 meter and 200 kg respectively are expected.

The percentage of non-compliance with the "Coding" or "Range", in case no corrections would be done by contributors on inconsistencies, can be used as quality indicator.

Checks after the uploading phase

During the second phase i.e. **after uploading,** the followings checks have to be performed:

1) *"Filling rate"* for each field (Completeness of covariate).
   Percentage of null or empty data for each field will be calculated and could be used as a quality indicator.

2) *"Unlikely variables combinations".*
   For fields which have some interdependence with others fields, cross checks will be performed (as reported in fields "All Business Rules"). For example it can be checked whether the patient's birth date is correct and a flag field with information on adult or paediatric transplant match. Another example is that patient's birth date has to be earlier in time than date of patient death or graft failure.
   Unlikely combinations can be checked also among variables of the four different files listed above.

   The unlikely combinations have to be reported to contributors for corrections.

3) *"Follow-up"* for each transplant (Completeness of outcome data).
   Percentage of transplants with the follow-up in due time (for example 1 years after transplantation) can be calculated and used as quality indicator.

4) *"Recorded Transplants"* (Completeness Dataset).
   It has to be checked if all performed transplants are in the registry.

5) "*Data comparison*" (Consistency).
   The consistency between data already in database and new uploaded data has to be checked. *For example, data on transplants in 2005 received in 2007 have to match the data on transplants in 2005 received in 2008.*
   The inconsistencies have to be reported to contributors for corrections.

6) "Identification of possible duplicate registrations".

   This is an emerging aspect of merging registries across the different Organ Exchange Organizations that will be taken into account. A way to avoid duplicate registrations could be to check the data by performing a probability match; using this method the data contributors are asked whether patients are listed on a second waiting list as this might have resulted in a double registration of the transplant. Another way to avoid duplicate registration is to start with a pan-European registration number, although we must remark that this is not legally allowed in some EU countries at this moment.

   All data sets provided by the contributors will be subject to the above presented checks.
   Inconsistencies detected during these checks have to be reported to the respective contributor for correction by using so called editorial tables.
   Only if data have passed all the quality checks, they can and will be added to the European Registry allowing further data processing and analysis.
   In case some of the above checks are not passed and no corrections are made, these data from the contributor will not be processed further.

   Data uploading takes place in two phases. All data submitted to the registry will initially be accepted. The above described quality controls will then take place. If some the delivered data do not pass the checks, they are sent back to the data contributors who perform the necessary corrections. This process might be repeated if the checks during the second uploading still detect errors. After all checks are cleared the second phase of the uploading will be triggered, allowing the data to be used for analysis purposes. The description of these two layer data base structure is given in the chapter on technical requirements.

9.2.4 Definition of quality indicators & certification levels

All different checks performed on data delivered can be used to define quality indicators to assess the level of quality of collected data.

In particular we can define four main indicators:

- **I1.**
  Percentage of non-compliance with the coding standards: for each field of type “Code list” we expect a defined value (as reported in the “List items” in the Annex). If during controls a value not in the list is detected, it will be counted as an error. In the same way numerical variables and values out of range can be checked and will be counted as an error if not corrected.

- **I2**.
  Percentage of null or empty data for each field will be calculated.

- **I3**.
  Percentage of transplants with the follow-up delivered in due time (for example 1 year after transplantation) can be calculated and used as a quality indicator at different times (1-3-5 years after transplantation).

- **I4.**
  Percentage of completeness of the data set.

Each of the above mentioned indicators defines a lack of some information:

I1 : lack of data compliance;
I2 : lack of information on different variables.;
I3 : lack of follow-up;
I4 : lack of transplants.

These indicators have different impact on data quality depending on the type of variables they are calculated on (Tier 1 or Tier 2) and also on data utilization.

For example for reporting annual data it is important to have an overview of all transplants performed in a certain era (i.e., a high value of I4) and in addition to have information on basic demographics (i.e. good values of I1 and I2 for the Tier 1 variables).
Instead, for example, for estimating unadjusted transplant survival rates it is important to have a high value of follow-up update (I3) and low missing values for Tier 1 variables (I2 low) while for adjusted analysis we have to ask also a low value of I2 for Tier 2 variables.

To characterize the data quality delivered to the European Registry it is suggested to define different quality levels of the data provided based on the four indicators mentioned above. The lower the value for indicator I1 and I2 and the higher the value for I3 and I4, the higher the quality of the data delivered.
The data should fulfil a minimum quality standard in order to be used for analysis and reporting at all. In addition to this minimum level, 3 levels (Low, Medium, High) of data quality can be defined. This definition will be based on the quality level achieved with data delivered to the European Registry; hence it will be purely empirical and should be constantly re-evaluated and re-defined by the Registry Review Committee.

Low : with this level it is possible to use data for public annual report on transplants;

Medium : with this level it is possible to use data for descriptive and crude survival analysis;

High : with this level it is possible to use data for descriptive and adjusted survival analysis.

It is important to stress that at the beginning of the registry activities a definition of the “Minimum level” as well as of the other three levels is not possible. Initially the values for the different indicators for all contributors will be monitored and reported and based on these data definitions of the quality levels will be developed. It is expected that after a two years period a first definition can be provided. Thereafter the levels of quality might be subject to change based on the experiences with the data delivered and analysed by the European Registry. The definition of the quality levels of the provided data will increase transparency of data provided and stimulate continuous improvement of the quality of the data delivery.

9.2.5 Audits

Audits are an important means to assess data quality, by checking the consistency of medical records with data supplied by data contributors. For this purpose ad hoc committees on a national level should be installed. Internal or external committees should check during the audit process whether a data sample in the medical records is consistent with the data supplied by the data contributor. The usefulness of this tool for validating data and ensuring quality assurance is also shown by existing experiences of international registries such as the European Liver Transplant Registry[6]. The audit process will not be performed by the European Registry itself but should under the responsibility of the national registries. The existence of a national auditing procedure might be taken into account for the proposed certification process of the different national registries as described above.

9.3 Recommendations

While data collection on organ donation, allocation and the transplant process itself is compulsory in most countries participating in the EFRETOS project, for post-transplant data collection only half of the participants do have a compulsory system in place. Follow-up data completeness is currently often low especially in those countries without a mandatory data reporting system. Therefore efforts have to be made to increase the level of post-transplant data collection at central (national) level.

With regard to data quality, currently all partners perform checks on data format, internal consistency, accuracy and reliability of the data reported to them. On the other hand less than 50% of the partners require a minimal standard of quality and most do not have a system of quality indicators to assure data quality in place. For this reason it is considered important to establish quality indicators to evaluate and where necessary improve the quality of the data provided to a European Registry. This way the weaknesses of the data collection process as shown for example by the results of the pilot study performed in the framework of the EFRETOS project can be addressed. An important first step to improve the quality level of data could be achieved if data will be provided from all partners according to the requirements stated in the Annex. In particular, it would be helpful if the creation and delivery of the data by the contributors and the acquisition of the data by the European Registry were automatized.
After establishing a European Registry of registries quality levels based on different indicators should be developed. This will increase the transparency level of the data provided and could be used to define certification levels for the reported data from the different national registries. To establish these quality levels, a “training period” will be required during which all partners should make an effort to reach a minimum level of data quality. The time period foreseen for setting up these different quality levels is about two years, during which data quality targets will be adapted based on the experiences with the data collected during this period.

9.4 References

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9.5 Annex 1. Standard file structure

(REQUIREMENTS ON VARIABLES TO BE COLLECTED)

KIDNEY-DONOR										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Donor ID	Donor_ID	F								
Donor's Gender	Donor_Gender	D			**MaleFemale**					
Donor's Blood Group	Donor_Blood_Group	D			**BloodGroup**					
Donor's Height	Donor_Height	N	cm			0	250	3,0		
Donor's Weight	Donor_Weight	N	kg			0	200	3,0		
Donor Age in Years at Organ Donation	Donor_Age	N	years			0	100	3,1		
Donor's Cause of Death Code System	Donor_Cause_Death_Code_System	F								
Cause of Death coding system specific codes	Donor_Cause_Death_Codes	D			**DonorCauseDeathCodes**					
Unified Cause of Death	Unified_Donor_Cause_Death	D			**ICD-10**					
Cause of death: acute intoxication	Acute_Intox	D			**YesNo**				IF DONOR is a NON STANDAR RISK DONOR	
Agent of intoxication	Agent_Intox	D			**AgentIntox**				IF Acute_Intox = 'YES'	
Donor Type	Donor_Type	D			**DonorType**					
Perfusion Fluid	Perfusion_Fluid	D			**PerfusionFluid**					
Anti-CMV	Anti-CMV	D			**ReactiveNonReactive**					
Anti-EBV	Anti-EBV	D			**ReactiveNonReactive**					
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
Donor's HLA - typing A-B-DR (1-2) antigen	Donor_HLA	D						A1,A2,B1,B2,DR1,DR2		
Risk factor for infection: IV Drug user	Drug_User	D			**YesNo**					
Malignant tumors in the donor	Donor_Tumor	D			**YesNo**					
Moment of Diagnosis Conditional	Moment_Diagnosis_Tumor	D			**MomentDiagnosisTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed Conditional	Kind_Tumor	D			**KindTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor	D			**KindIntracranialTumor**				IF Kind of tumor Detailed is `Intracranial´	
Other Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor_Other	F							IF Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor	D			**KindExtracranialTumor**				IF Kind of tumor Detailed is `Extracranial´	
Other Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor_Other	F							IF Kind of `Extracranial´ Tumor is ´Other´	
Serum Creatinine Unit	Serum_Creatinine_Unit	D			**SerumCreatinineUnit**					
Serum Creatinine Values	Serum_Creatinine_Values	N	mg/dl	µmol/l		0 0	22,62 2000	mg/dl : 2,2 µmol/l : 4,0		

PANCREAS-DONOR										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Donor ID	Donor_ID	F								
Donor's Gender	Donor_Gender	D			**MaleFemale**					
Donor's Blood Group	Donor_Blood_Group	D			**BloodGroup**					
Donor's Height	Donor_Height	N	cm			0	250	3,0		
Donor's Weight	Donor_Weight	N	kg			0	200	3,0		
Donor Age in Years at Organ Donation	Donor_Age	N	years			0	100	3,1		
Donor's Cause of Death Code System	Donor_Cause_Death_Code_System	D								
Cause of Death coding system specific codes	Donor_Cause_Death_Codes	D			**DonorCauseDeathCodes**					
Unified Cause of Death	Unified_Cause_Death	F			**ICD-10**					
Cause of death: acute intoxication	Acute_Intox				**YesNo**				IF DONOR is a NON STANDAR RISK DONOR	
Agent of intoxication	Agent_Intox	D			**AgentIntox**				IF Acute_Intox = 'YES'	
Donor Type	Donor_Type	D			**DonorType**					
Perfusion Fluid	Perfusion_Fluid	D			**PerfusionFluid**					
Anti-CMV	Anti-CMV	D			**ReactiveNonReactive**					
Anti-EBV	Anti-EBV	D			**ReactiveNonReactive**					
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
Risk factor for infection: IV Drug user	Drug_User	D			**YesNo**					
Malignant tumors in the donor	Donor_Tumor	D			**YesNo**					
Moment of Diagnosis Conditional	Moment_Diagnosis_Tumor	D			**MomentDiagnosisTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed Conditional	Kind_Tumor	D			**KindTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor	D			**KindIntracranialTumor**				IF Kind of tumor Detailed is `Intracranial´	
Other Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor_Other	D							IF Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor	D			**KindExtracranialTumor**				IF Kind of tumor Detailed is `Extracranial´	
Other Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor_Other	D							IF Kind of `Extracranial´ Tumor is ´Other´	
Serum Creatinine Unit	Serum_Creatinine_Unit	D			**SerumCreatinineUnit**					
Serum Creatinine Values	Serum_Creatinine_Values	N	mg/dl	µmol/l		0	0 22,62 2000	mg/dl : 2,2 µmol/l : 4,0		

HEART-DONOR										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Donor ID	Donor_ID	F								
Donor's Gender	Donor_Gender	D			**MaleFemale**					
Donor's Blood Group	Donor_Blood_Group	D			**BloodGroup**					
Donor's Height	Donor_Height	N	cm			0	250	3,0		
Donor's Weight	Donor_Weight	N	kg			0	200	3,0		
Donor Age in Years at Organ Donation	Donor_Age	N	years			0	100	3,1		
Donor's Cause of Death Code System	Donor_Cause_Death_Code_System	D								
Cause of Death coding system specific codes	Donor_Cause_Death_Codes	D			**DonorCauseDeathCodes**					
Unified Cause of Death	Unified_Donor_Cause_Death	F			**ISHL**					
Cause of death: acute intoxication	Acute_Intox	D			**YesNo**				IF DONOR is a NON STANDAR RISK DONOR	
Agent of intoxication	Agent_Intox	D			**AgentIntox**				IF Acute_Intox = 'YES'	
Donor Type	Donor_Type	D			**DonorType**					
Perfusion Fluid	Perfusion_Fluid	D			**PerfusionFluid**					
Anti-CMV	Anti-CMV	D			**ReactiveNonReactive**					IgG
Anti-EBV	Anti-EBV	D			**ReactiveNonReactive**					IgG
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
Risk factor for infection: IV Drug user	Drug_User	D			**YesNo**					
History of Cigarette Use	Cigarette_Use	N	Packsyears			0	99	2,0		
Malignant tumors in the donor	Donor_Tumor	D			**YesNo**					
Moment of Diagnosis Conditional	Moment_Diagnosis_Tumor	D			**MomentDiagnosisTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed Conditional	Kind_Tumor	D			**KindTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor	D			**KindIntracranialTumor**				IF Kind of tumor Detailed is `Intracranial´	
Other Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor_Other	F							IF Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor	D			**KindExtracranialTumor**				IF Kind of tumor Detailed is `Extracranial´	
Other Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor_Other	F							IF Kind of `Extracranial´ Tumor is ´Other´	

LUNG-DONOR										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Donor ID	Donor_ID	F								
Donor's Gender	Donor_Gender	D			**MaleFemale**					
Donor's Blood Group	Donor_Blood_Group	D			**BloodGroup**					
Donor's Height	Donor_Height	N	cm			0	250	3,0		
Donor's Weight	Donor_Weight	N	kg			0	200	3,0		
Donor Age in Years at Organ Donation	Donor_Age	N	years			0	100	3,1		
Donor's Cause of Death Code System	Donor_Cause_Death_Code_System	D								
Cause of Death coding system specific codes	Donor_Cause_Death_Codes	D			**DonorCauseDeathCodes**					
Unified Cause of Death	Unified_Donor_Cause_Death	F			**ISHLT**					
Cause of death: acute intoxication	Acute_Intox				**YesNo**				IF DONOR is a NON STANDAR RISK DONOR	
Agent of intoxication	Agent_Intox	D			**AgentIntox**				IF Acute_Intox = 'YES'	
Donor Type	Donor_Type	D			**DonorType**					
Perfusion Fluid	Perfusion_Fluid	D			**PerfusionFluid**					
Anti-CMV	Anti-CMV	D			**ReactiveNonReactive**					
Anti-EBV	Anti-EBV	D			**ReactiveNonReactive**					
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
Risk factor for infection: IV Drug user	Drug_User	D			**YesNo**					
History of Cigarette Use	Cigarette_Use	N	Packyears			0	99	2,0		
Malignant tumors in the donor	Donor_Tumor	D			**YesNo**					
Moment of Diagnosis Conditional	Moment_Diagnosis_Tumor	D			**MomentDiagnosisTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed Conditional	Kind_Tumor	D			**KindTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor	D			**KindIntracranialTumor**				IF Kind of tumor Detailed is `Intracranial´	
Other Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor_Other	D							IF Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor	D			**KindExtracranialTumor**				IF Kind of tumor Detailed is `Extracranial´	
Other Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor_Other	D							IF Kind of `Extracranial´ Tumor is ´Other´	

LIVER-DONOR										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Donor ID	Donor_ID	F								
Donor's Gender	Donor_Gender	D			**MaleFemale**					
Donor's Blood Group	Donor_Blood_Group	D			**BloodGroup**					
Donor's Height	Donor_Height	N	cm			0	250	3,0		
Donor's Weight	Donor_Weight	N	kg			0	200	3,0		
Donor Age in Years at Organ Donation	Donor_Age	N	years			0	100	3,1		
Donor's Cause of Death Code System	Donor_Cause_Death_Code_System	D								
Cause of Death coding system specific codes	Donor_Cause_Death_Codes	D			**DonorCauseDeathCodes**					
Unified Cause of Death	Unified_Donor_Cause_Death	F			**ELTR**					
Cause of death: acute intoxication	Acute_Intox	D			**YesNo**				IF DONOR is a NON STANDAR RISK DONOR	
Agent of intoxication	Agent_Intox	D			**AgentIntox**				IF Acute_Intox = 'YES'	
Donor Type	Donor_Type	D			**DonorType**					
Perfusion Fluid	Perfusion_Fluid	D			**PerfusionFluid**					
Anti-CMV	Anti-CMV	D			**ReactiveNonReactive**					IgG
Anti-EBV	Anti-EBV	D			**ReactiveNonReactive**					IgG
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
Risk factor for infection: IV Drug user	Drug_User	D			**YesNo**					
Malignant tumors in the donor	Donor_Tumor	D			**YesNo**					
Moment of Diagnosis Conditional	Moment_Diagnosis_Tumor	D			**MomentDiagnosisTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed Conditional	Kind_Tumor	D			**KindTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor	D			**KindIntracranialTumor**				IF Kind of tumor Detailed is `Intracranial´	
Other Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor_Other	F							IF Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor	D			**KindExtracranialTumor**				IF Kind of tumor Detailed is `Extracranial´	
Other Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor_Other	F							IF Kind of `Extracranial´ Tumor is ´Other´	
INR	INR	N				0	10	2,0		
Total Bilirubin	Total_Bilirubin	N	mg/dl			0	58,47	2,2		

INTESTINE-DONOR										
Name	Variable Name	Field Type	Unit	Alternative Unit	Code list	Lowest value	Highest value	Length or Format of variable	All business rules	Comments
Donor ID	Donor_ID	F								
Donor's Gender	Donor_Gender	D			**MaleFemale**					
Donor's Blood Group	Donor_Blood_Group	D			**BloodGroup**					
Donor's Height	Donor_Height	N	cm			0	250	3,0		
Donor's Weight	Donor_Weight	N	kg			0	200	3,0		
Donor Age in Years at Organ Donation	Donor_Age	N	years			0	100	3,1		
Donor's Cause of Death Code System	Donor_Cause_Death_Code_System	D								
Cause of Death coding system specific codes	Donor_Cause_Death_Codes	D			**DonorCauseDeathCodes**					
Unified Cause of Death	Unified_Donor_Cause_Death	F			**ELTR**					
Cause of death: acute intoxication	Acute_Intox	D			**YesNo**				IF DONOR is a NON STANDAR RISK DONOR	
Agent of intoxication	Agent_Intox	D			**AgentIntox**				IF Acute_Intox = 'YES'	
Donor Type	Donor_Type	D			**DonorType**					
Perfusion Fluid	Perfusion_Fluid	D			**PerfusionFluid**					
Anti-CMV	Anti-CMV	D			**ReactiveNonReactive**					IgG
Anti-EBV	Anti-EBV	D			**ReactiveNonReactive**					IgG
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
Risk factor for infection: IV Drug user	Drug_User	D			**YesNo**					
Malignant tumors in the donor	Donor_Tumor	D			**YesNo**					
Moment of Diagnosis Conditional	Moment_Diagnosis_Tumor	D			**MomentDiagnosisTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed Conditional	Kind_Tumor	D			**KindTumor**				IF Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor	D			**KindIntracranialTumor**				IF Kind of tumor Detailed is `Intracranial´	
Other Kind of Intracranial Tumor Conditional	Kind_Intracranial_Tumor_Other	F							IF Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor	D			**KindExtracranialTumor**				IF Kind of tumor Detailed is `Extracranial´	
Other Kind of Extracranial Tumor Conditional	Kind_Extracranial_Tumor_Other	F							IF Kind of `Extracranial´ Tumor is ´Other´	
INR	INR	N				0	10	2,0		
Total Bilirubin	Total_Bilirubin	N	mg/dl			0	58,47	2,2		

Code List	List Items
MaleFemale	M F
BloodGroup	A B AB O Unknown
DonorCauseDeathCodes	Depend on Country (has to be supplied)
ELTR	ELTR List
ISHL	ISHL List
ICD-10	ICD-10 List
YesNo	Yes No Unknown
DonorType	DCD DBD Living
AgentIntox	Amanita Phalloides Barbiturics Benzodiazepines Carbon Monoxide Chloroquines Cocaine Cyanur Dextropropoxylen Escstasy Ethanol Ethylenglycol Hydrocarburs Isoniacid Lead Methanol Neuroleptic Organophosphorade pesticides Paracetamol Rodenticides (dicumarin) Theophylline Tricyclic antidepressants Unknown Other
ReactiveNonReactive	Reactive Non Reactive Unknown

Code List	List Items
PerfusionFluid	Euro Collins University Wisconsin Phosphate Buffered Sucrose (PBS) Celsior Bretschneider (or put this in HTK) Custodiol (or put this in HTK) Marshall (or put this in Hyperosmolar citrate) Soltran (or in HOC) Low Potassium Dextran St Thomas' Papworth Solution Perfadex Ringers
MomentDiagnosisTumor	Previously known Incidentally found before transplantation Incidentally found after transplantation
KindTumor	Intracranial Extracranial
KindIntracranialTumor	Medulloblastomas Astrocytomas Glioblastomas Oligodendrogliomas Ependymomas Meningiomas Other Unknown
KindExtracranialTumor	Renal Cell Carcinoma (RCC) Prostate Adenocarcinoma Breast Cancer Lung Cancer Colorectal Cancer Oesophagus Carcinoma Pancreatic Carcinoma Hepatocellular Carcinoma Thyroid Carcinoma Ovarian Cancer Chorioncarcinoma Sarcoma (including GIST) Malignant Melanoma Non Melanoma Skin Cancer (Basal Cell Carcinoma, Spinocellular Carcinoma) Carcinoma in situ Low grade Lymphoma High grade Lymphoma Leukemia Other Unknown
SerumCreatinineUnit	µmol/l mg/dl

KIDNEY-PATIENT_PRE_TRANSPLANTATION										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Patient's Gender	Patient_Gender	D			**MaleFemale**					
Patient's ABO Blood Group	Patient_Blood_Group	D			**BloodGroup**					
Primary Diagnosis Code	Primary_Diagnosis_Code	D			**PrimaryDiagnosisCode**					
Primary Diagnosis System Code	Primary_Diagnosis_Code_System	D			**PrimaryDiagnosisCodeSystem**					
Unified Primary Diagnosis	Unified_Primary_Diagnosis_Code_System	D			**ICD-10**					
Date of Birth	Recipient_Birth_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < '01-01-1900' CHECK;	
Country of Residence	Residence_Country	D			**ISO-Code-3166**					
Listing Date	Listing_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < Recipient_Birth_Date CHECK	Date recipient was added to the waiting list. Can be entered for every transplantation (first, second, etc.).
Date Candidate went on Dialysis.Conditional	Dialysis_Date	Z						DD-MM-YYYY	If it is > Now CHECK ;If it is < Recipient_Birth_Date CHECK	Date the recipient went on dialysis for the first time, before his first transplantation.For second and third transplantations, this variable is not entered.99-99-9999 must be used for 'No Dialysis'.
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
National ID number for Recipient	Recipient_National_ID	F								

PANCREAS-PATIENT_PRE_TRANSPLANTATION										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Patient's Gender	Patient_Gender	D			**MaleFemale**					
Patient's ABO Blood Group	Patient_Blood_Group	D			**BloodGroup**					
Primary Diagnosis Code	Primary_Diagnosis_Code	F			**PrimaryDiagnosisCode**					
Primary Diagnosis System Code	Primary_Diagnosis_Code_System	D			**PrimaryDiagnosisCodeSystem**					
Unified Primary Diagnosis	Unified_Primary_Diagnosis_Code_System	D			**ICD-10**					
Date of Birth	Recipient_Birth_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < '01-01-1900' CHECK;	
Country of Residence	Residence_Country	D			**ISO-Code-3166**					
Listing Date	Listing_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < Recipient_Birth_Date CHECK	Date recipient was added to the waiting list. Can be entered for every transplantation (first, second, etc.).
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
National ID number for Recipient	Recipient_National_ID	F								

HEART-PATIENT_PRE_TRANSPLANTATION										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Patient's Gender	Patient_Gender	D			**MaleFemale**					
Patient's ABO Blood Group	Patient_Blood_Group	D			**BloodGroup**					
Primary Diagnosis Code	Primary_Diagnosis_Code	F			**PrimaryDiagnosisCode**					
Primary Diagnosis System Code	Primary_Diagnosis_Code_System	D			**PrimaryDiagnosisCodeSystem**					
Unified Primary Diagnosis	Unified_Primary_Diagnosis_Code_System	D			**ISHLT**					
Date of Birth	Recipient_Birth_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < '01-01-1900' CHECK;	
Country of Residence	Residence_Country	D			**ISO-Code-3166**					
Listing Date	Listing_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < Recipient_Birth_Date CHECK	Date recipient was added to the waiting list. Can be entered for every transplantation (first, second, etc.).
Urgency of candidate at time of transplantation	Urgency_Candidate	D			**UrgencyCandidate**					Variable reflecting severity of disease. If a transplantation is not registered as urgent or with high priority, it is elective.
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
Life Support Medication (inotropes)	Life_Support_Med	D			**YesNo**					
Life Support Ventilation	Life_Support_Vent	D			**YesNo**					
Life Support Mechanical Assist Device	Life_Support_Device	D			**LifeSupportDevice**					
National ID number for Recipient	Recipient_National_ID	F								

LUNG-PATIENT_PRE_TRANSPLANTATION										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Patient's Gender	Patient_Gender	D			**MaleFemale**					
Patient's ABO Blood Group	Patient_Blood_Group	D			**BloodGroup**					
Primary Diagnosis Code	Primary_Diagnosis_Code	F			**PrimaryDiagnosisCode**					
Primary Diagnosis System Code	Primary_Diagnosis_Code_System	D			**PrimaryDiagnosisCodeSystem**					
Unified Primary Diagnosis	Unified_Primary_Diagnosis_Code_System	D			**ISHLT**					
Date of Birth	Recipient_Birth_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < '01-01-1900' CHECK;	
Country of Residence	Residence_Country	D			**ISO-Code-3166**					
Listing Date	Listing_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < Recipient_Birth_Date CHECK	Date recipient was added to the waiting list. Can be entered for every transplantation (first, second, etc.).
Urgency of candidate at time of transplantation	Urgency_Candidate	D			**UrgencyCandidate**					Variable reflecting severity of disease. If a transplantation is not registered as urgent or with high priority, it is elective.
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
Life Support Medication (inotropes)	Life_Support_Med	D			**YesNo**					
Life Support Ventilation	Life_Support_Vent	D			**YesNo**					
Life Support Mechanical Assist Device	Life_Support_Device	D			**LifeSupportDevice**					
National ID number for Recipient	Recipient_National_ID	F								

LIVER-PATIENT_PRE_TRANSPLANTATION										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Patient's Gender	Patient_Gender	D			**MaleFemale**					
Patient's ABO Blood Group	Patient_Blood_Group	D			**BloodGroup**					
Primary Diagnosis Code	Primary_Diagnosis_Code	F			**PrimaryDiagnosisCode**					
Primary Diagnosis System Code	Primary_Diagnosis_Code_System	D			**PrimaryDiagnosisCodeSystem**					
Unified Primary Diagnosis	Unified_Primary_Diagnosis_Code_System	D			**ELTR**					
Date of Birth	Recipient_Birth_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < '01-01-1900' CHECK;	
Country of Residence	Residence_Country	D			**ISO-Code-3166**					
Listing Date	Listing_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < Recipient_Birth_Date CHECK	Date recipient was added to the waiting list. Can be entered for every transplantation (first, second, etc.).
Last Absolute Creatinine before transplantation Unit	Last_Creatinine_Before_Transplant_Unit	D			**LastCreatininUnit**					
Last Absolute Creatinine before transplantation	Last_Creatinine_Before_Transplant	N	mg/dl	µmol/l		0 0	22,62 2000	mg/dl : 2,2 µmol/l : 4,0		
Date Candidate went on Dialysis.Conditional	Dialysis_Date	Z						DD-MM-YYYY	If it is > Now CHECK ;If it is < Recipient_Birth_Date CHECK	Date the recipient went on dialysis for the first time, before his first transplantation.For second and third transplantations, this variable is not entered.99-99-9999 must be used for 'No Dialysis'.
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
Vaccination for hepatitis B	Vaccination_Hepatitis	D			**YesNo**					
B Delta	B_Delta	D			**ReactiveNonReactive**				If recipient is HBV positive	
Duration of Abstinence of drinking before transplantation	Abstinence_Drink_Before_Transplant	N	Months			0	999	3,0		999 = Never drank
Serum Albumin (Liver: for CPT)	Serum_Albumin	N	g/l			0	99,9	2,1		
Total Serum Bilirubin (Liver: for MELD/CPT)	Total_Serum_Bilirubin	N	mg/dl			0	58,47	2,2		
INR (used for MELD)	INR	N				0	10	2,0		
Prothrombin Time used for CPT	Prothrombin_Time	N				0	100	3,1		
Last Serum Sodium (used for MELD Sodium or UK MELD)	Last_Serum_Sodium	N	mg/dl			183,9	459,8	3,1		
Recipient presence of Ascites prior to transplantation (used for CPT)	Ascite_Presence	D			**AscitePresence**					
Recipient presence of Encephalopathy prior to transplantation (used for CPT)	Encephalopathy_Presence	D			**EncephalopathyGrading**					
National ID number for Recipient	Recipient_National_ID	F								

INTESTINE-PATIENT_PRE_TRANSPLANTATION										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Patient's Gender	Patient_Gender	D			**MaleFemale**					
Patient's ABO Blood Group	Patient_Blood_Group	D			**BloodGroup**					
Primary Diagnosis Code	Primary_Diagnosis_Code	F			**PrimaryDiagnosisCode**					
Primary Diagnosis System Code	Primary_Diagnosis_Code_System	D			**PrimaryDiagnosisCodeSystem**					
Unified Primary Diagnosis	Unified_Primary_Diagnosis_Code_System	D			**ELTR**					
Date of Birth	Recipient_Birth_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < '01-01-1900' CHECK;	
Country of Residence	Residence_Country	D			**ISO-Code-3166**					
Listing Date	Listing_Date	Z						DD-MM-YYYY	If it is > Now CHECK; If it is < Recipient_Birth_Date CHECK	Date recipient was added to the waiting list. Can be entered for every transplantation (first, second, etc.).
HIV (I/II) Ab	HIV_Ab	D			**ReactiveNonReactive**					
HBsAg	HBs_Ag	D			**ReactiveNonReactive**					
HBsAb	HBs_Ab	D			**ReactiveNonReactive**					
HBc Ab	HBc_Ab	D			**ReactiveNonReactive**					
HCV Ab	HCV_Ab	D			**ReactiveNonReactive**					
Number of central venous acces sites	Venus_Access	N				0	9	1,0		
Indication: impaired QoI	Impaired_QoI	D			**YesNo**					
Indication: loss of venous access	Loss_Venus_Access	D			**YesNo**					
Indication: TPN induced liver cirrhosis	TPN_Induced_Cirrhosis	D			**YesNo**					
Indication: recurrent line sepsis	Recurrent_Line_Sepsis	D			**YesNo**					
National ID number for Recipient	Recipient_National_ID	F								

Code List	List Items
MaleFemale	M F
BloodGroup	A B AB O Unknown
PrimaryDiagnosisCodeSystem	1 = ICD-10 2 = ICD-10 german 3 = ERA 4 = Snowmed 5 = EDTA ER 6 = ELTR 7 = ISHLT …..
PrimaryDiagnosisCode	Depend on Country (has to be supplied)
ICD-10	ICD-10 List
ISHLT	ISHLT List
ELTR	ELTR List
ISO-Code-3166	ISO-Code-3166 List
YesNo	Yes No Unknown
ReactiveNonReactive	Reactive Non Reactive Unknown
UrgencyCandidate	Urgent Elective
LifeSupportDevice	ECMO IABP VAD Novalung ILA other devices
LastCreatininUnit	µmol/l mg/dl
Ascite_Presence	None Controlled with medication Refractory (poorly controlled)
EncephalopathyGrading	Grade 1 Grade 2 Grade 3 Grade 4

PrimaryDiagnosisCodeSystem = NOTR-ENIS	
PrimaryDiagnosisCode	Thoracic Lung disease
1500	Eisenmenger's Syndrome
1600	Other Congenital, specify
1601	Primary Pulmonary Hypertension
1602	Cystic Fibrosis
1603	Inhalation burns / trauma
1604	Idiopathic Pulmonary Fibrosis
1605	Sarcoidosis
1606	Alpha-1 Antitrypsin Deficiency
1607	COPD / Emphysema
1608	Bronchiectasis
1609	Rheumatoid Disease
1610	Occupational Lung Disease, specify
1611	Lymphangioleimyomatosis
1612	Obliterative Bronchiolitis (non-retransplant)
1613	Other Pulmonary Fibrosis, specify
1614	Pulmonary Vascular Disease
1997	Other Lung Disease, specify
1998	Other, specify
1615	Failure of tranplant

PrimaryDiagnosisCodeSystem = NOTR-ENIS	
PrimaryDiagnosisCode	Thoracic Heart disease
1000	Dilated Cardiomyopathy; Idiopathic
1009	Dilated Cardiomyopathy; Non-idiopathic, specify
1050	Restrictive Cardiomyopathy; Idiopathic
1059	Restrictive Cardiomyopathy; Non-idiopathic, specify
1200	Coronary Artery Disease
1201	Hypertrophic Cardiomyopathy
1202	Valvular Heart Disease
1203	Congenital Heart Disease
1204	Cardiac Cancer, specify
1497	Other Cardiac Disease, specify
1498	Other, specify
1499	Failure of transplant

PrimaryDiagnosisCodeSystem = ELTR		
PrimaryDiagnosisCode	ELTR	Description
1	A01	Acute hepatic failure - Fulminant of Subfulm hepatitis - Virus A
2	A02	Acute hepatic failure - Fulminant of Subfulm hepatitis - Virus B
3	A03	Acute hepatic failure - Fulminant of Subfulm hepatitis - Virus C
4	A04	Acute hepatic failure - Fulminant of Subfulm hepatitis - Virus D
5	A05	Acute hepatic failure - Fulminant of Subfulm hepatitis - Other known
6	A06	Acute hepatic failure - Fulminant of Subfulm hepatitis - Other unknown
7	A07	Acute hepatic failure - Fulminant of Subfulm hepatitis - Paracetamol
8	A08	Acute hepatic failure - Fulminant of Subfulm hepatitis - Other drug related: specify
9	A09	Acute hepatic failure - Fulminant of Subfulm hepatitis - Toxic (non drug)
10	A10	Acute hepatic failure - Post operative
11	A11	Acute hepatic failure - Post traumatic
12	A12	Acute hepatic failure - Others: specify
13	A13	Subacute hepatitis - Virus A
14	A14	Subacute hepatitis - Virus B
15	A15	Subacute hepatitis - Virus C
16	A16	Subacute hepatitis - Virus D
17	A17	Subacute hepatitis - Other known
18	A18	Subacute hepatitis - Other unknown
19	A19	Subacute hepatitis - Paracetamol
20	A20	Subacute hepatitis - Other drug related: specify
21	A21	Subacute hepatitis - Toxic (non drug)
22	B01	Cholestatic disease- Secondary biliary cirrhosis
23	B02	Cholestatic disease-Primary biliary cirrhosis
24	B03	Cholestatic disease- Primary sclerosing cholangitis
25	B04	Cholestatic disease- Others: specify
26	C01	Congenital biliary disease - Caroli disease
27	C02	Congenital biliary disease - Extrahepatic biliary atresia
28	C04	Congenital biliary disease - Congenital biliary fibrosis
29	C05	Congenital biliary disease - Choledocal cyst
30	C06	Congenital biliary disease - Alagille syndrome
31	C07	Congenital biliary disease - Others: specify
32	D01	Cirrhosis - Alcoholic cirrhosis
33	D02	Cirrhosis - Autoimmune cirrhosis
34	D03	Cirrhosis: Virus B related cirrhosis
35	D04	Cirrhosis: Virus C related cirrhosis
36	D05	Cirrhosis: Virus BD related cirrhosis
37	D06	Cirrhosis - Virus BC related cirrhosis
38	D07	Cirrhosis - Virus BCD related cirrhosis
39	D08	Cirrhosis - Virus related cirrhosis - Other viruses (specify)
40	D09	Cirrhosis - Post hepatitic cirrhosis - Drug related
41	D10	Cirrhosis - Other cirrhosis : specify

PrimaryDiagnosisCode	ELTR	Description
42	D11	Cirrhosis - Cryptogenic (unknown) cirrhosis
43	E01	Cancers - Hepatocellular carcinoma and cirrhosis
44	E02	Cancers - Hepatocellular carcinoma and non cirrhotic liver
45	E03	Cancers - Hepatocellular carcinoma - Fibrolamellar
46	E04	Cancers - Biliary tract carcinoma (Klatskin)
47	E05	Cancers - Hepatic cholangiocellular carcinoma
48	E06	Cancers - Hepatoblastoma
49	E07	Cancers - Epithelioid hemangioendothelioma
50	E08	Cancers - Angiosarcoma
51	E09	Cancers - Secondary liver tumors - Carcinoid
52	E10	Cancers - Secondary liver tumors - Other neuroendocrine
53	E11	Cancers - Secondary liver tumors - Colorectal
54	E12	Cancers - Secondary liver tumors - GI non colorectal
55	E13	Cancers - Secondary liver tumors - Non gastrointestinal
56	E14	Cancers - Other liver malignancies: specify
57	F01	Metabolic diseases - Wilson disease
58	F02	Metabolic diseases - Hemochromatosis
59	F03	Metabolic diseases - Alpha 1 - Antitrypsin deficiency
60	F04	Metabolic diseases - Glycogen storage disease
61	F05	Metabolic diseases - Homozygous Hypercholesterolemia
62	F06	Metabolic diseases - Tyrosinemia
63	F07	Metabolic diseases - Familial amyloidotic polyneuropathy
64	F08	Metabolic diseases - Primary hyperoxaluria
65	F09	Metabolic diseases - Protoporphyria
66	F10	Metabolic diseases - Other porphyria
67	F11	Metabolic diseases - Crigler - Najjar
68	F12	Metabolic diseases - Cystic fibrosis
69	F13	Metabolic diseases - Byler disease
70	F14	Metabolic diseases - Others
71	G	Budd Chiari
72	H01	Benign liver tumors or Polycistic dis - Hepatic adenoma
73	H02	Benign liver tumors or Polycistic dis - Adenomatosis
74	H03	Benign liver tumors or Polycistic dis - Hemangioma
75	H04	Benign liver tumors or Polycistic dis - Focal nodular hyperplasia
76	H05	Benign liver tumors or Polycistic dis - Polycystic disease
77	H06	Benign liver tumors or Polycistic dis - Nodular regenerative hyperplasia
78	H07	Benign liver tumors or Polycistic dis - Other benign tumors: specify
79	I01	Parasitic disease - Schistosomia (Bilharzia)
80	I02	Parasitic disease - Alveolar echinococcosis
81	I03	Parasitic disease - Cystic hydatidosis
82	I04	Parasitic disease - Others: specify
83	J	Other liver diseases

KIDNEY-TRANSPLANTATION AND FOLLOW UP UNTIL TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Transplant Number ID	TX_ID	F								
Transplant Date	TX_Date	Z						DD-MM-YYYY	If it is >Now CHECK; if it is < "01-01-1900" CHECK	
Country	RX_Country	D			ISO-Code 3166					
Previous Transplants	Previous_TX	D			OrganType					
Height	RX_Height	N	cm			0	250	3,0		
Weight	RX_Weight	N	kg			0	200	3,0		
Donor Warm Ischemic Time	Warm_Ischemic_Time	N	Minutes			0	200	3,0		
Total Ischemic Time	Total_Ischemic_Time	N	Hours,Minutes			00:00	99:60	HH:MM	if MM > 60 CHECK	
Organ Type	Organ_Type	D			OrganType					
Induction therapy	Induction_Therapy	D			InductionTherapy					
Initial Immunosuppression at discharge	Immunosuppression_at_Discharge	D			Immunosuppression					
Incidental tumor found in Recipient at time of transplant	Incidental_Tumor	D			YesNo					
Incidental tumor Type	Incidental_Tumor_Type	F							if Incidental_Tumor="YES"	
Recipient's HLA - typing A-B-DR (1-2) antigen	Recipient_HLA	F						A1,A2,B1,B2,DR1,DR2		
Type of Kidney transplant	Kidney_Type	D			KidneyType					
DGF (Delayed Graft Function)	DGF	D			YesNo					
Date last dialysis		Z						DD-MM-YYYY	If the answer on DGF is "Yes"; If it is >Now CHECK	
Date of follow up before discharge	Date_Followup_Before_Discharge	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Primary Cause of Graft Failure Code	Graft_Failure_Code_System	F								
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode					
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_System	D			ICD-10					
Date of Irreversible Graft Failure	Date_Irreversible_Failure	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Date of Death	Date_Death	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Cause of Death Code System	Cause_Death_Code_System	F								
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode					
Unified Cause of Death	Unified_Cause_Death_Code_System	D			ICD-10					
Diabetes onset during the follow-up	Diabetes	D			YesNo					
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	

PANCREAS-TRANSPLANTATION AND FOLLOW UP UNTIL TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Transplant Number ID	TX_ID	F								
Transplant Date	TX_Date	Z						DD-MM-YYYY	If it is >Now CHECK; if it is < "01-01-1900" CHECK	
Country	RX_Country	D			ISO-Code 3166					
Previous Transplants	Previous_TX	D			OrganType					
Height	RX_Height	N	cm			0	250	3,0		
Weight	RX_Weight	N	kg			0	200	3,0		
Donor Warm Ischemic Time	Warm_Ischemic_Time	N	Minutes			0	200	3,0		
Total Ischemic Time	Total_Ischemic_Time	N	Hours,Minutes			00:00	20:00	HH:MM	if MM > 60 CHECK	
Organ Type	Organ_Type	D			OrganType					
Induction therapy	Induction_Therapy	D			InductionTherapy					
Initial Immunosuppression at discharge	Immunosuppression_at_Discharge	D			Immunosuppression					
Incidental tumor found in Recipient at time of transplant	Incidental_Tumor	D			YesNo					
Incidental tumor Type	Incidental_Tumor_Type	F							if Incidental_Tumor="YES"	
Recipient's HLA - typing A-B-DR (1-2) antigen	Recipient_HLA	F						A1,A2,B1,B2,DR1,DR2		
Insulin dependent (within time frame)	Insulin_Dependent	D			YesNo					
Date of follow up before discharge	Date_Followup_Before_Discharge	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Primary Cause of Graft Failure Code System	Graft_Failure_Code_System	F								
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode					
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_System	D			ICD-10					
Date of Irreversible Graft Failure	Date_Irreversible_Failure	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Date of Death	Date_Death	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Cause of Death Code System	Cause_Death_Code_System	F								
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode					
Unified Cause of Death	Unified_Cause_Death_Code_System	D			ICD-10					
Diabetes onset during the follow-up period	Diabetes	D			YesNo					
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	
Technique for pancreas drainage	Techn_Drainage	D			TechnDrainage					

HEART-TRANSPLANTATION AND FOLLOW UP UNTIL TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Transplant Number ID	TX_ID	F								
Transplant Date	TX_Date	Z						DD-MM-YYYY	If it is >Now CHECK; if it is < "01-01-1900" CHECK	
Country	RX_Country	D			ISO-Code 3166					
Previous Transplants	Previous_TX	D			OrganType					
Height	RX_Height	N	cm			0	250	3,0		
Weight	RX_Weight	N	kg			0	200	3,0		
Total Ischemic Time	Total_Ischemic_Time	N	Hours,Minutes			00:00	20:00	HH:MM	if MM > 60 CHECK	
Organ Type	Organ_Type	D			OrganType					
Induction therapy	Induction_Therapy	D			InductionTherapy					
Initial Immunosuppression at discharge	Immunosuppression_at_Discharge	D			Immunosuppression					
Incidental tumor found in Recipient at time of transplant	Incidental_Tumor	D			YesNo					
Incidental tumor Type	Incidental_Tumor_Type	F							if Incidental_Tumor="YES"	
Status at Time of transplant	Status_Time_Transplant	D			StatusAtTransplant					
Date of follow up before discharge	Date_Followup_Before_Discharge	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Primary Cause of Graft Failure Code System	Graft_Failure_Code_System	F			GraftFailureCodeSystem					
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode					
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_System	D			ISHLT					
Date of Irreversible Graft Failure	Date_Irreversible_Failure	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Date of Death	Date_Death	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Cause of Death Code System	Cause_Death_Code_System	F			CauseDeathCodeSystem					
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode					
Unified Cause of Death	Unified_Cause_Death_Code_System	D			ISHLT					
Diabetes onset during the follow-up period	Diabetes	D			YesNo					
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	

LUNG-TRANSPLANTATION AND FOLLOW UP UNTIL TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Transplant Number ID	TX_ID	F								
Transplant Date	TX_Date	Z						DD-MM-YYYY	If it is >Now CHECK; if it is < "01-01-1900" CHECK	
Country	RX_Country	D			ISO-Code 3166					
Previous Transplants	Previous_TX	D			OrganType					
Height	RX_Height	N	cm			0	250	3,0		
Weight	RX_Weight	N	kg			0	200	3,0		
Donor Warm Ischemic Time	Warm_Ischemic_Time	N	Minutes			0	200	3,0		
Total Ischemic Time	Total_Ischemic_Time	N	Hours,Minutes			00:00	60:00	HH:MM	if MM > 60 CHECK	
Organ Type	Organ_Type	D			OrganType					
Induction therapy	Induction_Therapy	D			InductionTherapy					
Initial Immunosuppression at discharge	Immunosuppression_at_Discharge	D			Immunosuppression					
Incidental tumor found in Recipient at time of transplant	Incidental_Tumor	D			YesNo					
Incidental tumor Type	Incidental_Tumor_Type	F							if Incidental_Tumor="YES"	
Graft Type Lung	Graft_Type	D			GraftType					
Status at Time of transplant	Status_Time_Transplant	D			StatusAtTransplant					
Date of follow up before discharge	Date_Followup_Before_Discharge	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Primary Cause of Graft Failure Code System	Graft_Failure_Code_System	F			GraftFailureCodeSystem					
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode					
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_System	D			ISHLT					
Date of Irreversible Graft Failure	Date_Irreversible_Failure	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Date of Death	Date_Death	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Cause of Death Code System	Cause_Death_Code_System	F			CauseDeathCodeSystem					
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode					
Unified Cause of Death	Unified_Cause_Death_Code_System	D			ISHLT					
Diabetes onset during the follow-up period	Diabetes	D			YesNo					
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	

LIVER-TRANSPLANTATION AND FOLLOW UP UNTIL TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Transplant Number ID	TX_ID	F								
Transplant Date	TX_Date	Z						DD-MM-YYYY	If it is >Now CHECK; if it is < "01-01-1900" CHECK	
Country	RX_Country	D			ISO-Code 3166					
Previous Transplants	Previous_TX	D			OrganType					
Height	RX_Height	N	cm			0	250	3,0		
Weight	RX_Weight	N	kg			0	200	3,0		
Donor Warm Ischemic Time	Warm_Ischemic_Time	N	Minutes			0	200	3,0		
2nd Warm Ischemic Time = Anastomosis Time	Anastomosis_Time	N	Minutes			0	999	3,0		
Total Ischemic Time	Total_Ischemic_Time	N	Hours,Minutes			00:00	99:60	HH:MM	if MM > 60 CHECK	
Organ Type	Organ_Type	D			OrganType					
Induction therapy	Induction_Therapy	D			InductionTherapy					
Initial Immunosuppression at discharge	Immunosuppression_at_Discharge	D			Immunosuppression					
Incidental tumor found in Recipient at time of transplant	Incidental_Tumor	D			YesNo					
Incidental tumor Type	Incidental_Tumor_Type	F							if Incidental_Tumor="YES"	
Graft Type Liver	Graft_Type	D			GraftType					
Split Type	Split_Type	D			SplitType				If Graft_Type is "SPLIT"	
Date of follow up before discharge	Date_Followup_Before_Discharge	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Primary Cause of Graft Failure Code System	Graft_Failure_Code_System	F								
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode					
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_System	D			ELTR					
Date of Irreversible Graft Failure	Date_Irreversible_Failure	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Date of Death	Date_Death	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Cause of Death Code System	Cause_Death_Code_System	F								
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode					
Unified Cause of Death	Unified_Cause_Death_Code_System	D			ELTR					
Diabetes onset during the follow-up period	Diabetes	D			YesNo					
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	

INTESTINE-TRANSPLANTATION AND FOLLOW UP UNTIL TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Transplant Number ID	TX_ID	F								
Transplant Date	TX_Date	Z						DD-MM-YYYY	If it is >Now CHECK; if it is < "01-01-1900" CHECK	
Country	RX_Country	D			ISO-Code 3166					
Previous Transplants	Previous_TX	D			OrganType					
Height	RX_Height	N	cm			0	250	3,0		
Weight	RX_Weight	N	kg			0	200	3,0		
Donor Warm Ischemic Time	Warm_Ischemic_Time	N	Minutes			0	60	2,0		
Total Ischemic Time	Total_Ischemic_Time	N	Hours,Minutes			00:00	99:60	HH:MM	if MM > 60 CHECK	
Organ Type	Organ_Type	D			OrganType					
Induction therapy	Induction_Therapy	D			InductionTherapy					
Initial Immunosuppression at discharge	Immunosuppression_at_Discharge	D			Immunosuppression					
Incidental tumor found in Recipient at time of transplant	Incidental_Tumor	D			YesNo					
Incidental tumor Type	Incidental_Tumor_Type	F							if Incidental_Tumor="YES"	
Date of follow up before discharge	Date_Followup_Before_Discharge	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Primary Cause of Graft Failure Code System	Graft_Failure_Code_System	F								
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode					
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_System	D			ELTR					
Date of Irreversible Graft Failure	Date_Irreversible_Failure	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Date of Death	Date_Death	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Cause of Death Code System	Cause_Death_Code_System	F								
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode					
Unified Cause of Death	Unified_Cause_Death_Code_System	D			ELTR					
Diabetes onset during the follow-up period	Diabetes	D			YesNo					
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	

Code List	List Items
ISHLT	ISHLT List
ICD-10	ICD-10 List
ELTR	ELTR List
GraftFailureCode	Depend on Country (has to be supplied)
CauseDeathCode	Depend on Country (has to be supplied)
ISO-Code-3166	ISO-Code-3166 List
OrganType	Heart Intestine Kidney Liver Lung Pancreas Heart + Intestine Heart + Kidney Heart + Liver Heart + Lung Heart + Pancreas Intestine + Kidney Intestine + Liver Intestine + Lung Intestine + Pancreas Kidney + Liver Kidney + Lung Kidney + Pancreas Liver + Lung Liver + Pancreas Lung + Pancreas Heart + Intestine + Kidney Heart + Intestine + Liver Heart + Intestine + Lung Heart + Intestine + Pancreas Heart + Kidney + Liver Heart + Kidney + Lung Heart + Kidney + Pancreas Heart + Liver + Lung Heart + Liver + Pancreas Heart + Lung + Pancreas Intestine + Kidney + Liver Intestine + Kidney + Lung Intestine + Kidney + Pancreas Intestine + Liver + Lung Intestine + Liver + Pancreas Intestine + Lung + Pancreas Kidney + Liver + Lung Kidney + Liver + Pancreas Kidney + Lung + Pancreas Liver + Lung + Pancreas Heart + Intestine + Kidney + Liver Heart + Intestine + Kidney + Lung Heart + Intestine + Kidney + Pancreas Heart + Intestine + Liver + Lung Heart + Intestine + Liver + Pancreas Heart + Intestine + Lung + Pancreas Heart + Kidney + Liver + Lung Heart + Kidney + Liver + Pancreas Heart + Kidney + Lung + Pancreas Heart + Liver + Lung + Pancreas Intestine + Kidney + Liver + Lung Intestine + Kidney + Liver + Pancreas Intestine + Kidney + Lung + Pancreas Intestine + Liver + Lung + Pancreas Kidney + Liver + Lung + Pancreas Heart + Intestine + Kidney + Liver + Lung Heart + Intestine + Kidney + Liver + Pancreas Heart + Intestine + Kidney + Lung + Pancreas Heart + Intestine + Liver + Lung + Pancreas Heart + Kidney + Liver + Lung + Pancreas Intestine + Kidney + Liver + Lung + Pancreas Heart + Intestine + Kidney + Liver + Lung + Pancreas
GraftTypeLiver	Whole Graft Domino Reduced Split
SplitType	Left lobe Left liver Right liver Posterial sector

Code List	List Items
TechnDrainage	ET List (has to be supplied)
GraftTypeLung	Whole Lungs Lobe Transplantation Split Lungs Tailored Lungs
InductionTherapy	ATG rATG OKT3 Basiliximab Daclizumab (Anti CD25 Monoclonal antibody) None Other (text variable) Unknown
Immunosuppression	Sandimun oral Steroïds oral Cyclosporin Azathioprine Neoral Mycofenolate Tacrolimus (FK-506) Steroïds IV OKT3 ALG/ATG *Simulect* Rapamune *Zenapax* Certican *Campath-1* FTY MNA (FK778) Sirolimus I / Everolimus TLI Methotrexate Other (text variable) Unknown
YesNo	Yes No Unknown
KidneyType	Left Right Double
StatusAtTransplant	Home Hospitalized Intensive Care
KindTumorGeneral	De Novo Donor Related Recurrence of Pre Transplant Tumor Unknown
KindTumor	Intracranial Extracranial
KindIntracranialTumor	Medulloblastomas Astrocytomas Glioblastomas Oligodendrogliomas Ependymomas Meningiomas Other Unknown
KindExtracranialTumor	Renal Cell Carcinoma (RCC) Prostate Adenocarcinoma Breast Cancer Lung Cancer Colorectal Cancer Oesophagus Carcinoma Pancreatic Carcinoma Hepatocellular Carcinoma Thyroid Carcinoma Ovarian Cancer Chorioncarcinoma Sarcoma (including GIST) Malignant Melanoma Non Melanoma Skin Cancer (Basal Cell Carcinoma, Spinocellular Carcinoma) Carcinoma in situ Low grade Lymphoma High grade Lymphoma Leukemia Other Unknown

GraftFailureCodeSystem = NOTR-ENIS			
GraftFailureCode	**Thoracic fail cause NOTR**		**Translation thoracic -> ENIS**
2000	Graft failure: Primary Organ failure	40	Primary Non-Function (non-renal)
2001	Graft failure: Rejection, Hyperacute	1	Hyperacute Rejection
2002	Graft failure: Rejection, Acute	41	Rejection (acute / chronic) (non-renal)
2003	Graft failure: Rejection, Chronic (AGAS [heart], BOS [lung])	41	Rejection (acute / chronic) (non-renal)
2004	Graft failure: Technical	42	Technical problems (non-renal)
2005	Graft failure: Graft Infection, specify	45	Infection (non-renal)
2006	Graft failure: Non-specific	46	Other / specify (non-renal)
2007	Graft failure: Other, specify	46	Other / specify (non-renal)
2008	Graft failure: Heart transplant: Restrictive/Constrictive	48	Constrictive / Restrictive disease (heart)
2009	Graft failure: Lung transplant: Airway Dehiscence	42	Technical problems (non-renal)
2010	Patient died with functioning graft	47	Patient died with functioning transplant

GraftFailureCodeSystem = ELTR		
GraftFailureCode	ELTR	Description
146	B01	Bacterial infection
147	B02	Viral infection
148	B03	HIV
149	B04	Fungal infection
150	B05	Parasitic infection
151	B06	Other known infection: specify
152	C01	Acute rejection
153	C02	Chronic rejection
154	C03	Arterial thrombosis
155	C04	Hepatic vein thrombosis
156	C05	Primary non function (retx or death before 7 days)
157	C06	Primary graft dysfunction (retx or death after 7 days)
158	C07	Anastomotic biliary complications
159	C08	Non anastomotic biliary complications
160	C09	Recurrence of original disease BB virus B
161	C10	Recurrence of original disease BB virus C
162	C11	Recurrence of original disease BB virus D
163	C12	Recurrence of original disease - alcoholic
164	C13	Recurrence of original disease BB PBC
165	C14	Recurrence of original disease BB PSC
166	C15	Recurrence of original disease BB autoimmune
167	C16	Recurrence of original disease BB budd chiari
168	C17	Recurrence of original disease BB other non tumoral: specify
169	C18	De novo hepatitis B virus
170	C19	De novo hepatitis C virus
171	C20	De novo hepatitis D virus
172	C21	Massive hemorrhagic necrosis
173	C22	Other viral hepatitis
174	C23	Liver infection
175	C24	Liver complications - other: specify
176	G01	Recurrence of original tumor
177	G02	Recurrence of previously unrelated tumor
178	G03	De novo solid organ tumor
179	G04	Donor transmitted tumor
180	G05	Lympho proliferation disease
181	H01	Kidney failure
182	H02	Urinary tract infection
183	J01	Non compliance immunosuppressive therapy
184	J03	Social Complications-trauma (motor, vehicle)
185	L01	None of the above: specify

CauseDeathCodeSystem = ELTR		
CauseDeathCode	ELTR	Description
1	A01	Intraoperative death
2	B01	Bacterial infection
3	B02	Viral infection
4	B03	HIV
5	B04	Fungal infection
6	B05	Parasitic infection
7	B06	Other known infection: specify
8	D01	GI haemorrhage
9	D02	Pancreatitis
10	D03	Visceral perforation
11	D04	Other gastrointestinal complication: specify
12	E01	Myocardial infarction
13	E02	Other cardiovascular complication : specify
14	F01	Intracranial haemorrhage
15	F02	Ischemic stroke
16	F03	Cerebral oedema
17	F04	Cerebral infection
18	G01	Recurrence of original tumor
19	G02	Recurrence of previously unrelated tumor
20	G03	De novo solid organ tumor
21	G04	Donor transmitted tumor
22	G05	Lympho proliferation disease
23	H01	Kidney failure
24	H02	Urinary tract infection
25	I01	Pulmonary embolism
26	I02	Pulmonary infection
27	J01	Non compliance immunosuppressive therapy
28	J02	Suicide
29	J03	Trauma (motor, vehicle, YY..)
30	K01	Bone marrow depression
31	L01	None of the above (specify)

KIDNEY-FOLLOW UP AFTER TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Date of follow up	Date_Followup	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK;If it is < Date_Followup_Before_Discharge CHECK	
Lost To Follow Up	Lost_Followup	D			YesNo					Only if a center denotes a patient as lost to follow up. No automatic setting to lost to follow up.
Date of Irreversible Graft Failure	Date_Graft_Lost	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK ; if (Graft_failure_Code is not NULL AND Date_Graft_Lost is NULL) CHECK	For Kidney and Pancreas: requirement of permanent replacement therapy. For Heart, Lung and Liver: Date of retransplantation or Date of Death; for Small Bowel: Date of graft removal
Primary Cause of Graft Failure Code System	Graft_Failure_Code_System	F								
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode				if (Date_Graft_Lost is not NULL AND Graft_failure_Code is NULL) CHECK	
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_System	D			ICD-10					
Date of Death	Date_Death							DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK ; if (Cause_Death_Code is not NULL AND Date_Death is NULL) CHECK	
Cause of Death Code System	Cause_Death_Code_System	F								
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode				if (Date_Death is not NULL AND Cause_Death_Code is NULL) CHECK	
Unified Cause of Death	Unified_Cause_Death_Code_System	D			ICD-10					
Serum Creatinine Unit	Serum_Creatinine_Unit	D			SerumCreatinineUnit					
Serum Creatinine	Serum_Creatinine	N	mg/dl	µmol/l		0 0	22,62 2000	mg/dl : 2,2 µmol/l : 4,0		
Weight	Weight	N				0	200	3,0	Weight is registered at time of follow up	
Immunosuppression at follow up	Immunosuppression	D			Immunosuppression					
Diabetes onset during the follow-up period	Diabete	D			YesNo					
If Diabetes onset, chronic treatment	Chronic_treatement	D			YesNo				If Diabete="YES"	
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	
Serology of HIV	Serology_HIV	D			ReactiveNonReactive					
HBsAg	HBsAg	D			ReactiveNonReactive					
HCVAb	HCVAb	D			ReactiveNonReactive					

PANCREAS-FOLLOW UP AFTER TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Date of follow up	Date_Followup	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK;If it is < Date_Followup_Before_Discharge CHECK	
Lost To Follow Up	Lost_Followup	D			YesNo					Only if a center denotes a patient as lost to follow up. No automatic setting to lost to follow up.
Date of Irreversible Graft Failure	Date_Graft_Lost	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	For Kidney and Pancreas: requirement of permanent replacement therapy. For Heart, Lung and Liver: Date of retransplantation or Date of Death; for Small Bowel: Date of graft removal
Primary Cause of Graft Failure Code System	Graft_Failure_Code_System	F			GraftFailureCodeSystem					
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode					
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_System	D			ICD-10					
Date of Death	Date_Death							DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Cause of Death Code System	Cause_Death_Code_System	F								
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode					
Unified Cause of Death	Unified_Cause_Death_Code_System	D			ICD-10					
Serum Creatinine Unit	Serum_Creatinine_Unit	D			SerumCreatinineUnit					
Serum Creatinine	Serum_Creatinine	N	mg/dl	µmol/l		0 0	22,62 2000	mg/dl : 2,2 µmol/l : 4,0		
Weight	Weight	N				0	200	3,0	Weight is registered at time of follow up	
Immunosuppression at follow up	Immunosuppression	D			Immunosuppression					
Diabetes onset during the follow-up period	Diabete	D			YesNo					
If Diabetes onset, chronic treatment	Chronic_treatement	D			YesNo				If Diabete="YES"	
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	
Serology of HIV	Serology_HIV	D			ReactiveNonReactive					
HBsAg	HBsAg	D			ReactiveNonReactive					
HCVAb	HCVAb	D			ReactiveNonReactive					
Technique for pancreas drainage	Techn_Drainage	D			TechnDrainage					

HEART-FOLLOW UP AFTER TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Date of follow up	Date_Followup	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK;If it is < Date_Followup_Before_Discharge CHECK	
Lost To Follow Up	Lost_Followup	D			YesNo					Only if a center denotes a patient as lost to follow up. No automatic setting to lost to follow up.
Date of Irreversible Graft Failure	Date_Graft_Lost	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	For Kidney and Pancreas: requirement of permanent replacement therapy. For Heart, Lung and Liver: Date of retransplantation or Date of Death; for Small Bowel: Date of graft removal
Primary Cause of Graft Failure Code System	Graft_Failure_Code_System	F			GraftFailureCodeSystem					
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode					
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_Sy	D			ISHLT					
Date of Death	Date_Death							DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Cause of Death Code System	Cause_Death_Code_System	F			CauseDeathCodeSystem					
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode					
Unified Cause of Death	Unified_Cause_Death_Code_Sy	D			ISHLT					
Serum Creatinine Unit	Serum_Creatinine_Unit	D			SerumCreatinineUnit					
Serum Creatinine	Serum_Creatinine	N	mg/dl	µmol/l		0 0	22,62 2000	mg/dl : 2,2 µmol/l : 4,0		
Dialysis	Dialysis	D			YesNo					
Weight	Weight	N				0	200	3,0	Weight is registered at time of follow up	
Immunosuppression at follow up	Immunosuppression	D			Immunosuppression					
Diabetes onset during the follow-up period	Diabete	D			YesNo					
If Diabetes onset, chronic treatment	Chronic_treatement	D			YesNo				If Diabete="YES"	
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	
Serology of HIV	Serology_HIV	D			ReactiveNonReactive					
HBsAg	HBsAg	D			ReactiveNonReactive					
HCVAb	HCVAb	D			ReactiveNonReactive					

LUNG-FOLLOW UP AFTER TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Date of follow up	Date_Followup	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK;If it is < Date_Followup_Before_Discharge CHECK	
Lost To Follow Up	Lost_Followup	D			YesNo					Only if a center denotes a patient as lost to follow up. No automatic setting to lost to follow up.
Date of Irreversible Graft Failure	Date_Graft_Lost	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	Kidney ,Pancreas: requirement of permanent replacement therapy.Heart, Lung, Liver: Date of retransplantation or Date of Death.Small Bowel: Date of graft removal.
Primary Cause of Graft Failure Code System	Graft_Failure_Code_System	F			GraftFailureCodeSystem					
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode					
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_Syst	D			ISHLT					
Date of Death	Date_Death							DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Cause of Death Code System	Cause_Death_Code_System	F			CauseDeathCodeSystem					
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode					
Unified Cause of Death	Unified_Cause_Death_Code_Syst	D			ISHLT					
Serum Creatinine Unit	Serum_Creatinine_Unit	D			SerumCreatinineUnit					
Serum Creatinine	Serum_Creatinine	N	mg/dl	µmol/l		0 0	22,62 2000	mg/dl : 2,2 µmol/l : 4,0		
Dialysis	Dialysis	D			YesNo					
Weight	Weight	N				0	200	3,0	Weight is registered at time of follow up	
Immunosuppression at follow up	Immunosuppression	D			Immunosuppression					
Diabetes onset during the follow-up period	Diabete	D			YesNo					
If Diabetes onset, chronic treatment	Chronic_treatement	D			YesNo				If Diabete="YES"	
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	
Serology of HIV	Serology_HIV	D			ReactiveNonReactive					
HBsAg	HBsAg	D			ReactiveNonReactive					
HCVAb	HCVAb	D			ReactiveNonReactive					
Bronchiolitis Obliterans Syndrome	Bronch_Obliterans_Syndrome	D			YesNo					

LIVER-FOLLOW UP AFTER TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of**	**All business rules**	**Comments**
Date of follow up	Date_Followup	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK;If it is < Date_Followup_Before_Discharge CHECK	
Lost To Follow Up	Lost_Followup	D			YesNo					Only if a center denotes a patient as lost to follow up. No automatic setting to lost to follow up.
Date of Irreversible Graft Failure	Date_Graft_Lost	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	For Kidney and Pancreas: requirement of permanent replacement therapy. For Heart, Lung and Liver: Date of retransplantation or Date of Death; for Small Bowel: Date of graft removal
Primary Cause of Graft Failure Code System	Graft_Failure_Code_System	F			GraftFailureCodeSystem					
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode					
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_System	D			ELTR					
Date of Death	Date_Death	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Cause of Death Code System	Cause_Death_Code_System	F								
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode					
Unified Cause of Death	Unified_Cause_Death_Code_System	D			ELTR					
Serum Creatinine Unit	Serum_Creatinine_Unit	D			SerumCreatinineUnit					
Serum Creatinine	Serum_Creatinine	N	mg/dl	µmol/l		0 0	22,62 2000	mg/dl : 2,2 µmol/l : 4,0		
Weight	Weight	N				0	200	3,0	Weight is registered at time of follow up	
Immunosuppression at follow up	Immunosuppression	D			Immunosuppression					
Diabetes onset during the follow-up period	Diabete	D			YesNo					
If Diabetes onset, chronic treatment	Chronic_treatement	D			YesNo				If Diabete="YES"	
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	
Serology of HIV	Serology_HIV	D			ReactiveNonReactive					
HBsAg	HBsAg	D			ReactiveNonReactive					
HCVAb	HCVAb	D			ReactiveNonReactive					
INR	INR	N				0	10	2,0		
Total Serum Bilirubin	Total_Serum_Bilirubin	N	mg/dl			0	58,47	2,2		

INTESTINE-FOLLOW UP AFTER TRANSPLANTATION DISCHARGE										
Variable Description	**Variable Name**	**Field Type**	**Unit**	**Alternative Unit**	**Code list**	**Lowest value**	**Highest value**	**Length or Format of variable**	**All business rules**	**Comments**
Date of follow up	Date_Followup	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK;If it is < Date_Followup_Before_Discharge CHECK	
Lost To Follow Up	Lost_Followup	D			YesNo					Only if a center denotes a patient as lost to follow up. No automatic setting to lost to follow up.
Date of Irreversible Graft Failure	Date_Graft_Lost	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	Kidney ,Pancreas: requirement of permanent replacement therapy.Heart, Lung,Liver: Date of retransplantation or Date of Death.Small Bowel: Date of graft removal.
Primary Cause of Graft Failure Code System	Graft_Failure_Code_System	F			GraftFailureCodeSystem					
Primary Cause of Graft Failure Code	Graft_Failure_Code	D			GraftFailureCode					
Unified Cause of Graft Failure	Unified_Graft_Failure_Code_System	D			ELTR					
Date of Death	Date_Death	Z						DD-MM-YYYY	If it is >Now CHECK; If it is < TX_Date CHECK	
Cause of Death Code System	Cause_Death_Code_System	F			CauseDeathCodeSystem					
Cause of Death Code	Cause_Death_Code	D			CauseDeathCode					
Unified Cause of Death	Unified_Cause_Death_Code_System	D			ELTR					
Serum Creatinine Unit	Serum_Creatinine_Unit	D			SerumCreatinineUnit					
Serum Creatinine	Serum_Creatinine	N	mg/dl	µmol/l		0 0	22,62 2000	mg/dl : 2,2 µmol/l : 4,0		
Weight	Weight	N				0	200	3,0	Weight is registered at time of follow up	
Immunosuppression at follow up	Immunosuppression_Fup	D			Immunosuppression					
Diabetes onset during the follow-up period	Diabete_Fup	D			YesNo					
If Diabetes onset, chronic treatment	Diabete_Chronic	D			YesNo				If Diabete="YES"	
Post transplant Malignancy	Post_Transplant_Malignancy	D			YesNo					
Kind of tumor/Type of Tumor General	Kind_Tumor_General	D			KindTumorGeneral				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of tumor/Type of tumor Detailed	Kind_Tumor	D			KindTumor				Conditional 2: Only when Post Transplant Malignancy is `Yes`.	
Kind of Intracranial Tumor	Kind_Intracranial_Tumor	D			KindIntracranialTumor				Conditional 2: Only when Kind of tumor is `Intracranial´	
Other Kind of Intracranial Tumor	Kind_Intracranial_Tumor_Other	F							Conditional 2: Only when Kind of Intracranial Tumor is ´Other´	
Kind of Extracranial Tumor	Kind_Extracranial_Tumor	D			KindExtracranialTumor				Conditional 2: Only when Kind of tumor is `Extracranial´	
Other Kind of Extracranial Tumor	Kind_Extracranial_Tumor_Other	F							Conditional 2: Only when Kind of Extracranial Tumor is ´Other´	
Serology of HIV	Serology_HIV	D			ReactiveNonReactive					
HBsAg	HBsAg	D			ReactiveNonReactive					
HCVAb	HCVAb	D			ReactiveNonReactive					
Modified Karnofsky score	Modified_Karnofsky_Score	N				0	100	3,0		

Code List	List Items
YesNo	Yes No Unknown
GraftFailureCode	Depend on Country (has to be supplied)
ICD-10	ICD-10 List
ELTR	ELTR List
ISHLT	ISHLT List
CauseDeathCode	Depend on Country (has to be supplied)
SerumCreatinineUnit	µmol/l mg/dl
Immunosuppression	Sandimun oral Steroïds oral Cyclosporin Azathioprine Neoral Mycofenolate Tacrolimus (FK-506) Steroïds IV OKT3 ALG/ATG *Simulect* Rapamune *Zenapax* Certican *Campath-1* FTY MNA (FK778) Sirolimus I / Everolimus TLI Methotrexate Other (text variable) Unknown
KindTumorGeneral	De Novo Donor Related Recurrence of Pre Transplant Tumor Unknown

Code List	List Items
KindTumor	Intracranial Extracranial
KindIntracranialTumor	Medulloblastomas Astrocytomas Glioblastomas Oligodendrogliomas Ependymomas Meningiomas Other Unknown
KindExtracranialTumor	Renal Cell Carcinoma (RCC) Prostate Adenocarcinoma Breast Cancer Lung Cancer Colorectal Cancer Oesophagus Carcinoma Pancreatic Carcinoma Hepatocellular Carcinoma Thyroid Carcinoma Ovarian Cancer Chorioncarcinoma Sarcoma (including GIST) Malignant Melanoma Non Melanoma Skin Cancer (Basal Cell Carcinoma, Spinocellular Carcinoma) Carcinoma in situ Low grade Lymphoma High grade Lymphoma Leukemia Other Unknown
ReactiveNonReactive	Reactive Non Reactive Unknown
TechnDrainage	ET List (has to be supplied)

10 Organ vigilance

10.1 Introduction

The development of a vigilance system (V-System) applied to organ donation and transplantation is a requirement of *Directive 2010/53/EU of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation*, in force since the 26th of August, 2010 (hereinafter, *the Directive*)[10]. European Union (EU) Member States should transpose the provisions of *the Directive* into their national legislations within two years following such date.

Organ transplantation has become a consolidated therapy, which saves the life and improves the quality of life of about 100,000 patients yearly worldwide.[11] Consolidation of this therapy is the consequence of the excellent results achieved with all types of transplanted organs, both in terms of survival and quality of life. Nevertheless, the probability of occurrence of a harmful end point (risk) is present due to a potential deviation in the sophisticated chain which extends from donation to transplantation or due to the simple transfer of biologic material from one individual to another, as this implies a risk of disease transmission. This risk has to be seen under the perspective of a relatively low reported complication rate confronted with the great benefits provided by organ transplants and the universal challenge of organ shortage. Because of the scarcity of organs, patients deteriorate or even die while waiting to be transplanted. It has been estimated that twelve EU patients die each day while on the waiting list for an organ transplant.[12] This almost unique feature of organ transplantation along with the time constraints of the organ donation and transplantation process, make it necessary in case of every organ offer that the clinician (and the patient) have to balance the risk of accepting an organ offer with a potential risk of disease transmission against the risk derived from not proceeding with the transplantation (and thus the risk of clinical deterioration or even death of the recipient on the waiting list).

Due to the need to allocate each organ to the most appropriate recipient within a territory, every time a donation occurs, each organ travels to a recipient, more or less far away from the donor and from other recipients transplanted with organs from the same donor. This also applies to tissues and cells obtained from that donor. This form of organization, specific to the donation and transplantation system, makes the involved community become a network in which every team (recovering, allocating or transplanting organs) is a node. One peculiarity of this network is that the teams involved in one donation share a group of factors (known or unknown) that might influence the results of transplantation and the appearance of serious adverse events (SAE) and/or reactions (SAR) (see below), regardless of the distance or the different health care system. In other words, patients far off from each other may be submitted to equal or similar risks as their transplanted organs come from the same donor. Team working is crucial: communicating to the other stakeholder/partners involved a health problem detected in one recipient would improve the diagnostic and therapeutic capacity of the teams treating the other recipients from the same donor. Therefore, establishing a system for systematic reporting and managing this information (including alerting other centres concerned), as well as connecting it with the system in place for tissues and cells, is absolutely necessary in this community. In order to allow this communication to occur effectively and find the recipients wherever they are, it is essential to keep **traceability** of organs at all phases from donor to recipient (or disposal) and *vice versa*. Traceability is understood as the ability to locate all organs (as well as tissues and cells) along all phases from donation to transplantation (where they are and where they have been). This information must be securely stored in case a patient needs to be diagnosed, treated or followed-up. Ensuring traceability is also a requirement of *the Directive.*

The main objective of a vigilance system is **PREVENTION (primary, secondary and tertiary)**. The immediate preventive action is on affected or potentially affected patients. However, there is an additional prevention strategy based on the concept of surveillance: the analysis of pooled data may provide indicators and information on stratification of the risks that might be very useful for future risk management and interpretation of the cases reported. In the field of organ donation and transplantation, pooled data analyses could ideally integrate **the systematic follow-up of recipients**

transplanted with organs from non-standard risk donors, a safety management tool specifically recommended by EFRETOS as part of its European Registry. This approach would broaden the possibilities in prevention. Another way to protect patients can derive from the interaction between national networks. Rapid transmission of European public health alerts, affecting organ safety, may allow local centres to consider low prevalence diseases when making a risk analysis.

Classically, **SURVEILLANCE IN PUBLIC HEALTH** is defined as the systematic and continuous collection, analysis, interpretation, and dissemination of health data, seeking to reduce morbidity and mortality and to improve the health of the population. Surveillance is based on a careful **VIGILANCE**.[13] The system is based on several steps: **detection**, **reporting**, **assessment** and **management** of the case under study, **including alerting without delay** (**figure 1**).

Figure 1: Steps of a vigilance and surveillance system.

A V-System of human organs intended for transplantation should aim at the **PREVENTION OF SAE AND/OR SAR (see below) THEREBY PROTECTING THE HEALTH OF ALL ORGAN RECIPIENTS AND THE LIVING ORGAN DONORS.** As a V-System operates in a given administrative framework, it is necessary that its design fits such framework and the peculiarities in which its activities are to be developed. However, independent of the administrative and operational organization in place, an effective support from regulatory agencies taking action in certain situations in which risks may arise is of great importance, as well as the strong commitment of all participants.

Reference to the importance of V-systems applied to the transplantation of human organs has been previously made in other international standards, either from the **Council of Europe or the World Health Organization (WHO)**. The need to ensure traceability for medical purposes is already foreseen in *Article 3* of the *Additional Protocol to the Convention of Human Rights and Biomedicine on transplantation of organs and tissues of human origin*.[14] A V-system to ensure the protection of donors and recipients is also a recommendation of the Council of Europe´s Committee of experts on donation and transplantation issues, as reflected in the *Guide on safety and quality for the transplantation of human organ, tissues and cells*,[15] prepared by this committee. The *Guide* recommends the development of "*a system which should foresee the rapid investigation of any untoward incident occurring in relation to the transplantation services, so timely corrective and/or preventive actions can be taken"*. The *Guide* makes also reference to the importance of traceability, understood as a "*system that enables the path taken by each donation from the donor to recipient/disposal and vice versa"*.

The recently updated *WHO Guiding Principles on the transplantation of organs, tissues and cells* included a new Guiding Principle number 10, which states that "*the level of safety, efficacy and quality of human cells, tissues and organs for transplantation, as health products of an exceptional nature, must be maintained and optimized on an on-going basis*. *This requires implementation of quality systems including traceability and vigilance, with adverse events (AE) and reactions (AR) reported, both nationally and for exported human products".*[16] These currently existing international standards have guided and profoundly influenced the development of national legislations and practices on donation and transplantation and they share an undisputed consistency with regards to the importance of safety (and quality), including the principles of vigilance, surveillance and traceability. However, the *Additional Protocol* is only binding for those Member States of the Council of Europe who have signed and ratified the protocol, something only performed by a limited number of countries (twelve countries in June 2010)[17] and the *WHO Guiding Principles* are not binding by nature.

Therefore, we are involved in a rather new scenario where EU countries are legally obliged to develop a V-system applied to human organs intended for transplantation. Little information is available on the current situation of organ vigilance in the European setting, except for that provided through the work performed by the DG SANCO during the period preceding the preparation of the *Directive*. In a survey carried out to the 27 Member States, along with Norway and Turkey, it was stated that 25 countries had a national registry containing data on the origin and destination of organs (such system was mandatory by law in 18 of these countries), 20 had a system for the reporting of adverse events and adverse reactions (this was only mandatory in 8 countries, according to their national legislations) and no system was in place allowing to trace in cross-border cases, although more than 4,000 organs were being exchanged between Member States each year.[18]

Chapter 10 provides first an overview of the current situation of V-systems applied to human organs intended for transplantation in countries represented at the EFRETOS consortium and in the United States, a summary of the provisions of the *Directive* 2010/53/EU and an update of the lessons learnt from the development of vigilance in the EU applied to tissues and cells, since the new organs Directive lays down the obligation of creating a link between this system and the one to be developed for organs, at a Member State level. Besides, recently learnt lessons in the development of these systems could and should inspire the work to be applied to organs.

Chapter 10 also provides a minimum set of recommendations for the development of a V-System applied to organ donation and transplantation in the European setting. Member States could broaden the scope of the V-System beyond this minimum, but these recommendations may serve as a common basis for the transposition and overall for the subsequent implementation of provisions related to organ vigilance, as reflected in the *Directive*, to be applied at a Member State level and in those situations where organs are to be exchanged between Member States. Recommendations provided by EFRETOS are based on the limited experience on organ V-Systems currently in place in Europe as described in this chapter and in the United States. These recommendations are also based on expert opinions and on the interpretations of the relevant provisions within the *Directive,* as discussed and agreed upon during the corresponding meetings held by the EFRETOS consortium. A **pilot experience** to validate these recommendations is therefore essential and a matter of further work. Also, the impact assessment of implementing these recommendations from the point of view of human and material resources and the resulting financial implications needs to be subsequently performed.

10.2 State of the art of vigilance and surveillance systems in organ donation and transplantation

10.2.1 Methodology

A specific questionnaire was designed and agreed upon by the EFRETOS partners to systematically collect information on the current situation of V-systems applied to organ donation and transplantation in the countries represented at the consortium. The survey integrated questions on the following issues:

- Existence of a V-system applied to organ donation and transplantation;
- Existence of legal provisions regulating the previously mentioned system;
- Responsible organization or institution for organ V-System;
- Procedures applied to the reporting and management of AE and AR;
- Definitions applied for AE and AR at the existing systems;
- Information reported and collected on AE and AR;
- Link to the V-system on tissues and cells;
- Preparation of periodic reports on AE and AR;
- Traceability issues.

Once the questionnaire was agreed, each partner completed the corresponding information on behalf of the country or countries which the partner was representing at the consortium. The information was then compiled by the Organización Nacional de Trasplantes (ONT) who summarized the findings. This information was then double checked by the partners to ensure a proper description of their systems had been performed.

Additional information on V-systems applied to organs as well as to other substances of human origin was collected from the review of the information available in the literature, through other EU funded projects and from personal contacts with the institutions/organizations in charge. Particularly, contact with Dr. Michael G. Ison, chair of the *Disease Transmission Advisory Committee* of the OPTN/UNOS (see below), provided highly valuable information on the US system.

10.2.2 Vigilance and surveillance for human organs intended for transplantation in countries in the EFRETOS consortium

Main findings of the survey on organ V-systems in countries represented at the EFRETOS consortium are summarized below. Information for France (FR), Italy (IT), Spain (SP) and United Kingdom (UK) was provided by ABM, CNT, ONT and NHSBT, respectively. Eurotransplant (ET) provided information for Austria, Belgium, Croatia, Germany, Luxembourg, The Netherlands and Slovenia. Scandiatransplant (SK) provided information for Denmark, Finland, Iceland, Norway and Sweden.

Existence of a V-system for human organs intended for transplantation

Legal provisions for the reporting and/or management of AE and AR applied to organs are only in place in FR. Particularly, the system is regulated by the *Biovigilance Decree of December 12, 2003* and the *Biovigilance Decree of July 17, 2007*. It should also be mentioned the *Decision of February 19, 2008 about the Model of Biovigilance Annual Report and the Notification Form for the Reporting of Adverse Events and Reactions*. Notably, the V-system developed in FR under the corresponding

legislation is targeted to "*the supervision and assessment of the risks of events and events in relation with products and activities in the field of biovigilance and on adverse reactions in the living donor or in the recipient*". Moreover, the French V-system for organs is included under a broader V-system targeted to human organs, tissues, cells (except gametes) and preservation liquid.

There are no specific legislative provisions establishing the obligation for reporting and/or managing AE and AR in the field of organ transplantation in the rest of the countries represented in the consortium. However, it is to be highlighted that such reporting, analysis and management of AE and AR do take place in the daily practice in the rest of the countries, although in most of them without a pre-established formal procedure (**table 1**).

In SK countries, vigilance for organs is to be considered as a part of a general system for reporting reactions in all type of hospitalized patients (transplanted and not transplanted patients). All incidents are communicated to an "Accident Register" established at each hospital. The system is computerized at most of the twelve transplant hospitals in SK countries; therefore, the register contains reports on all types of reactions in patients, including transplant patients and living donors.

Table 1: Countries reporting AE and AR at the EFRETOS consortium

AR in recipients after organ transplantation	IT; FR; IT; SK (part of a general reporting system); SP; UK
AR in living donors	IT; FR; IT; SK (part of a general reporting system); SP; UK
AE in the process of donation	IT; ET; FR; SK (part of a general reporting system); SP; UK

Specifications on the V&S system for human organs intended for transplantation

Definitions and triggers for reporting. (WHAT?)

FR has a specific definition for AE, SAE, AR and SAR. These definitions are provided in the *Biovigilance Decree of July 17, 2007*, mentioned above. They are specified in **table 2**.

Table 2: Definitions of AR, SAR, AE and SAE in the French Biovigilance System, according to the Biovigilance Decree of July 17, 2007.

Adverse event (AE)	Failure from an element at one step of the process that results in an adverse reaction in the living donor or in the recipient.
Serious adverse event (SAE)	Adverse event can result in serious adverse reactions.
Adverse reaction (AR)	Unexpected and untoward clinical manifestation that happens in the living donor or in the recipient, linked or possibly linked to a product or an activity in the field of biovigilance.
Serious adverse reaction (SAR)	Adverse reaction can result in the death, or is life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity.

Criteria for the reporting of AE and AR are also provided in the French G*uide for the reporting of AR and AE for Establishment Biovigilance coordinators.* As illustration, some examples are given by the ABM:

- **Examples of Adverse Events: i)** Mistake of blood group in donor or recipient; **ii)** Lack of conformity of donor selection (serology, HLA-typing); **iii)** Tumour diagnosed in the donor when at least one organ has already been transplanted; **iv)** Microbiological contamination of the preservation liquid**; v)** Other AE.

- **Examples of Adverse Reactions:**
  - **In a living donor:** unexpected clinical reaction.
  - **In a recipient of an organ (often related to an AE): i)** Death; **ii)** Removal of the organ; **iii)** Infectious disease**; iv)** Viral seroconversion; **v)** Tumour diagnosed in a recipient; **vi)** Other AR (i.e. allergic reaction in a recipient).

IT has also recently developed definitions and triggers for their system:

- **Serious adverse event:** any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life- threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalization or morbidity. Within this category, for the purpose of classification, other subcategories have been identified:

  - **Error:** failure in planning and carrying out a series of actions leading to the failed, non-casual, achievement of the desired objective. Among which the following are included:

    - failed identification of potential donor;

    - failed transplantation due to organizational, logistic or casual issues that prevent organ use in the identified recipient.

  - **Medical error:** missed intervention or inappropriate intervention, from which a clinically significant AE is derived.

  - **Minor adverse event:** sudden event connected with any phase of the donation and transplant process leading to an unintended and undesirable damage to the patient.

  - **Sentinel event:** particularly serious AE, potentially highlighting a malfunctioning of the system that causes a loss of trust in the system by citizens, independently from the provoked damage.

  - **Near miss:** error that has concrete potential to provoke a SAR, that does not take place by hazard or preventive remedial action or does not have consequences for the patient, the system or the staff.

- **Serious adverse reaction:** Unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalization or morbidity. Within this category fall the following reactions:

  - **Unexpected primary infections possibly transferred from the donor to the recipient:** it includes viral, bacterial, parasitic, fungal, prion infections. Those cases when organs from infection-positive donors are transplanted on the basis of a risk-benefit assessment and in the framework of specific programs are excluded.

  - **Transmitted infection:** it includes viral, bacterial, parasitic, fungal, prion infections possibly due to contamination or cross contamination by an infectious agent on the procured organs or associated materials from procurement to clinical application;

  - **Hypersensitivity reactions:** it includes allergy, anaphylactoid reactions or anaphylaxis;

- **Malignant disease, possibly transferred by the organ**, whatever the origin, donor or process;

- **Immunological reactions** Unexpectedly delayed or absent engraftment, graft failure (including mechanical failure)

SP is currently developing a model for organ vigilance, including reporting criteria. The rest of the partners do not have specific definitions for AE, SAE, AR and SAR particularly referred to organs. Corresponding definitions do exist for other human products in EU countries, according to *Directives 2002/98/EC* (blood and blood derivatives) and *2004/23/EC* (tissues and cells).

In the UK, a monitoring process is in place to detect statistically significant deteriorations in the mortality or graft failure rate at a centre, compared to previous performance. The process is based on the cumulative sum (CUSUM) of differences between observed and expected outcomes, and is known as CUSUM monitoring. Triggers in this regard are recipient death (for all organs) and graft loss (only for kidney and pancreas).

In SK countries, the decision of reporting is left to the head of the units in the general reporting system referred to in section 1 and the trigger for reporting is rather unspecific: "when the doctors and/or nurses involved *feel* that the incident should be reported". However, deaths in the operating room (including those occurring in transplanted patients) have to be reported to the police and incidents involving technical equipment are to be reported to a special unit in the hospital dealing with this type of devices.

Procedure for reporting. (WHO and HOW?)

Procedures applied for the reporting of AE, SAE, AR and SAR specifically applied to organs in the EFRETOS countries are summarized in **tables 3 and 4.** Specific written procedures for vigilance applied to organs as part of the broader biovigilance system are available in FR [The *French Health Safety Agency for Medical Products* (*AFSSAPS) Guide for the reporting of AR and AE for Establishment Biovigilance coordinators*) and IT and are being developed in SP. Further details on the French and Italian system regarding responsibilities in the reporting and vigilance applied to organs in general terms is provided in **figures 2 and 3,** respectively. **Table 3** provides information on those responsible for the reporting and the institution to which cases are reported to for all the countries represented at the consortium.

Table 3: Responsibilities in the reporting of AE and AR in the EFRETOS consortium.

Responsible for reporting
ET: Transplant centre **FR:** Establishment biovigilance coordinator and ABM biovigilance coordinator. **IT:** Regional transplant coordinator. **SK:** Head of each unit. Anyone may report, but the Head of the unit must sign the incident form. **SP:** Hospital donor coordinator. **UK:** No one person.
Reporting to
ET: Eurotransplant **FR:** AFSSAP. See figure 1. **IT:** Italian National transplant centre (CNT). **SK:** The hospital administration with an *ad hoc* committee **SP:** Spanish National Transplant Organization (ONT) and regional transplant coordination (that where the AE or AR occurs). There are specific persons at ONT responsible for V&S. **UK:** Associate Medical Director of NHSBT, who will take it to the clinical governance group if appropriate. CUSUM signals are also reported to the centre concerned and the chair of the relevant *Organ Advisory Group*.

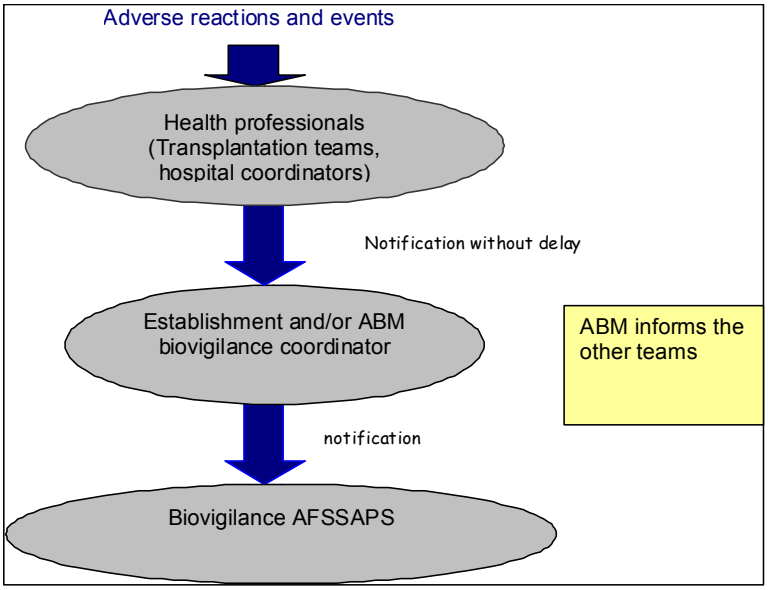


Figure 2: French Biovigilance system for products of human origin (organs included). In summary, the responsibility of Biovigilance is supervised by the French Health Safety Agency for Medical Products (AFSSAPS). Health professionals (transplant teams, hospital coordinators) must notify AR and AE to a biovigilance coordinator appointed locally, and/or directly to the ABM, who takes care of informing potentially affected teams/centres.

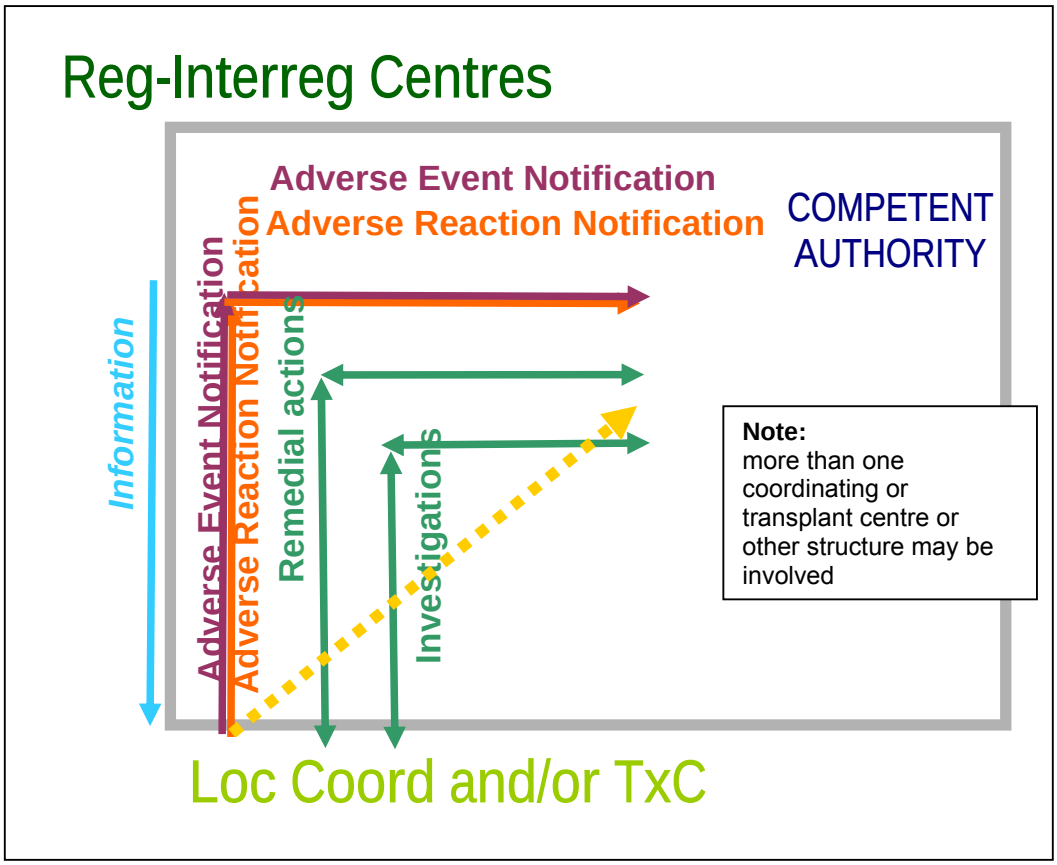


Figure 3: Scheme of information flow in the Italian system. *Loc Coord: Local donor coordinator. TxC: Transplantation Centre..*

In SK countries, the system foresees that all incidents are reported from the head of the units to the hospital administration. Incidents are collected in the ”Accident Register” which is under the Medical Director´s responsibility. The Medical Director chairs an *ad hoc* Committee consisting of senior consultants, a nurse, a representative from the medical equipment department and a lawyer. The Committee meets once a month to evaluate the incidents. In case of a SAR, the committee may meet extraordinarily to address the case. The Committee reports yearly to the Board and forwards the report to the *Ministry of Health´s Inspectorate of Health*.

The timeline established for the reporting is “without delay” for FR, with no specifications in the rest of the countries. In ET countries and in IT, the reporting is performed in paper format. In FR and SP, the format is open, either in paper or in electronic form. In SK, the format varies between the hospitals; in Oslo (Norway) the reporting is known to be electronic, but no information is available on the format used in the rest of the hospitals, including the remaining eleven transplant centres. In the UK, for CUSUM analysis, CUSUM charts are available electronically, but for other events and reactions, the format is currently under review. **Table 4** provides an overview of the type of data which is collected. Only FR and IT have a specifically designed form for the reporting of AR/SAR and AE/SAE (**Annex 1 and 2**). The severity and the attributability of AR will be reported on the next AFSSAPS notification form. IT uses a pre-specified classification for the evaluation of the severity and attributability of AR and for the impact assessment of AE and AR. These tools are inspired in those developed in the EUSTITE project for the vigilance of tissues and cells.

Table 4: Information collected in the reporting of AR/SAR and AE/SAE in EFRETOS countries.	
Particular form used	**FR:** (CF. Notification form for reporting adverse events and reactions); **IT**; **SK:** each hospital has a particular form for the reporting of incidents; **SP:** In progress.
Person reporting/centre/contact details	ET; FR; IT; SK; SP
Organs transplanted	ET; FR; IT; SK; SP; UK
Date of detection	ET; FR; IT; SK; SP; UK
Type of AE / AR	ET; FR; IT; SK; SP; UK (the AE/AR description is reported)
Date of finalization	ET; FR; IT; SK; SP (other document)
Severity of reaction	ET; FR (in the next AFSSAPS notification form); IT; SK; SP
Attributability of reaction to the donor/donation process	ET; FR (in the next AFSSAPS notification form); IT; SK; SP
Actions taken	ET; FR; IT; SK; SP; UK
Other	FR: Information about other recipients is reported (organ, centre of transplantation)

Procedure for management (WHO and HOW)?

Procedures applied for the management of AE and AR specifically applied to organs in the EFRETOS countries are summarized in **tables 5 and 6.** As previously described, specific written procedures for vigilance applied to organs as part of the broader biovigilance system are available in FR (The *AFSSAPS Guide for the reporting of AR and AE for Establishment biovigilance coordinator*) and IT and are in progress in SP. **Table 5** provides information on those responsible for the management of AE and AR. Further details on the French system regarding responsibilities in the management of AE and AR in general terms are provided in **figure 1.**

1.1 **Table 5:** Responsibilities in the management of AR/SAR and AE/SAE
ET: Transplant centre **FR:** AFSSAPS (French Health Safety Agency for Medical Products) **IT:** Regional transplant coordinator **SK:** Transplant centre **SP:** Responsible person at the ONT; regional donor coordinator; hospital donor coordinators of centres involved and Transplant teams involved. **UK:** no one person

Who finds out whether there are other recipients or not?	**ET**: ET **FR**: If other recipients are concerned, Agence de la Biomedecine (regional office) inform the other teams. **IT:** Regional transplant coordinating centre. **SK:** The consultant in charge of the affected patient. **SP:** ONT **UK:** The transplant unit, via NHSBT.
Who searches for the other recipients, if any?	ET: ET **FR**: ABM **IT:** Italian National Transplant Centre **SK:** Hospital donor coordinator **SP:** ONT **UK:** NHSBT
Who communicates the situation to other authorities / physicians?	ET: ET FR: ABM **IT:** Italian National Transplant Centre **SK:** The consultant in charge of the affected patient. **SP:** ONT and/or regional coordinator **UK:** NHSBT
Who decides whether the other recipients should be communicated or not?	**ET:** Transplant centre. ET informs the transplant centre, not the patient. **FR:** Recipient physician **IT:** Regional transplant coordinating centre and Italian National Transplant Centre. **SK:** Consultant in charge of potentially affected recipients **SP:** Transplant centre **UK:** Local clinician.
What are the criteria for the communication of the situation to patients?	**ET:** Local practice **FR**: Local practice **IT:** Local practice **SK:** Local practice **SP:** Local practice **UK:** Local practice
Who communicates the problem to other affected recipients?	**ET:** Transplant team **FR:** Transplant team **IT:** Regional transplant coordinating centre and Italian National Transplant Centre **SK:** Consultant in charge of potentially affected recipients **SP:** Transplant team **UK:** Transplant team

Table 6 provides information on the activities which are performed in EFRETOS countries under the broad concept of management of AE and AR.

Table 6: Activities performed for the management of AE and AR.	
Investigation/evaluation	FR; IT; SK; SP; UK
Re-assess severity/attributability	FR (next notification form); IT; SK; SP; UK
Follow-up assessment	FR; IT; SK; SP; UK (if necessary)
Raise conclusion	FR; IT; SK; SP; UK
Propose corrective or preventive measures	FR; IT; SK; SP; UK (if necessary)
Implement corrective or preventive measures	FR; IT; SK; SP; UK (if necessary)
Completion of a report	FR; IT; SK; SP; UK
Maintenance of the records	FR; IT; SK; SP; UK
Statistical analysis	FR; UK (for patient death and graft loss, others under consideration); SP

Reports on AE and AR

Periodic national reports on AE and AR are prepared by FR and IT. This kind of reports are in progress in ET, SP and UK. In SK, the medical director of each hospital and the *ad hoc Committee* prepares an annual report to the Board of the hospital which is then sent to the national health authorities. In SP, reports are routinely prepared for AE and AR, containing information on the particular case, recipients potentially affected and their outcome, information on attributability and severity of reactions, measures taken and related recommendations if deemed appropriate. Details on the preparation of the reports are provided in **table 7** for FR and SK. **Figure 4** represents the annual biovigilance report for organs prepared in FR.

Table 7: Details on the preparation of the national reports on AE and AR in FR and SP.	
Who prepares the report?	**FR:** ABM prepares the report, then AFSSAPS writes the final report (organ, tissue and cell) **SK:** Medical Director with an *ad hoc* committee for each hospital.
Frequency of development	**FR:** Yearly **SK:** Yearly
Addressees of the report	**FR:** Health Ministry **SK:** Hospital Board and Ministries of Health Inspectorate of Health.
Statistical indicators provided	**FR:** Adverse reactions number Adverse events number Procurement and transplantation activities

Figure 4: Example of report on AR/SAR and AE/SAE in FR.

AR / SAR and AE / SAE notified to ABM in 2008

52 adverse events were notified in 2008

- Mistake of blood group in recipient: 2
- Lack of conformity of donor selection (serology, HLA, typing): 3
- Tumour diagnosed in donor when at least one organ has already been transplanted: 19
- Microbiological (fungus) contamination of preservation liquid without any adverse reaction in recipient: 27
- Other: 1

20 adverse reactions were notified in 2008

In living donor: clinical reaction: 1
In recipient:

- Deaths: 5
- Removal of the organs: 4
- Infectious disease: 3
- Viral seroconversion: 2
- Tumour diagnosed in recipient: 2
- Other: 3

Actions taken by Agence de la Biomedecine

- Alert system: in case of emergency, the regional support office (RSO) informs the other teams and takes the appropriate measures
- Remind health professionals of the relevant law or recommendations
- Elaboration of recommendations, survey

Example of adverse reaction and actions taken by Agence de la biomedecine

2005-2008: 6 deaths reported in transplant recipients related to a general *candida* infection
Actions taken: elaboration of recommendations

- Recommendations on the prevention of *candida* infection following renal graft (2005)
- General recommendations on bacterial and fungal agents in organ recipients (2008)

Link between the organ V&S system and the tissues and cells V&S systems

In ET the link between the V-system for organs and that of tissues and cells in ensured since there is a unique identifier communication with BISLIFE (www.bislife.org).

In FR, as already stated, the V-system is common for all products of human origin and therefore the link exists with the system applied to tissues and cells and that applied to blood and blood derivatives. Moreover, since AFSSAPS is in charge of other vigilance systems (i.e. pharmacovigilance), links with other systems are also in place.

In IT and SP, the link exists, but not necessarily through a national electronic record. Particularly in IT, the Italian National Transplant Information System (SIT) records each donation of organs, tissues and cells. However, for tissues and cells the information is centrally collected until banking. Afterwards, tissue banks keep their own records. In SP the situation is rather similar: information is centrally collected on whether organ donors are also tissue donors, but there is a separate register for all tissue

donors. Centres do keep a unique identifier for each donation of organs, tissues and cells. No link with blood and blood derivatives exists in IT and SP.

In SK and the UK, the link between the systems is not ensured.

Traceability

ET, FR (Operating System CRISTAL), IT (SIT), SK, SP (Donation and Transplantation Spanish Data System) and UK (UK Transplant Registry maintained by NHSBT) do possess a Unique Identifier System for each organ donor and donation and for each organ recipient, which ensures traceability from donor to recipient (s) and vice versa. All countries involved have data protection and confidentiality measures applied to their corresponding systems.

10.2.3 Vigilance and surveillance of human organs intended for transplantation outside of the EU: The US example

Introduction[19]

The Organ Procurement and Transplantation Network (OPTN) is the unified transplant network established by the United States Congress under the *National Organ Transplant Act* of 1984. The act called for the network to be operated by a private, non-profit organization under federal contract. The OPTN is a unique public-private partnership that links all of the professionals involved in the donation and transplantation system. The primary goals of the OPTN are to:

- increase the effectiveness and efficiency of organ sharing and equity in the national system of organ allocation, and to
- increase the supply of donated organs available for transplantation.

The United Network for Organ Sharing (UNOS), based in Richmond, Virginia, administers the OPTN under contract with the Health Resources and Services Administration of the US. Department of Health and Human Services. UNOS has developed a collaborative policy development, monitoring, and enforcement process for the OPTN, and also has systems in place for making member inquiries, conducting peer reviews, maintaining data production for reviewing membership applications, and monitoring member compliance with OPTN policies.

The OPTN acts through its Board of Directors. The current UNOS Board also presently serves as the OPTN Board of Directors. Board members, chosen through an open, comprehensive nomination process, bring a wealth of commitment and technical knowledge to guide the OPTN in establishing and maintaining policies and procedures for the field of transplantation. There are currently representatives from each of the 11 UNOS regions, as well as from transplant professional societies, the recipient and donor populations, and experts in the various fields of transplantation.

OPTN policies on V&S of organs. The Disease Transmission Advisory Committee[20,21]

The OPTN Policy 4.7 requires that "*when a transplant program is informed that an organ recipient at that program is confirmed positive for or has died from a transmissible disease or medical condition for which there is substantial concern that it could be from donor origin, the transplant program must notify by phone and provide available documentation, as soon as possible, and not to exceed one complete working day, to the procuring Organ Procurement Organization (OPO)".* The OPO shall then:

- communicate the results to all recipient transplant centres & tissue banks
- manage the investigation;
- notify the OPTN as soon as possible;
- submit a final written report to the OPTN within 45 days.

The *Disease Transmission Advisory Committee* (DTAC) was first established in 2005 as an advisory group to the OPTN/UNOS Operations Committee to identify and review potential donor derived transmission events; it is now a standalone committee reporting directly to the OPTN Board. The DTAC´s core task is to consider issues related to the transmission of diseases through organ transplantation. The Committee examines individual potential disease transmission cases reported to the OPTN in an effort to confirm transmissions where possible. It reviews aggregate data on all reported cases to assess the risk of donor disease transmission in organ transplantation in the US with the goal of providing; **i**) education and guidance to the transplant community toward preventing future disease transmission and **ii**) input in developing policy to improve the safety of organ donation through the reduction of donor derived transmission events. It may identify disease-transmission related patient safety issues to be addressed, as appropriate, by the OPTN.

Workflow

Reporting to OPTN

Anyone may report a potential case – including patients, transplant centres, or OPOs. Although there are multiple potential ways to report cases, including telephone based reports, submission via the web based *OPTN Patient Safety System* is preferred (**Annex 2**). Once an initial report is received, the OPTN Patient Safety staff collects patient, OPO, and transplant centre identifiers from initial reports and supporting data and then uploads these materials to a password-protected secure website.

DTAC evaluation

Once the redacted materials for a case have been uploaded, DTAC members are alerted by email. Then DTAC engages in an e-mail based confidential medical peer review process. DTAC provides queries and recommendations over 24-48 hours of the initial report for more information that may be needed to determine if transmission has occurred; although the group may recommend steps and studies to investigate the potential transmission, these recommendations are non-binding and evaluation decisions are made by the individual care teams. DTAC cannot make treatment recommendations. The committee then continues electronic discussions as further details are received from the OPO or transplant centre concerned. Specific event conference calls may be conducted to advance an investigation expeditiously, although this is done in the minority of cases. If warranted, health authorities (i.e. CDC) are involved in this process.

DTAC also reviews the 45 day report previously mentioned to be sent by OPOs on each reported case, including the findings of their investigations. DTAC is involved in a process to ensure that OPOs and transplant centres are made aware of its determination once the 45 day report has been reviewed, in order to close the loop; this process is still being refined.

DTAC holds monthly conference calls to review reports and 45 day reports over the past month, as well as outstanding queries. The Committee also meets twice a year to review reports over the past 6 months and categorize events as specified below (classification system for events). DATC prepares an Annual Report on its activity to the OPTN/UNOS Board and performs annual publications.

Management

Management of each particular case is dependent on the centre and OPO concerned. Information on the actions taken and driven investigation is reported to DTAC as already stated. Although DTAC may recommend how to proceed best with the evaluation of the case, the decisions about testing and patient care are taken by the individual care teams. Frequently, the CDC may become involved in the case and provide expert advice and laboratory support for the investigation.

Classification system for events

All potential donor derived transmission reports are classified by DTAC with regard to whether they were **expected** based on material available to all centres at the time of transplantation and classifies **likelihood of the event being a true donor derived transmission**. For the classification of the event, a consensus has to be reached by the entire Committee and often requires significant discussion of available details.

Expected vs. unexpected Event
An event is categorized as "Expected" if information about the potential donor derived transmission report was known before transplantation or for which recognized standard guidelines for routine prevention of the pathogen are available (i.e. CMV, EBV).

Probability of donor derived nature
DTAC has devised a classification scheme for events as with regards to the likelihood of the reported events being transmitted from the donor (**table 8**).

Table 8: Classification system for determining likelihood of the transmission event being donor derived	
Proven	Identification of the same pathogen in the donor and recipient or a malignancy of documented donor origin.
Probable	Pathogen in one or more recipients with suggestive data about the donor.
Possible	Evidence to suggest but not proven transmission.
Intervention without documented transmission	No transmission recognized all or most of recipients received active therapy for pathogen of interest (impossible to determine if a transmission would have occurred without the intervention).
Unlikely	Transmission is possible but there is insufficient data but the evidence strongly suggests against donor-origin.
Excluded	No evidence to support a donor origin of infection or clear evidence of an alternative source of the disease (i.e. recipient origin or post-transplant onset).

Further specifications are provided about the criteria to apply in classifying events**Error! Bookmark not defined.**:

Proven: all of the following conditions must be met
- suspected transmission event;
- laboratory evidence of suspected organism or malignancy in recipient;
- laboratory evidence of the same organism or malignancy in the donor;
- if there is pre-transplant laboratory evidence, it must indicate that the same recipient was negative for this organism prior to transplantation.

Probable: both of the following two conditions must be met
- suspected transmission event and
- laboratory evidence of the suspected organism or malignancy in a recipient.

And at least one of the following criteria must be met
- laboratory evidence of the same organism or malignancy in other recipients:
- laboratory evidence of the same organism or malignancy in the donor (pathogen or malignancy similar, but not proven).

If there is pre-transplant laboratory evidence, it must indicate that the same recipient was negative for this organism prior to transplantation.

Possible: suspected transmission event
- laboratory evidence of the suspected organism or malignancy in a single recipient OR
- data that strongly suggest but does not prove a transmission event.

AND

Intervention without documented transmission: no transmission recognized all or most of recipients received active therapy for pathogen of interest (impossible to determine if a transmission would have occurred without the intervention).

Unlikely: transmission is possible but there is insufficient data but the evidence strongly suggests against donor origin.

Excluded: suspected transmission event and at least one of the following conditions is met

- there is clear evidence for an alternative reason for the event;
- lack of infection with the same organism in any other recipients, from the same donor, given appropriate testing;
- laboratory evidence that the recipient had infection with this organism or malignancy prior to transplantation.

Confirmed: any case that is classified as proven, probable or possible.

Limitations of the classification system

Although DTAC provides suggestions regarding additional testing to the OPO and transplant centres, the current OPTN policy does not require these groups to conduct the recommended evaluation. Additionally, there are frequently insufficient materials to do the appropriate testing to rule-in or rule-out donor origin of disease. Therefore, there is not always the possibility of validating or definitely document the likelihood of transmission.

Results of the V&S system for organs in the US and future steps

Results of the previously described system were published in the *American Journal of Transplantation* in 2009. This publication has served as the basis for the description of the system in this report. The information was broadened at the *Organ Donation Congress* held in Berlin in October 2009. In a presentation performed by Dr. Michael G. Ison at that congress, an update of the results of the system was provided. It is to be highlighted that the number of reported cases had progressively increased along the years: 7 in 2005, 60 in 2006, 97 in 2007, 102 in 2008 and 152 in 2009. This increase likely represents improved reporting and not a true increase in the incidence of donor derived disease transmission. In the publication and the mentioned presentation, information was provided on the reports received by DTAC regarding potential donor derived infectious and malignant events. Information was provided particularly on the type of infection or malignancy and, for each type, the number of donors with reported events, the number of recipients with confirmed transmission (for the first years of DTAC, this corresponded to the proven, probable and possible cases, according to the classification system now in place) and the number of recipient deaths related to the transmission.

Future challenges for the system were identified:

- education of the transplant community about the identification and reporting of events;
- utilization of existing data bases to better identify disease transmission, in a complementary way to the reporting system (cluster analysis, analysis of mortality and malignancy data for recipients transplanted from donors with reports);
- refinement of data collection and management;
- provision of recommendations for the revision of OPTN policy.

10.2.4 Vigilance and surveillance of human organs intended for transplantation: the requirements of the EU Directive

This section intends to summarize the main provisions of the recently approved organs *Directive*.**Error! Bookmark not defined.** Particularly, those provisions relevant for the vigilance of organs are to be reviewed. However, it is important to describe first the subject matter of the *Directive* (*Article 2*), which

specifies that the *Directive* applies to the donation, testing, characterization, procurement, preservation, transport and transplantation of human organs intended for transplantation. As specified in the *Lisbon Treaty*, donation and clinical use of substances of human origin are out of the competences of the EU. Therefore, donation and transplantation are included under the subject of the *Directive* in the only sense of issues related to the quality and the safety of the organs.

The Competent Authority

The Directive establishes that **Member States shall designate one (or more than one) Competent Authority** (CA), defined as an authority, body, organization and/or institution responsible for the implementation of the provisions of the Directive (*Article 17*). *Article 17* also specifically describes the measures that are to be taken by the CA. Noteworthy, this same article includes the **principle of delegation**, by which Member States may delegate or may allow a CA to delegate part or all the tasks assigned to another body which is deemed suitable under national provisions. Such body may also assist the CA in carrying out its functions.

Reporting system and management procedure for SAE and SAR

Among the tasks to be developed by the CA it is to be highlighted that related to the development of a **System for Reporting and a Management Procedure for SAE and SAR**. Definitions for SAE and SAR are provided in *Article 3*:

- **Serious Adverse Event:** any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life-threatening, disabling, or incapacitating conditions for patients or which results in, or prolongs, hospitalization or morbidity.

- **Serious Adverse Reaction:** an unintended response, including a communicable disease, in the living donor or in the recipient that might be associated with any stage of the chain from donation to transplantation that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity.

The need for developing **operating procedures** for the accurate, rapid and verifiable reporting of SARE and for their management is specified in *Article 4*, operating procedures being defined as written instructions describing the steps in a specific process, including the materials and methods to be used and the expected end outcome (*Article 3*).

Article 11 is further focused on the Reporting System and Management Procedure for SAE and SAR. The article re-states the responsibility of Member States on the existence of such System and procedure. It is also specified that notification of SAE and SAR shall occur **"in due time" to the CA and to the concerned procurement organization and transplantation centre**. Additionally, **the management measures taken with regards to SAR have also to be communicated to the CA**.

The same article establishes the obligation of Member States of ensuring the **interconnection between the reporting system for organs and that established in accordance with *Directive 2004/23/EC* (tissues and cells)**, although *recital 16* explains that this does not mean that the systems have to be electronically linked, if an electronic system has been settled down for that purpose.

Notably, *Article 11* refers to the **reporting of SAE and SAR when organs are exchanged between Member States.** For such purpose, **the Commission has to develop a specific procedure**.

As a conclusion of what mentioned above, the *Directive* will oblige EU Member States to develop a system for the reporting and management of SAE and SAR. Some specifications are provided for such system and procedure. Moreover, it is established that the system has to be linked to the one applied for tissues and cells. But Member States have the sovereignty of developing their own systems. However, if a specific procedure for organs exchanged between Member States is expected to be

developed by the Commission, it is evident that procedures followed by Member States should have a set of minimum common requirements.

Traceability

Article 10 is based on the obligation of Member States **to ensure traceability**, so all organs procured, allocated and transplanted within their territory can be traced from the donor to the recipient and *vice versa*. For such purpose, Member States have to implement a **donor and recipient identification system** that can identify each donation and each of the organs and recipients associated with it. Information required to ensure traceability is to be kept, so the ability to identify the donor and the procurement organization, the recipient(s) at the transplantation centre(s) and to locate and identify all relevant non-personal information relating to products and materials coming into contact with that organ is ensured. Information on a set of variables for organ characterization as specified in an *annex* to that *Directive* is also to be kept, according to the provisions of this article.

Traceability being maintained, the principles of **protection of personal data, confidentiality and security of processing** are to be respected, as specified in *Directive 95/46/EC of the European Parliament and of the Council on the protecting of individuals with regard to the processing of personal data and on the free movement of such data.*[22]

10.2.5 Vigilance and surveillance applied to tissues and cells in the EU

The EU Legislative Framework: Directive 2004/23/EC

Directive 2004/23/EC *of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells***Error! Bookmark not defined.** established the following provisions to be fulfilled by MS, concerning a V&S system applied to tissues and cells:

- **Designation of one or more CA,** responsible for the implementation of the provisions of the Directive
- **Have a system in place to report, investigate, register and transmit information** about SAE which may influence the quality and safety of tissues and cells and which may be attributed to the procurement, testing, processing, storage and distribution of tissues and cells, as well as any SAR observed during or after clinical application which may be linked to the quality and safety of tissues and cells. The procedure for the notification was to be established by the European Commission.
- Each tissue establishment shall ensure that an **accurate, rapid and verifiable procedure is in place which enables it to recall from distribution any product which may be related to an AE or AR.**
- **Ensure traceability**, so all tissues and cells procured, processed, stored or distributed can be traced from the donor to the recipient and vice versa, and also applying to products and materials coming into contact with these tissues and cells. For this purpose, **a donor identification system**, which assigned a unique code to each donation and each of the associated products, was to be implemented. While ensuring traceability**, data protection and confidentiality and no unauthorized disclosure of information** were also to be ensured.

For the purpose of this Directive, the following definitions were applied when referring to SARE:

- **Serious adverse event:** any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalization or morbidity;

- **Serious adverse reaction:** an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalization or morbidity.

The implementing Directives

Directive 2004/23/EC entered into force in April 2004. Member States had two years for the transposition of the provisions of the Directive into their national legislations. Following this Directive, two implementing Directives resulted which complemented the provisions of the aforementioned Directive:

- ***Commission Directive 2006/17/EC*Error! Bookmark not defined.** *of February 8, 2006 as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.*
- ***Commission Directive 2006/86/EC*Error! Bookmark not defined.** *of October 24, 2006 as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.*

In particular, ***Directive 2006/86/EC*Error! Bookmark not defined.** laid down requirements for the notification of SARE. In general terms, the following provisions were established:

- **Responsibilities** of procurement organizations, tissue establishments and organizations responsible for the human application of human tissues and cells on the reporting of SARE, including notification to the corresponding CA.
- **Responsibilities** of tissue establishments on the investigation and evaluation of any suspected SAR and on the evaluation of any SAE and on the investigation and outcome of any SARE, and notification of the result of the investigation raised and the outcome to the CA, including any conclusion for each of these cases.
- **Information to be reported** on SARE was specified in an annex. This included:
  - **PART A ANNEX III (Information for the rapid notification of SAR):** tissue establishment, report identification, reporting date, individual affected, date and place of procurement or human application, unique donation identification number, date of suspected SAR, type of tissues and cells involved in the suspected SAR, type of suspected SAR.
  - **PART B ANNEX III (Conclusions of SAR investigation):** tissue establishment, report identification, confirmation date, date of SAR, unique donation identification number, confirmation of SAR, change of type of SAR (if yes, specification is required), clinical outcome if known) (complete recovery, minor sequelae, serious sequelae), outcome of the investigation and final conclusions, recommendations for preventive and corrective actions.
  - **PART A ANNEX IV (Rapid notification for suspected SAE):** tissue establishment, report identification, reporting date, date of SAE, stage of the process where deviation occurred (procurement, testing, transport, processing, storage, distribution, materials, others), specification (tissues and cells defect, equipment failure, human error, other).
  - **PART B ANNEX IV (Conclusions of SAE investigation):** Tissue establishment, report identification, confirmation date, date of SAE, root cause analysis, corrective measures taken).
- **Obligation to prepare a report on SARE annually by MS on the notification of SARE received by the CA.** The format and content of this report was further specified in Annex V of this Directive.

Transposition and Implementation of Directive 2004/23/EC in Member States of the EU

The European Commission recently prepared a report on the transposition and implementation of *Directive 2004/23/EC*. Results covered the year 2007. Regarding the notification of SAE and SAR:

- All Member States, except for Greece and Latvia, had a vigilance system in place to report, investigate, register and transmit information about SAE and SAR for tissues and cells. Information was not received from Luxembourg.
- Twenty-two MS had defined criteria for the reporting of AE to the CA.
- Twenty-one MS had defined criteria for the reporting of AR to the CA.
- The first annual report on the notification of AR and AE received was submitted from the CA to the Commission by only thirteen MS.

The EUSTITE project: tools for V&S for tissues and cells

EUSTITE (www.eustite.org) is an EU funded project which has, as one of its objectives, to develop optimal systems for the notification and management of AE and AR related to the quality and safety of tissues and cells. EUSTITE is being carried out by a consortium of organizations from ten Member States and the WHO, and is led by the Italian Centre Nazionale Trapianti. EUSTITE provided general recommendations on the functioning of a V&S system applied to tissues and cells that could be useful for the implementation of some of the provisions of *Directives 2004/23/EC***Error! Bookmark not defined.***, 2006/17/EC***Error! Bookmark not defined.** *and 2006/86/EC***Error! Bookmark not defined.**. The consortium also constructed a set of tools for V&S of human tissues and cells. Particularly these tools were developed for the evaluation and grading of AE and AR.

Although the obligation of Member States, according to *Directive 2004/23/EC,* is targeted to the reporting of SARE, EUSTITE project recommended that **all AE and AR are notified** in practice so tissue establishments, which play a key role in this regard, can monitor them for continuous improvement. The tissue establishments could then apply the tools provided in the project to assess **i)** severity (Severity Grading Tool); **ii)** imputability (Imputability Tool); **iii)** and impact (Impact Tool), in cooperation with the corresponding stakeholders. Subsequent response would be based on the impact, as assessed through the last tool.

The EUSTITE tools**Error! Bookmark not defined.** were applied in a pilot study carried out during the project to assess its feasibility and derived benefits. The pilot involved 22 CA of 20 MS. It was organized in a way that corresponding tissue establishments and other establishments reported SARE to their CA in the normal way in the corresponding countries. Each SAR was scored using the Severity Grading Tool and the Imputability Tool and then the Impact Tool was applied. Evaluation of SAEs used the Impact Tool only. A report of SARE notifications received, the scores applied, and information regarding their investigation and any relevant corrective or preventive action, was sent to the pilot coordinator each quarter by the identified contact person in each participating CA. SARE were grouped according to the stage of activity at which the incident occurred, in line with the requirements of *Directive 2006/86/EC***Error! Bookmark not defined.**. The pilot demonstrated the feasibility of multi-national cooperation in V&S in the area of tissue and cells for human application. The tools developed during the EUSTITE project were tested in multiple countries on a large number of real SARE and were found to be easily applied. The consortium finally proposed some changes to the EUSTITE tools on the basis of the experience and the knowledge acquired during the pilot study and subsequent discussions. The updated version of these tools is summarized in the sections below.

Serious Adverse Events and Reactions reporting

EUSTITE provided a set of **TRIGGERS**, including clinical symptoms or situations that could raise the alert for reporting an AR, either for a recipient of a tissue/cell or a living donor. In particular, the following triggers were provided: **i)** Unexpected primary infection possibly transferred from the donor to

the recipient (**Infection-Donor**); **ii)** Transmitted infection possibly due to contamination or cross-contamination by an infectious agent on the procured tissues, cells or associated materials from procurement to clinical application (**Infection-Tissue/cells**); **iii)** Hypersensitivity reactions (**Hypersensitivity**); **iv)** Malignant disease possibly transferred from the tissue/cell (**Malignancy**); **v)** Unexpectedly delayed or absent engraftment, graft failure (**Failure**); **vi)** Toxic effects from tissues and cells or associated materials (**Toxicity); vii)** Unexpected immunological reactions due to tissue/cell mismatch (**Mismatch**); **viii)** Aborted procedure involving unnecessary exposure to risk (**Undue risk**); **ix)** Suspected transmission of genetic disease (**Genetic abnormality**); **x)** Suspected transmission of other (non-infectious) illness (**Other transmission**); **xi)** Other (**Other**).

For AE, EUSTITE recommended reporting as SAE those deviations from standard operating procedures, or other AE when one or more of the following criteria apply: **i) inappropriate tissues/cells had been distributed for clinical use**, even if not used; **ii) the event could have implications for other patients or donors** because of shared practices, services, supplies or donors; **iii) the event resulted in a mix-up of gametes or embryos; iv) the event resulted in loss** of any irreplaceable autologous tissues or cells or any highly matched allogeneic tissues or cells; **v) the event resulted in the loss of significant quantity** of unmatched allogeneic tissues or cells.

Severity grading tool (table 9)

This tool was proposed by EUSTITE in order to assess the severity of adverse reactions. After a number of different grading systems had been reviewed, the following was adapted from the International Society of Blood Transfusion (ISBT) severity classification. Subsequent modifications resulted from the pilot as mentioned above.

Table 9: Severity Grading Tool for ADVERSE REACTIONS. EUSTITE project.

SEVERITY	COMMENTS
Non-serious	Mild clinical/psychological consequences No hospitalization. No anticipated long-term consequence/disability
Serious	• hospitalization or prolongation of hospitalization and/or • persistent or significant disability or incapacity or • intervention to preclude permanent damage or • evidence of a serious transmitted infection or • birth of child with a serious genetic disease following ART with donor gametes or embryos.
Life-threatening	• major intervention to prevent death or • evidence of a life-threatening transmissible infection or • birth of child with a life-threatening genetic disease following ART with donor gametes or embryos.
Death	Death

Imputability grading tool

This tool was targeted to adverse reactions. It was adapted from the one provided in the Blood Directive (*2005/61/EC*). Subsequent modifications resulted from the pilot as mentioned above.

Table 10: **Imputability** Grading Tool for ADVERSE REACTIONS EUSTITE project		
IMPUTABILITY LEVEL		**EXPLANATION**
NA	Not assessable	Insufficient data for imputability assessment.
0	Excluded	Conclusive evidence beyond reasonable doubt for attributing to alternative causes.
1	Unlikely	Evidence clearly in favour of attributing to other causes.
2	Possible	Evidence is indeterminate.
2	Likely, Probable	Evidence in favour of attributing to the tissues/cells.
3	Definite, Certain	Conclusive evidence beyond reasonable doubt for attributing to the tissues/cells.

Impact assessment tool

This EUSTITE tool is intended to assist in the assessment of the importance of a specific SAE or SAR, in terms of the actual or potential impact on public health, public support and risk to the supply of tissues and cells. This tool intends to assist in planning the response to a given AE or AR (figure 2). This tool is applied through a set of steps to evaluate: **1)** Likelihood of occurrence/recurrence; **2)** Impact/Consequences of SARE should it recur; **3)** Impact matrix (to grade the AR and AE by taking into account, both the likelihood of recurrence and the impact of recurrence simultaneously); **4)** Response: recommendations are provided then on the type of response, so it is proportionate to the potential impact, as assessed by the previous matrix:

- **Green area:** requires CA to keep a "watching brief", leaving the TE to manage the corrective and preventive actions.

- **Yellow area:** requires a more proactive response from CA. The CA may wish to conduct an inspection or to notify another authority if the inspection should be conducted at a site for which they are not the CA. The CA may also request the supply of follow-up data to confirm that the corrective and preventive actions have been carried out effectively, including evidence of effective recall, where necessary. It may be appropriate for the CA to issue a regulatory action notice to the field to ensure that the implications are considered at TEs not involved in the SARE.

- **Red area:** requires the CA to have a very active response. The CA may wish to participate in the development of the corrective and preventive Action Plan, perhaps leading a task force that addresses the broader implications, with the participation of policy makers. It is likely that the CA would conduct an inspection that focuses on the subject of the SARE and would request the supply of follow-up data to confirm that the corrective and preventive actions have been carried out effectively. Depending on the details of the SARE, it may be appropriate for the CA to issue a regulatory action notice to the field or a rapid alert and possibly to notify CAs in other Member States and the EC where there may be implications outside the Member State.

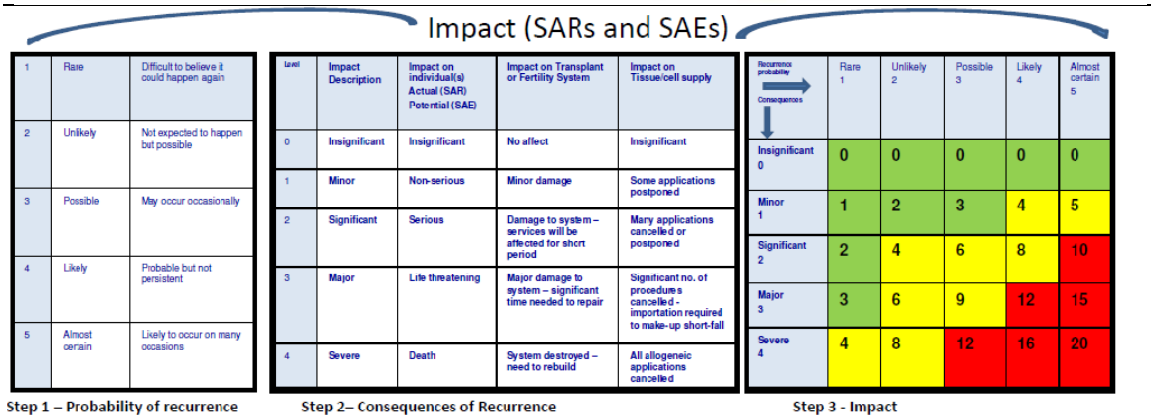


Figure 4: EUSTITE impact assessment tool.

Besides the updating of the tools, other important recommendations arose from the experience acquired in the pilot study in EUSTITE and in subsequent discussions within the group. The consortium stressed the need to continue promoting EU wide guidance, training and more technical work in the field of vigilance of tissues and cells. Part of the recommendations for future work are now being developed in the context of another EU funded project: SOHO V&S (*Vigilance and Surveillance of Substances of Human Origin*).

10.2.6 Conclusions

- V&S applied to organs represents an undisputed principle already reflected in the existing international legal instruments, as the *Additional Protocol to the Convention of Human Rights and Biomedicine on transplantation of organs and tissues of human origin***Error! Bookmark not defined.** and the *WHO Guiding Principles***Error! Bookmark not defined.**. These international documents have largely influenced national legislations and professional practices. However, the first has only been ratified by twelve Member States of the Council of Europe and the second one is not binding by nature. The new *Directive of the European Parliament and of the Council on standards of quality and safety of human organs intended for transplantation***Error! Bookmark not defined.** makes it mandatory for Member States to develop a reporting system and a management procedure for SARE.

- In the EFRETOS consortium, specific legal national provisions for V&S of organs already in place only exist in FR, in which safety in transplantation is regulated by a *Decree*. However, in practice, all partners use different mechanisms to report and manage AE and AR, although it is only FR which follows a written standardized system. In the UK, CUSUM monitoring uses the existing post-transplant register to detect deviations in practice, as an additional utility of this kind of tools which represent the main basis of the EFRETOS project.

- In practice, organ V&S in the EFRETOS countries involve the national transplant organizations and the supranational European organ exchange organizations. In some countries, the system seems also to involve the donor coordinators at a hospital and at a regional level, these figures apparently assuming responsibilities in the reporting and the management of AE and AR with the corresponding stakeholders.

- Many of the EFRETOS countries have implemented a V&S system applied to tissues and cells, as requested in Directive *2004/23/EC.* Notably, the new EU organ´s Directive establishes the requisite that the V&S system to be developed for organs must be linked to that created for tissues and cells.

- Non-EU countries, particularly US, are moving in the same direction of standardizing V&S in organs. Good communication between the EU initiatives and those of OPTN/UNOS through DTAC should be maintained.

- Lessons learnt during the implementation of the Directive *2004/23/EC,* through the practical use of the tools developed by the EUSTITE project, and from the existing system inside and outside the EFRETOS consortium provide a good basis for constructing specific recommendations for Member States of the EU in the construction of a V&S system applied to organs, as a requisite of the new Directive. Moreover, a minimum common approach would benefit most Member States, since it would help them to establish their system and would help the Commission in its first approach to establish procedures for those situations in which organs are exchanged between Member States.

- The proposed steps to build a standardized European V&S system are the following:
  - detection;
  - reporting;
  - investigation / evaluation;
  - assessment of severity and attributability;
  - identification of recipients or living donors affected;
  - proposal of corrective or preventive measures;
  - completion of a report;
  - information to responsible agency in each country;
  - statistical analyses.

- It is necessary to establish a coordination board, maybe formed by a responsible from every transplant organization, and define their functions and responsibilities

10.3 Recommendations on the vigilance of human organs intended for transplantation

10.3.1 Objective of a vigilance system of human organs intended for transplantation

To prevent the avoidable occurrence of a health problem to organ transplant recipient(s), associated with the donor or to the different procedural steps extending from donation to transplantation and to prevent the avoidable occurrence of a health problem to living organ donors, associated with donation, testing, characterization or procurement.

10.3.2 The organ donation and transplantation process

Although the reality of donation and transplantation is often complex and the limits of their processes are many times grey areas, for the purpose of the design of a V-System, the phases extending between donation and transplantation (or disposal) have to be clear regarding their limits and meaning. The process to be covered by the V-System applied to organ donation and transplantation is already defined in *Directive 2010/53/EU*. It includes the following phases: donation, testing, characterization, procurement, preservation, transport, transplantation and disposal. For the purpose of this project, in line with the *Directive*, EFRETOS proposes the following definitions and suggested limits for each of these phases:

- **DONATION:** donating organs for transplantation (*Source: Directive 2010/53/EU*). The non-specific definition provided by the Directive makes it difficult to establish limits for this phase. For practical purposes, and taking into account that donor testing and characterization are considered separately, it is suggested that other critical steps of the donation process in which deviations might affect the quality and safety of the organs to be transplanted are included under this term.

- **TESTING:** carrying out the corresponding complementary tests (i.e. laboratory, radiology, pathology studies) relevant for donor and organ characterization, according to established standards.

- **CHARACTERIZATION:**

  - **Donor characterization:** the collection of relevant information on the characteristics of the donor to evaluate his/her suitability for organ donation, in order to undertake a proper risk assessment and minimize the risks for the recipient, and optimize organ allocation. *(Source: Directive 2010/53/EU)*
  - **Organ characterization:** the collection of the relevant information on the characteristics of the organ needed to evaluate its suitability, in order to undertake a proper risk assessment and minimize the risks for the recipient, and optimize organ allocation. *(Source: Directive 2010/53/EU)*
  - **The exchange of information** on donor and organ characterization within and between centres and other bodies involved is to be included in this phase.

- **PROCUREMENT:** the process by which the donated organs become available. *(Source: modified from Directive 2010/53/EU).*

- **PRESERVATION:** the use of chemical agents, alterations in environmental conditions or other means to prevent or retard biological or physical deterioration of organs from procurement to transplantation. *(Source: Directive 2010/53/EU)*

- **TRANSPORT:** the transfer of an organ from the operating theatre where procurement takes place to the operating theatre where transplantation is to take place.

- **TRANSPLANTATION:** a process intended to restore certain functions of the human body by transferring an organ from a donor to a recipient. *(Source: Directive 2010/53/EU).* The inclusion of patients into the waiting list and the follow-up of the transplanted recipients are both included under this phase.

- **DISPOSAL:** The final placement of an organ where it is not used for transplantation *(Source: Directive 2010/53/EU).*

Another critical step in the process is the **ALLOCATION** of human organs, consisting of the assignment of the donated organs to the corresponding transplant candidates, based on a set of rules (definition modified from *WHO glossary*). A deviation in the procedures of allocation might lead to health risks to patients if there is an incorrect matching. This might concern both the patients (incorrectly) receiving an organ and the patients skipped in the allocation process and thereby not receiving an organ).

For establishing a comprehensive V-System addressing all the phases of the process that might potentially imply a health risk to patients, EFRETOS recommends that Member States consider the inclusion of all the relevant steps in the process in this regard, as depicted in figure 2. Note that these phases **are not necessarily ordered in time sequence**, as they may run parallel or in different order.

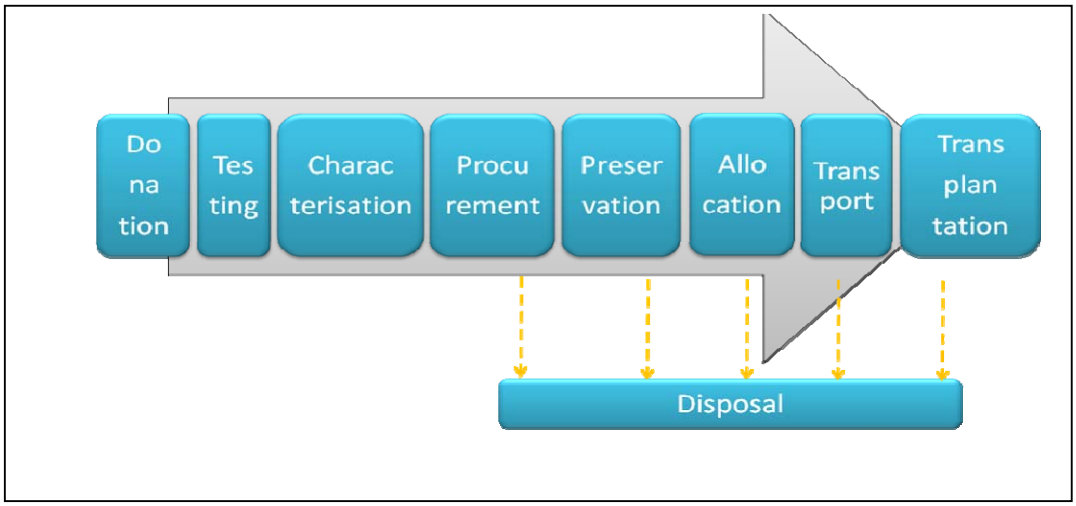


Figure 2: Process extending from donation to transplantation (or disposal) of human organs.

Member States can go into more level of detail in the description of the process, but for the purpose of homogeneity across the EU, the organization of the phases should avoid overlapping of concepts, keeping the same boundaries for the mentioned stages or phases.

10.3.3 Design and elements of a vigilance system of human organs intended for transplantation

Population

The population to be protected by this V-System is composed by **those individuals who have been allocated an organ** or those **who donate organs during lifetime** and may have a health problem as a result of any steps of the chain from donation to transplantation.

Case

A case in a V-System of human organs intended for transplantation would be a Serious Adverse Event (SAE) or a Serious Adverse Reaction (SAR), according to the definitions[22] established in the *Directive 2010/53/EU (article 3).*

"serious adverse event" means any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of a communicable disease, to death or life- threatening, disabling or incapacitating conditions for patients or which results in, or prolongs, hospitalization or morbidity.

"serious adverse reaction" means an unintended response, including a communicable disease, in the living donor or in the recipient that might be associated with any stage of the chain from donation to transplantation that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity.

Network

It is essential that the proposed V-System respects both the administrative and the health care organization within each country. Notwithstanding the necessary respect for the internal organization of each Member State, some common basic items regarding structure and functions need to be considered.

Structure

The network is constituted by the following **bodies** (references from *Directive 2010/53/EC*):

- **Procurement Organization (PO):** "*A health care establishment, a team or a unit of a hospital, a person, or any other body which undertakes or coordinates the procurement of organs, and is authorized to do so by the competent authority under the regulatory framework in the Member State concerned*" (Article 3).

- **Transplantation centre (TC):** *"A health care establishment, a team or a unit of a hospital or any other body which undertakes the transplantation of organs and is authorized to do so by the competent authority under the regulatory framework in the Member State concerned"* (Article 3).

- **Competent Authority (CA):** "An *authority, body, organization and/or institution responsible for implementing the requirements of this Directive*" (Article 3). With regard to an organ V-System, the CA shall "*put in place a reporting system and management procedure for SAE and SAR*" (Article 17).

- **Delegated Body (DB): "***A body deemed suitable under national provisions in whom the CA delegates part or all the tasks assigned to it under the Directive or which assists the CA to carry out its functions*" (modified from Article 17). Hence, the task related to the V-System could be delegated totally or partially to a DB. According to the terms of such delegation, DB would be a node within the network.

- **European Organ Exchange Organizations (EOEO):** *"A non-profit organization, whether public or private, dedicated to national and cross-border organ exchange, in which the majority of its member countries are Member States"* (Article 3). Some CA might totally or partially delegate the task of organ vigilance to an EOEO; hence the EOEO would be acting as a DB. Independent of that, when cases suspected to fulfil criteria occur in countries members of an EOEO, these should also be reported in any case to the EOEO and the EOEO should participate in the management of the cases.

- **European Commission (EC)**

[22] The practical interpretation given by the Consortium to the concepts included in the definitions can be found in section VI. Reporting.

Functions

Regardless of the above, main tasks in a V-System are organized in different levels. As a minimum, the **level of the centre** and that of the **vigilance coordination** have to be recognized (figure 3).

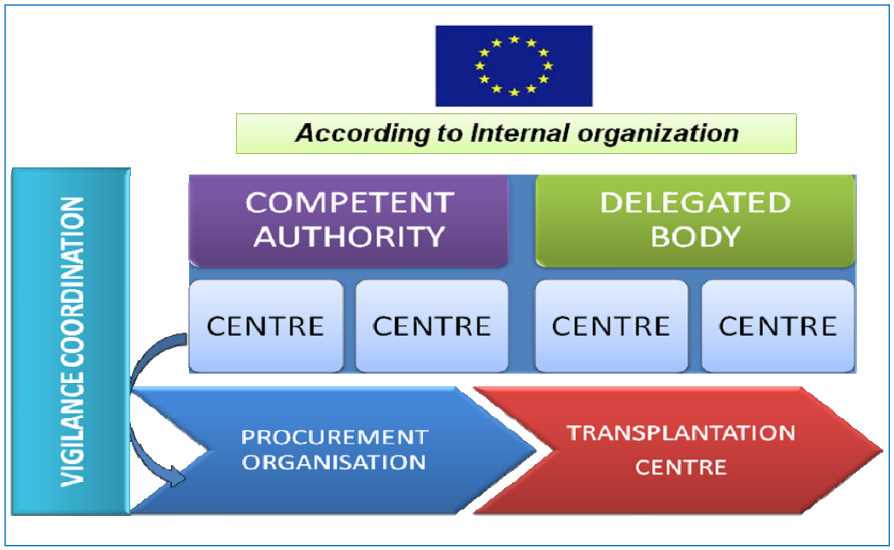


Figure 3: Minimum levels of the Organ V-System. The arrow specifies that the centre level is composed of POs and TCs.

a) Centre level (composed of PO and TC) involves at least the following functions:

- Reporting identified cases.
- Assessment and management of cases at local level in full cooperation with the level of the vigilance coordination (see below), including the alert to other centres concerned.

b) Vigilance coordination level, with at least the following tasks:

- Reception of reported cases.
- Coordination of the assessment and management of cases in cooperation with the centre level and other relevant bodies when applicable, including the alert to other centres concerned.
- Pooled analysis of reported cases and relevant information from other sources.
- Establishment of the procedures for the correct functioning of the V-System.

To properly develop the functions of the vigilance coordination, the assigned body is recommended to have deep knowledge of the organ transplantation system as well as of the related safety matters, the ability of tracing organs, donors and recipients, the capability of contacting the V-System for tissues and cells, and the availability 24 hours / 7 days / 365 days.
This coordination level can be assigned to any of the bodies of the network as described above or even be shared between several bodies, always according to the decision and internal organization of each Member State.

The participation of the EC regarding organs exchanged between Member States will be defined through the on-going implementing procedures foreseen in *Directive 2010/53/EU*.
Additional participation of the EC is to be agreed upon with the network of Competent Authorities.
A summary of the functions of each of the levels of the vigilance network is provided in **Annex 1**.

10.3.4 Resources

Staff

Each node of the network should have appropriate staff, in number and qualification:

a) **Centre level:** on the basis of the most experienced organ V-systems (see Deliverable 3), it is **recommended** the figure of a **"Go to" person,** so professionals identifying cases of SAE and SAR can share this information with a specific figure familiar with the procedures to follow.

b) **Vigilance coordination level:** the assigned body (or bodies) should have specific and **qualified p**rofessionals for **the development** of the aforementioned tasks.

Personnel participating in the network of organ donation and transplantation in a Member State would act as the vigilance network. Whe**n the reporting** activity increases, the need of staff might need to be recalculated.

Equipment

Although a **transmission platform, with high security standards is the ideal,** for setting up the system, the following resources are desirable, as a minimum:

- Telephone (multiconnection and mobile);
- Computer (with data base, electronic mail and Word processor);
- Printer;
- Fax;
- Photocopier.

Operating procedures

Operating procedures, defined as "*written instructions describing the steps in a specific process, including the material and methods to be used and the expected end outcome"* (Source *Directive 2010/53/EU*, Article 3), as foreseen in this Directive, "*shall be adopted and implemented*"(Article 4) for:

- "*The accurate rapid and verifiable reporting of SAE and SAR"*
- "*The management of SAE and SAR"*

Both procedures should be components of the "Framework for Quality and Safety" that Member States (through CA and/or DB) shall establish. Moreover, "these procedures shall specify, inter alia, the responsibilities of PO, EOEO and TC".

Advisory role

Support from a wide range of professional expertise is desirable for an organ V-System: haematology, infectious diseases, intensive care, oncology, radiology, laboratory or epidemiology.

At a centre level, professionals at reach might be easily consulted. At the level of the vigilance coordination, it is recommended that this expertise is also available, if feasible, in the form of an advisory committee. This could also support another type of decisions (i.e. regulatory) taken at a coordination level.

Information service

Information is essential for an effective a V-System. Access to up-to-date publications and results of series published is crucial for assessing cases reported. On the other hand, providing information to others in the form of final reports, periodical reports or alerts is a good element to stimulate reporting.
Sharing SAE/SAR evaluations would also be strongly advisable, on the basis of the principle that all donation and transplant network "nodes" can take advantage from the knowledge and the experience of others, which might help them to prevent similar SAE/SAR. Using secure web based platforms for the appropriate dissemination of this information would also be desirable.

10.3.5 Reporting

Reporting criteria (what to report?)

Directive 2010/53/EU sets down the obligation of reporting SAE and SAR as previously defined. Through this document, the EFRETOS consortium sets down a number of situations fulfilling the mentioned definitions, and which would represent **a minimum set of cases to be reported to the organ V-System in each MS**. In addition, the consortium has also reviewed situations considered out of this minimum, but which could be included under the scope of the V-system in those Member States willing to do so. Both relations of situations are the result of the available experience in running organ V-systems, as well as expert opinions within the group, in accordance with a number of criteria:

- Seriousness understood in the context of the common critical health status of patients in need of an organ transplant or already transplanted, since severe complications in these patients are common.

- Frequent assumption of risks in organ transplantation when balanced with the risk of not proceeding with the transplant procedure. Although evidence needs to be built in this area, through a dedicated follow-up registry (see part I of Deliverable 10), reporting these situations to the V-system would imply an unnecessary overburden on transplant professionals.

- Need to rapidly provide information on newly identified and shared risks for an appropriate management of the transplanted patients.

- Deviations in the procedures applied to the process extending from donation to transplantation are considered to be locally assessed and eventually corrected through a quality control system, foreseen to be developed within the Framework for Quality and Safety, as provided for in the *Directive 2010/53/EU*. As an exception, those deviations with a direct or potentially high impact on the health of the transplanted recipient have been included in the minimum set of cases to be reported to the organ V-System, unless covered by the local quality control system.

SERIOUS ADVERSE EVENTS

Directive 2010/53/EU only establishes the obligation of reporting a SAE if this might potentially imply the risk of a SAR in the recipient or if it in fact leads to a SAR. In the EU setting, an Adverse Event is defined as an "*undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation*". Below is described the minimum set of cases to be reported to the V-System as SAE:

a) Deviations from operating procedures or other Adverse Event during the chain from donation to transplantation that might lead to a SAR, when at least one patient has been transplanted or subjected to anaesthesia for the purpose of transplantation (even if the organ has not been transplanted in the end).

Examples of SAE related to:

- **Testing:** test not performed in accordance with standard criteria; inappropriate interpretation of a test.
- **Characterization:** inappropriate transmission of the information on the donor/organ characterization (HBs-Ag, Anti-HCV, Anti-HIV, HLA, blood group), characterization not performed in accordance with *Directive 2010/53/EU.*
- **Preservation:** fungal contamination of preservation solution.

b) Deviations in operating procedures or steps during the chain from donation to transplantation, with a potential high impact on the health of the patient and easy to be prevented, even if the patient was not subjected to anaesthesia for the purpose of transplantation, unless covered by the local Quality control system.

The Consortium recognizes the need of further work to identify those critical operating procedures or steps. As a minimum, the Consortium agreed on one situation meeting the mentioned criteria: **the inappropriate transmission of the information on the donor characterization with regard to ABO group, Anti-HIV, HBsAg, and Anti-HCV.**

c) Infection or positive serological status discovered in an organ donor (deceased or living) when at least one organ has been transplanted after an appropriate characterization of the donor/organ or after an incomplete characterization based on the particular circumstances of the case (as foreseen in article 7 of *Directive 2010/53/EU*).

Reporting to the system should be limited to those conditions that would have prevented the transplantation of the organ (contraindication) or modified allocation (restricted allocation) should have these been known in advance*.

Example: p24Ag positive in an anti-HIV negative donor identified after the transplantation of at least one organ.

***It is not infrequent that results of cultures or serologies of a donor are known after transplantation. The corresponding information should be communicated from the PO to the TC, directly or through the CA/DB/EOEO as foreseen in the corresponding MS. This is essential for good practice as this information might lead to preventive measures in the recipient. However, this does not imply that all positive cultures/serologies which are received after transplantation (i.e. positive anti-CMV, positive Anti-EBV, positive urine, blood or other types of cultures) should lead to the reporting of the case to the organ V-system, since overburden could occur. As a cut-off point and because they could definitely lead to a SAR, only those conditions that would have prevented the transplantation of the organ or those that could have modified the allocation are considered the ones to be reported to the system.*

d) Malignant tumour discovered in an organ donor (deceased or living) when at least one organ has been transplanted, after an appropriate characterization of the donor/organ or after an incomplete characterization based on the particular circumstances of the case (as foreseen in article 7 of *Directive 2010/53/EU*).

Example: necropsy reveals a glioblastoma multiforme in a donor whose cause of death was a spontaneous intracranial bleeding.

e) Discovery of any other potentially transmissible disease in an organ donor (deceased or living) when at least one organ has been transplanted, after an appropriate characterization of the donor/organ or after an incomplete characterization based on the particular circumstances of the case (as foreseen in article 7 *Directive 2010/53/EU*).

Example: Metabolopathy in the donor undiagnosed at the moment of organ transplantation.

f) Other.

SERIOUS ADVERSE REACTIONS IN TRANSPLANT RECIPIENTS

Below is described the minimum set of cases to be reported to the V-System as SAR in the recipient:

a) Unexpected and serious immunological reactions that are outside of the inherent known risk of the transplantation procedure.

Example: death of a transplant recipient due to non-intended ABO mismatch, because of inappropriate characterization of donor.

b) **Abandoned transplantation procedure due to a deviation in an operating procedure in the process or to other AE involving unnecessary exposure to risk.**

Example: deviation in an operating procedure in the chain from donation to transplantation or other type of AE that leads to discarding the organ, when the potential recipient has already been subjected to anaesthesia.

c) **Unexpected infection or unexpected serological conversion in an organ transplant recipient that might be donor derived or derived from the donation to transplantation process.**

d) **Malignant tumour in an organ transplant recipient that might be donor transmitted.**

e) **Other unexpected disease in an organ transplant recipient that might be donor derived (i.e. a metabolopathy transmitted through liver transplantation).**

f) **Death of recipient that might be the consequence of a SAR.**

g) **Other.**

SERIOUS ADVERSE REACTIONS IN LIVING DONORS

A SAR in the living donor refers to those serious unintended responses in the living donor as a consequence of donation. The importance of the appropriate follow-up of living donors is reflected in international standards, including *Directive 2010/53/EU*. Moreover, the *Directive* establishes the obligation for Member States to develop a dedicated follow-up registry of the living donor to which serious complications derived from the donation process could be systematically reported. Whether (some of) the information provided to this registry is to be complemented with the simultaneous notification of these SAR to the V-system has not been fully agreed by the consortium.

Should SAR in the living donors be decided to be included under the organ V-System by Member States, the following minimum situations are recommended to be notified:

a) **Death of a living donor as a consequence of donation.**

b) **Serious surgical and non-surgical complications in a living donor related to donation.**

c) **Loss of a graft from a living donor before transplantation is performed.**

SITUATIONS NOT INCLUDED IN THE MINIMUM SET OF CASES TO BE REPORTED

The consortium considers the following situations not to be included in the minimum set of cases to be reported mentioned above (1.1 – 1.3). However, individual MS might broaden the scope of their organ V-system and foresee their reporting, as previously explained:

a) **Losses of donors and organs along the process extending from donation to transplantation, if there is not direct exposure to a health risk.**
Losses of donors and organs along this process imply indirect health risks to potential recipients due to the lost opportunities for transplantation. However, these losses may fall under the scope of a quality system. Although Member States might decide that these problems are to be consistently communicated to their V-system, the consortium has considered these situations to be out of the minimum recommendations.

b) **Deviations from operating procedures applied to the process from donation to transplantation, except if exposure to a direct health risk is implied or if significant avoidable potential impact could result (see 1.1.a and 1.1.b).**

c) **Situations where certain risk is known and taken by the clinicians (and the patient) before transplantation is performed. If a health problem associated with this risk occurs in the recipient, reporting should be limited to those situations which are unexpected or expected to occur infrequently.**
Assuming risks is a common practice in organ donation and transplantation, as there are situations in which the clinician weighs up a risk derived from the donor or the process with the risk derived of not proceeding with the transplantation. Reporting such cases to a V-system would generate a remarkable load of work. However, systematically collecting information on the follow-up of recipients from non-standard risk donors in a dedicated registry (and in the registry of registries) is recommended as part of a safety management system in transplantation (see part I of Deliverable 10).

Finally, cases that are to be reported to **other** V-Systems **should be excluded**, in order to avoid duplication of work and inconsistencies due to the necessary differences between systems, i.e.:

- drug related adverse events or reactions;
- devices related adverse events or reactions;
- working accidents, unless the diagnosis was unknown.

Reporting staff (Who reports and to whom)

REPORTING BY WHOM

Effective systems for organ vigilance are primarily dependent on the notification of SAE or SAR by the corresponding professionals at the PO and the TC (centre level). Hence **the culture of notifying** cases should be fostered by all the bodies within the vigilance network.
As previously stated, the appointment of a "**go to" person** at a centre level would be recommended, so professionals identifying SAE and SAR could share the corresponding information and gain knowledge on the procedures to follow. This "go to" person could be then the final responsible for reporting the case.

REPORTING TO WHOM

If a SAE or SAR is identified in a PO or TC, the PO and TC detecting the case should report it **to the vigilance coordinating level**, whatever the body within the network is assuming this role.
When the case involves organs exchanged between Member States or with a third country, "Member States shall ensure the reporting of SAE and SAR in conformity with the procedures established by the Commission (…)" (Article 11.4 of *Directive 2010/53/EU*).
When a case is identified, the immediate actions are ITS PRELIMINARY ASSESSMENT AT A LOCAL LEVEL AND ALERTING OTHER CENTRES POTENTIALLY INVOLVED (both PO and / or TCs).
Alerting other centres and patients at risk is hence part of the management of the case. This is referred to in the corresponding section; however a warning message on this key action is kept in this section, so staff in charge is reminded on the importance of the alert.

Procedures for reporting (how and when to report?)

TRANSMISSION OF INFORMATION

Reporting should be simple and inexpensive. Fax and/or e-mail are good options when an electronic secure alert system is not available. Where fax or e-mails are used, receipt should be checked by phone, especially if there may be other patients at risk. If there is no other option, a phone call might alert the system until the case report arrives.

When it is necessary to establish communication with other Member States, EFRETOS recommends using English for the exchange of information, unless a different language is of common use and/or agreed between those involved.

MINIMUM DATA TO BE REPORTED

The **minimum information to be reported** on identified cases would consist of:

- **Regarding the REPORTER:** identification of the reporter (including contact details), identification of the reporting centre, identification of coordinator/go to person (including contact details). (This information is considered confidential and to be used only for completion, verification and follow- up of the case).

- **ORGAN(s) or other substances CONCERNED:** type of organ (s), its (their) right / left location(s) if applicable, tissue(s) and cells, if applicable.

- **Regarding the DONOR and the RECIPIENT:** necessary information for their identification (identifiers).

- **Regarding the SAR:** start date, detection date, description (nature, severity, characteristics), results of diagnostic tests or other investigations, measures taken* (description, information to centres involved), course and outcome.

- **Regarding the SAE:** start date (or suspected or confirmed start stage), detection date, description (nature, severity, characteristics), related phase of the process (if appropriate), results of diagnostic tests or other investigations, measures taken* (description, information to centres involved), course and outcome.

- **Regarding DISPOSALS (IF ANY):** number and type of organs disposed due to an event) during any stage(s) of the process from donation to transplantation (if it is disposed in the transplantation operating theatre) should be reported. Reason for the disposal.

* *Directive 2010/53/EU* establishes that 'MS shall ensure that operating procedures are in place for the notification, in due time of, […] '*the management measures with regard to SAE and SAR to the Competent Authority*'

REPORTING PERIOD

Directive 2010/53/EU establishes that '*MS shall ensure that operating procedures are in place for the notification in due time, of SAE and SAR (…)*' (Article 11.3.a).
It is advisable that SAE and/or SAR are reported to the coordinating level **IN DUE TIME after its detection. Please note that the concept "in due time" can imply WITHOUT ANY DELAY in certain situations when time is of paramount importance in the prevention of the health problem** (i.e. alerting/ reporting is crucial when a new finding has been identified in the donor which requires reassessing the risk and the benefit when the organs are about to be transplanted).
In order to make the final conclusion of the case (see investigation and management section), a **FINAL INVESTIGATION REPORT is expected to be released by the vigilance coordination level.**

RECEPTION OF REPORTING

Whenever a report is received at the coordinating level, prompt and careful evaluation is necessary to decide where actions are required and if these need to be immediate or can be delayed. It is necessary to ascertain whether the centres concerned have been warned or not.
In any case, an **acknowledgement of receipt** is to be sent to the reporter.

10.3.6 Assessment and management

This section summarizes the steps to be taken in the assessment and management of the identified and reported cases. These steps are not necessarily sequential but developed in parallel. Both

assessment and management need to be developed in close cooperation between the centre level (all centres involved) and the vigilance coordination level.

Alerting other centres concerned

Once a case has been raised, the corresponding mechanisms to alert other centres concerned should be activated. Alerting other centres is essential for the development of therapeutic or preventive measures on potentially affected recipients if appropriate. Moreover, the collective investigation starting as a result of the alert is required for the final assessment of the case (i.e. several recipients of organs from the same donor developed the same condition).
Traceability plays a key role as tracing is the step previous to alerting other teams concerned in the corresponding case. According to *Directive 2010/53/EU*, traceability means *"the ability to locate and identify the organ at each stage in the chain from donation to transplantation or disposal (…)*". Tracing should also include tissues and cells, which implies that a link between different systems should be ensured. In any case, the **capability of tracing should be guaranteed at the level of coordination.**
Notifications and alerts should be delivered in due time, (without delay in specific circumstances – see above) as prompt decisions on the management of the patients might need to be taken. However, the collection of information and the final assessment and report may take longer.

Assessment of cases reported

The first assessment should take place at the level centre, when the case is identified and decided to be reported. The centre reporting the case should ascertain the information relevant in order to make a first assessment of the case and the circumstances in which it occurred.
When receiving a report, the vigilance coordinating level will assess the report with the aim of its confirmation. For that purpose, the following items need to be covered:

- **Verify case report and check the quality of the notification.**
- **Complete the necessary information with the reporting centre: For the appropriate interpretation of the case, the centre mi**ght be asked to provide additional information, including clinical data or results of additional complementary tests.
- **Verify that the centres concerned have been alerted and compile from them all relevant information.**
- **Complete the necessary information with other sources:** information relevant to the assessment of the case might be available in published literature, on-going transplant and living donor follow-up registries (national and international registries) and ad-hoc registries (i.e. Deliverable 3 mentions specific registries / data collection performed in some Member States with regard to non-standard risk donors).
- **Assess SAR cases reported with regard to their ATTRIBUTABILITY to the organ donation and transplantation process or to the donor.** The compiled information should be analysed objectively and systematically in this regard. If necessary, the case may be assessed by a group of experts with different perspectives.

Other preventive and corrective measures

Along with the results of the investigation and assessment of the case, centres should be taking the necessary measures to protect the health of the patients concerned, when appropriate. Such actions, preventive and corrective, should be communicated to the vigilance coordination level. Actions to be taken locally could also be guided by the coordination level, based on the investigation of the case, pooled analysis and evidence gained through the system itself.
In order to raise a conclusion, the case should be followed up and the responses to the centres or other stakeholders registered by the coordination level.

Final report

A final report containing a brief description of the case/s, the assessment and investigation made and its final conclusions, as well as the actions taken should be prepared by the vigilance coordination level and delivered.

Other responses from ca /db

- **OTHER TYPES OF COMMUNICATION TO THE NETWORK:**
  - **Regulatory notifications** might be appropriate in certain situations in which a change in a procedure is recommended.
  - **Rapid Alerts:** a quick notification of a new threat potentially leading to a SAE or SAR coming from other V-Systems should be notified to the network (i.e. West Nile Virus). Those types of notifications are not expected to be transmitted within the organ vigilance network if they are under surveillance by other bodies (i.e. public health); however warnings coming from such bodies that might affect the quality and safety of the organs should be notified top-down to the centres for practical reasons.
- **COMMUNICATION TO OTHER STAKEHOLDERS:** in some specific cases, actions might require intervention with particular stakeholders (i.e. the media, or other health authorities). In these circumstances, it should be the CA/DB the one to react.
- **PERIODICAL REPORTING:** periodical analyses of pooled data of cases reported and might lead to conclusions or recommendations which might be useful to the network. This report should be made at least on a yearly basis by the vigilance coordinating level.

10.3.7 Special issues

Recording of cases and record keeping

All cases reported should be ASSIGNED A NUMBER by the vigilance coordinating level.
All records should be kept in appropriate format for at least 30 years, both at the centre and at the coordinating level, ideally.

Initially, case reports might be managed manually. This will contribute with no doubt to the familiarization with the reporting system and the assessment and management of the cases. However, when the number of notifications increases, it is essential to have a registry available for the cases, allowing an easier management and analysis of the compiled information. For registering the information, internationally recognized and used codification systems are advised to be used (i.e. ICD-9 or ICD-10). This will facilitate further international comparisons.

Education / training

Staff at each of the nodes of the network should be appropriately trained. Besides, each of these nodes should foster the culture of safety in general and reporting in particular, among professionals. This education activity together with appropriate assistance and feedback to the centres represents the best way of preventing underreporting.

Evaluation of the system

As any other V-system, that applied to organ donation and transplantation **should be evaluated on a periodical basis**, with the aim of improving its effectiveness.

10.3.8 Ethical principles applicable to the organ V-system

The following are core ethical principles that should guide the vigilance of organs in the EU setting:

CONFIDENTIALITY

The organ V-System should manage and process personal data and medical information in a confidential and secure way in accordance with *Directive 95/46/EC* (protection of personal data)[23].

COMPROMISE

As any other system of this nature, the organ V-System relies on the collaboration between the different nodes of the network. Participation, which needs to be encouraged at all levels, relies on trust and knowledge of the usefulness of the system. Rigor in the application of procedures and the scientific methodology applied, as well as giving feedback to any input to the system will contribute to the necessary participation. An excellent incentive to foster cooperation is by providing statistics and developing indicators.

NO PUNIBILITY

The system should never be punitive for raising an alert and communicating a case of SAE or SAR. The spurious use of the V-systems with punitive purposes will only lead to loss of confidence in the system, with the subsequent underreporting and waste of resources.

BALANCE BETWEEN NEEDS AND FEASIBILITY

Epidemiologic investigation requires a careful balance between information needs and the feasibility of the tasks. In the world of donation and transplantation, where activity is often determined by urgency and risk assumption, the lack of this balance will lead to a loss of the usefulness of the system.

[23] Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. European Union website. Available at url: http://ec.europa.eu/justice/policies/privacy/docs/95-46-ce/dir1995-46_part1_en.pdf. Last access: February 2011.

10.3.9 ANNEX 1: Functions by level in an organ V-system

	FUNCTIONS IN ORGAN VIGILANCE

CENTRE LEVEL	• Reporting identified cases.
	• Management of cases at local level in full cooperation with the coordination level:
	  • Investigation and first assessment of the case.
	  • Implementation of any corrective or preventive actions.
	• Record of reported and managed cases. Record keeping (30 years).
	• Training and education to foster locally the culture of safety.
	• "Go to" person designated and necessary equipment provided.
	• Development of operating procedures.

COORDINATION LEVEL	• Responses to queries on cases to be reported by the centres.
	• Reception of reported cases.
	• Coordination of the assessment and management of cases in cooperation with the centre level and other bodies, when applicable:
	  • Verification of the case report and revision of the notification, completing the necessary information with the reporting centre.
	  • Tracing, alerting the centres concerned, unless direct alerting between the centres is foreseen by the Member States, and compiling from them all relevant information.
	  • Searching for the necessary information from other sources and pooled analysis of previous cases.
	  • Assessment of the case reported, and if appropriate, its attributability to the process or to the donor.
	  • Proposal of possible corrective and preventive actions for each case.
	  • Delivery of a final report.
	• Other communications to the network or other stakeholders.
	• Periodical reporting.
	• Record of reported and managed cases. Record keeping (30 years).
	• Training and education to foster the culture of reporting.
	• Specific professionals appointed and provided with the necessary resources.
	• Development of operating procedures.
	• Control of the functioning of the V-System.

EUROPEAN COMMISSION	• Set up procedures for vigilance applied to organs exchanged between Member States.

10.3.10 ANNEX 2: Assessment of attributability

Over recent years, some tools have been developed to try to establish to what extent the occurrence of a SAR can be attributed to a donor or a deviation in a procedure. The tools developed so far (by the EU funded project EUSTITE[24], and by the DTAC[25] in the United States) do not result fully satisfactory as either has been developed not taking into account the idiosyncrasy of solid organ transplantation, or is not adapted to the requirements of the EU regulatory setting (see Deliverable 3, State of the Art):

- DTAC tool is specifically prepared to study donor derived diseases. This means that Adverse Reactions derived from the donation / transplantation process (i.e. infectious disease in recipient because of contamination of preservation fluid) are not specifically studied and hence graded, this being a requirement of *Directive 2010/53/EU*.

- The attributability tool applied to blood (per *Directive 2005/61/EC)* and cells and tissues (EUSTITE recommendations) is open to interpretation and not easily adapted to organs. In contrast, specifications provided by DTAC seem to be more objective.

For the common understanding on the management of risk and SARs in organ recipients and organ living donors, EFRETOS recognizes the need of a tool developed ad hoc for these situations in the EU setting, based on objective criteria and applicable to those situations in which the SAR is attributed to a donor transmitted disease and to those attributed to a deviation in the operating procedures applied. Some of the partners are developing their own tools, but this work is on-going and needs further validation before it can be recommended.

[24] EUSTITE website. Available at url: https://www.eustite.org.
[25] Ison MG, Hager J, Blumberg E, Burdick J, Carney K, Cutler J, DiMaio JM, Hasz R, Kuehnert MJ, Ortiz-Rios E, Teperman L and Nalesnik M. Donor-derived disease transmission events in the United States: Data derived by the OPTN/UNOS Disease Transmission Advisory Committee. Am J Transplant 2009; 9: 1929-1935.

10.3.11 ANNEX 3: Summary of EFRETOS recommendations on organ vigilance for the EU setting

Recommendation 1	Developing an effective V-System in the long term needs **vision, dedication, and institutional support.**
Recommendation 2	The objective of an organ V-System is to **prevent** the avoidable occurrence of a health problem to organ transplant recipient(s), associated with the donor or with the different procedural steps extending from donation to transplantation and to prevent the avoidable occurrence of a health problem to living organ donors, associated with donation, testing, characterization or procurement.
Recommendation 3	As for any other system, the main tasks to be carried out in organ vigilance are: • **Reporting of identified cases (SAE and / or SAR).** • **Assessment of the information reported (including tracing).** • **Management of the case.**
Recommendation 4	**For** establishing a comprehensive and homogeneous organ V-System in the EU context, EFRETOS recommends a **common basic structure and definitions for the phases extending from donation to transplantation / disposal** (section 3). If Member States wish to develop further detail in the description of the process, it would be advisable that they avoid overlapping of concepts, keeping the **same boundaries for all countries**.
Recommendation 5	It is essential that **the proposed organ V-System respects both the administrative and the health care organization within each country.** Notwithstanding the necessary respect for the internal organization of each MS, some common basic items regarding structure and functions need to be considered. • Two roles should be clearly differentiated: that of the **centre level** (composed of PO and TC) and that of the **vigilance coordination level.** • To properly develop the functions of the vigilance coordination, the assigned body is recommended to have **deep knowledge** of the organ transplantation system as well as of the related safety matters, the **ability of tracing** organs, donors and recipients, the capability of **contacting the V-System for tissues and cells**, and the **availability 24 hours / 7 days / 365 days.** • This coordination level can be **assigned to any of the bodies of the network or even be shared between several bodies**, always according to the decision and internal organization of each Member State.
Recommendation 6	Personnel participating in the network of organ donation and transplantation in a Member State could act as the vigilance network. When the reporting activity increases, the need of staff might need to be recalculated. At a centre level, on the basis of the most experienced organ V-systems, it is recommended the figure of a **"Go to" person**, so professionals identifying cases of SAE and SAR can share this information with a specific figure familiar with the procedures to follow. At the Vigilance coordination level, the assigned body (or bodies) should have **specific and qualified professionals** for the effective development of the corresponding tasks.
Recommendation 7	Although a V-System can be set up with a limited number of material resources, a **platform for the transmission and management of the information, with high security standards**, would be the ideal.

Recommendation 8	**Support from a wide range of professional expertise** is desirable for an organ V-System. At a centre level, professionals at reach might be easily consulted. At the level of the vigilance coordination, it is advisable that this expertise is also available, if feasible, in the form of an advisory committee.
Recommendation 9	The EFRETOS consortium has agreed a number of situations fulfilling the definitions of SAE and SAR, as defined in *Directive 2010/53/EU* (section 6.1). These situations are the result of the available experience in running organ V-systems, as well as expert opinions within the group, in accordance with a number of criteria, namely: • **Seriousness** understood in the context of the common critical health status of patients in need of an organ transplant or already transplanted, since severe complications in these patients are common. • **Frequent assumption of risks** in organ transplantation when balanced with the risk of not proceeding with the transplant procedure. • **Need to rapidly provide information on newly identified and shared risks.** • Inclusion of specific **deviations in** the **procedures** applied to the process extending from donation to transplantation when they imply a direct or a potentially high impact on the health of the transplanted recipient, unless covered by the local Quality control system. **EFRETOS recommends that all Member States report to their organ V-system at least this minimum set of cases, for the purpose of homogeneity and common understanding in the EU setting**, even though Member States might broaden the scope of their local V-System.
Recommendation 10	Bearing in mind that the *Directive* establishes the obligation for Member States to develop a dedicated follow-up registry of the **living donor** to which **SAR** derived from the donation process could be systematically reported, the consortium has not reached a unified interpretation on whether (some of) the information provided to this follow-up registry is needed to be complemented with the simultaneous notification of these SAR to the V-system. **A clarification** on such issue **should be provided at European level.**
Recommendation 11	When it is necessary to establish communication between Member States or with third countries, it is recommended using **English for the exchange of information**, unless a different language is of common use and/or agreed between those involved.
Recommendation 12	It is advisable that SAE and/or SAR are reported to the coordinating level **IN DUE TIME** after its detection. Please note that the concept ”in due time” can imply **WITHOUT ANY DELAY** in certain situations when time is of paramount importance in the prevention of the health problem.
Recommendation 13	**Alerting other centres is essential** for the development of therapeutic or preventive measures on potentially affected recipients if appropriate. Moreover, the collective investigation starting as a result of the alert is required for the final assessment of the case.
Recommendation 14	A **final investigation report** containing a brief description of each case, the assessment made and its final conclusions, as well as the actions taken, is recommended to be released by the vigilance coordination level.
Recommendation 15	**Staff at each of the nodes of the network should be appropriately trained and motivated regularly.** Hence, each of the levels within the vigilance network should foster the culture of safety in general and reporting in particular, among professionals. This education activity together with appropriate assistance and feedback to the centres represents the best way of preventing under reporting.
Recommendation 16	**Ethical principles** guiding an organ vigilance system should include, at a minimum, **confidentiality, compromise of all stakeholders involved, no audibility, and feasibility** (unnecessary overburden of the network should

	be avoided).
Recommendation 17	**A common tool for assessing attributability of SAR in organ recipients and / or organ living donors is necessary in the EU setting.** This tool should be based on **objective** criteria and be applicable to those situations in which the SAR is attributed to a donor transmitted disease and to those attributed to a deviation in the operating procedures applied. Some of the partners are developing their own tools, but this work is on-going and needs further validation before it can be recommended.
Recommendation 18	All recommendations above are based on the limited experience on organ Vigilance and on expert opinions. Hence, **a pilot experience to validate these recommendations is essential and a matter of further work.**

11 Pilot study

An important part of the EFRETOS project is to test the technical feasibility of a registry of registries, referred to as the European Registry, using a pilot study. The pilot study will address a question of scientific interest by combining data from as many national registries as possible.

The purpose of the pilot is to provide an indication about the ease with which different countries may be able to contribute to a European Registry, to identify problems in data format and submission, and to provide evidence that the functional requirements - such as organizational and data management issues - of a European Registry can be achieved. Because data for the pilot study will be collected, organized and maintained in a different manner from the way in which the European Registry will be designed, and the scope of the study is necessarily limited, this pilot will be limited value in setting legal and technical requirements for a European Registry. However, it is expected to provide “proof of concept”.

11.1 Design of the pilot study

The pilot study is designed to evaluate one and five year graft survival rates following kidney only-transplantation from a living or deceased donor. Comparisons between participating countries can then be made, with adjustment for between country differences in some important risk factors. The results of this study may have very limited scientific value, due to the lack of homogeneity in the provision of data from each partner. To avoid misinterpretation, the countries have been anonymized throughout.

Primary end points

Time from transplantation to graft failure

Study hypothesis

Evaluate post-transplant outcome data among countries; study the impact of confounding factors on graft and patient survival; and study the effect of confounding factors within each country.

Scope of Study

The study will encompass all types of donor, namely heart beating (deceased following brain death, DBD), non-heart beating (deceased following cardiac death, DCD) and living. Non-heart beating donors will further be categorized into controlled (Maastricht category 3, 4) and uncontrolled (Maastricht category 1, 2). The study will include kidney-only transplants in recipients of all ages, whether a single or double kidney are transplanted. Patients who had a kidney transplant before January 1, 2000 and then a later kidney transplant in the study period should be included; note that the graft number will be greater than one for such patients.

Time period

All patients receiving a transplant between January 1, 2000 and December 31, 2008 will be included.

11.1.1 Variables required for data set

The variables required for the data set, and the defined levels of categorical variables are listed below.

- Patient identifier [identifier used by national registry to label recipient]
- Donor type [1 = deceased heart beating, 2 = deceased non-heart beating (controlled), 3 = deceased non- heart beating (uncontrolled), 4 = living, 9 = unknown]
- Age of donor [in years, 99 = unknown]
- Gender of donor [1 = male, 2 = female, 9 = unknown]
- Age of recipient at time of transplant [in years, 99 = unknown]
- Gender of recipient [1 = male, 2 = female, 9 = unknown]
- Primary disease of recipient [1 = glomerular disease, 2 = diabetes, 3 = polycystic kidney, 4 = other, 9 = unknown]
- Single or double kidney transplanted [1 = single, 2 = double, 9 = unknown]
- Number of mismatches at A locus (broad antigen level) [0 = zero, 1 = one, 2 = two, 9 = unknown]
- Number of mismatches at B locus (broad antigen level) [0 = zero, 1 = one, 2 = two, 9 = unknown]
- Number of mismatches at DR locus (broad antigen level) [0 = zero, 1 = one, 2 = two, 9 = unknown]
- Total number of mismatches at A, B and DR loci [0 = zero, 1 = one, …, 6=six, 9 = unknown]
- Kidney graft number [1 = first, 2 = second, 3 = third, …, 9 = unknown]
- Total ischemic time (defined as time from arterial clamping in donor to reperfusion in the recipient) [time in hours, 99.9 = unknown]
- Date of transplant [day, month, year]
- Date of graft failure [day, month, year, 999 = unknown]
- Date of death [day, month, year, 999 = unknown]
- Date patient last known to be alive [day, month, year, 999=unknown]

11.1.2 Variable names and specification of values

To facilitate the combination of data from different countries, use of a common name for each of the variables in the data set was requested. These names, and the corresponding specifications of each variable, are shown below.

Variable	Variable name	Specification
Patient identifier	pt_id	characters
Donor type	dtype	integer
Age of donor	dage	integer
Gender of donor	dsex	integer
Age of recipient at transplant	rage	integer
Gender of recipient	rsex	integer
Primary disease of recipient	rpd	integer
Single or double kidney	tx_type	integer
No of mismatches at A locus	mma	integer
No of mismatches at B locus	mmb	integer
No of mismatches at DR locus	mmdr	integer
Total number of mismatches	total_mm	integer
Graft number	tx_no	integer
Total ischemic time	it	decimal (nn.n)
Date of transplant	tx_date	date (dd/mm/yy)
Date of graft failure	fail_date	date (dd/mm/yy)
Date of death	death_date	date (dd/mm/yy)
Date patient last known to be alive	alive_date	date (dd/mm/yy)

11.2 Definition of success indicators

A number of quantities will be used to gauge the success, or otherwise, of the pilot study. Some of these concern how the arrangements for the collection and combination of data have worked; others will focus on checks of internal data consistency. The indicators that have been used are listed below.

- Number of countries who supply national data, in a timely manner, out of the six EFRETOS partners (France, Italy, The Netherlands, Scandiatransplant, Spain, United Kingdom).
- Number of countries who provided data in a format that required less than ten minutes data manipulation to add to the data base, out of those who provided data.
- The percentage of missing values for each factor specified in the protocol.

During the data merger process, a record will be kept of any difficulties that occur in working with the data sets that have been submitted. This will include a note on the time taken to overcome any problems. A summary of any difficulties will be presented.

As was stressed at the outset of this chapter, data for the pilot study is being submitted and managed in a different manner from the way in which the European Registry will be designed. This pilot study is not expected to provide much guidance on the legal and technical requirements for a European Registry, and for this reason, we have not used any indicators of success in these areas.

11.3 Draft protocol for analysis of data from the pilot study

To demonstrate the feasibility of using data from a European Registry to inform clinical practice, the pilot study was designed to provide information on areas of interest to the participants. Specifically, the pilot study is designed to compare the characteristics of donors and recipients between countries and to examine geographical variation in outcomes. Because the pilot study has been designed to obtain information on a relatively small number of variables related to the outcome of a kidney transplant, a full analysis of the reasons for any observed differences between countries will not be possible. In particular, differences identified between countries may be directly attributable to differences in the demographic variables that we have no information on, particularly ethnicity, differences in patient management, and differences in transplant practice. However, bearing in mind these limitations, a number of analyses will be carried out to demonstrate the possibilities of a European Registry.

An outline of the analyses to be carried out was agreed with all participating countries, prior to data analysis, and this is summarized below.

11.3.1 Outline analysis

All analyses below based on known data values only.

Summary of data obtained (e.g. number of transplants by country).

Table showing means or percentages for each factor in the data set, by country.

Percentage of each donor type for each country. Bar chart; chi square test. Comment on comparison of percentages of HB, NHB, and living donors.

Mean donor age and recipient age for each country. Histograms; One way ANOVA. Comment on comparison of mean ages.

Percentage of male donors and recipients in each country. Bar chart; chi square test. Comment on any differences.

Distribution of forms of primary disease. Bar chart; chi square test. Comment on any differences in pattern between countries.

Proportion of single transplants carried out. Bar chart; chi square test. Comment on any differences in proportions.

Average mismatch score at A, B and DR locus, separately. Bar chart for each locus; chi square test. Comment on any differences in average score.

Calculate total mismatch score where data are given separately for A, B and DR mismatches and compare across countries.

Percentage of 000 mismatches transplants reported by each country.

Proportion of first, second and third transplants. Bar chart; chi square test. Comment on any differences.

Total ischemia time. Histogram for each country. One way ANOVA between countries. Comment on any differences in distribution.

Graft survival rates and 95% confidence limits at one and five years. Kaplan-Meier estimate of survivor function for each country. Log rank test to compare survival between countries. Comment on results.

Adjusted analyses based on Cox model. Differences between countries after adjusting for other factors in the data set. Does the impact of any factor on graft survival differ between countries; country x factor interactions. Numerical and graphical display of hazard ratios by country. Discussion of results.

11.4 Conduct of the pilot study

Five countries participated in the pilot study. They were asked to submit data in the format described in section 4.1. In addition, for the purposes of the pilot, countries were asked to submit data as a csv file, and to password protect files for data security. Only one country sent their file as csv file, but other file formats were able to be accommodated after some manipulation. Two countries password protected their files. The data set for the pilot study did not include any patient identifiable or sensitive information so there was minimal risk in this case, but when considering the mechanism for countries to send data to a European Registry, data security would need to be improved. It is unclear why countries did not password protect their files, as requested.

All five data sets required some manipulation to enable them to be compiled into one data set for analysis and the specific manipulation required is outlined below. Items highlighted in bold relate to deficiencies in the definition and specification of the pilot study data set, which could be improved based on the experience of the pilot study and with the inputs of Work Package 4. All non-bold items relate to countries failing to follow the pre-specified data set format for the pilot study. In general, the level of adherence to the required format was relatively poor, and required a significant period of time to rectify.

Data was manipulated in Microsoft Excel and SAS, and all analysis was performed using SAS.

Country A

- SAS data set, easy to manipulate.
- **Details of whether non-heart beating donors were controlled or uncontrolled were unknown for some donors.**
- **Total ischemia time is not collected, so was calculated from CIT + 15 minutes.**
- There was an unusually high proportion of patients whose graft failed on the day of transplant. After clarification, amendments were made to remove failure dates for those who died with a functioning graft.

Country B

- Excel data set, easy to manipulate.
- Variable names were not assigned as specified.
- Ischemia time provided to 9 decimal places so had to be rounded.
- **Primary disease sent as EDTA codes which had to be grouped appropriately.**
- Duplicate records in the data set
- There was an unusually high proportion of patients whose graft failed on the day of transplant. After clarification, amendments were made to remove failure dates in these cases, as unable to identify those who died with a functioning graft.

Country C

- SAS data set, easy to manipulate
- Donor age and recipient age provided to 9 decimal places so had to be rounded
- Unknown values indicated by "-" rather than the specified unknown value for HLA mismatch variables and IT
- Transplant number had 0 entries, suggesting that it was the number of previous transplants, rather than the transplant number of this graft and required amendment.
- There were no duplicate patient-IDs in the data set, indicating that none of the patients were regrafted. This was surprising, and may suggest that a transplant identifier was provided, rather than a patient identifier.

Country D

- csv data set, but separated by semicolons and these were sometimes missing which required quite a lot of manipulation.
- Dates provided in words in national language, which required translation and then converting to numeric values.
- Unknown values indicated by rather than the specified unknown value for donor age, transplant number and IT.
- Transplant on 1 January 2009 had to be removed.
- **Primary disease sent as EDTA codes which had to be grouped appropriately...**
- Patients with combined liver/kidney transplants were included and could not easily be identified for removal.
- Duplicate records in data set.
- Follow-up only available for the whole cohort until December 2007 but some death dates provided after this date and had to be removed to avoid potential biases.

Country E

- txt file, easily manipulated.
- Some ischemia times exceeded 100 hours and were changed to 99.9 to reflect unknown values.

11.5 Results from the pilot study

11.5.1 Success indicators

Five of the six EFRETOS partner countries were able to supply national data, in a timely manner, for the pilot study. Spain was unable to contribute data as there is no established national registry of kidney transplant outcomes in Spain and the compilation of regional data could not be undertaken in the timescales required.

Three of the five countries participating provided data in a format that required less than ten minutes data manipulation to add to the data base. 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. While the last of these may be resolved with the provision of more detailed definitions of each field in the data base under Work Package 4 of EFRETOS, the remaining issues are unlikely to be addressed elsewhere in the project. The required data format was clearly specified in advance, but two countries provided data that required significant manipulation prior to being incorporated. 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.

The proportion of missing data for each field requested is summarized in table 1 for each country. Data was most frequently missing for primary disease and ischemia time, but there was also missing data for HLA mismatch for around 10% of records. Ischemia time was missing for all living donor transplant in countries D and E.

Table 1 Percentage of missing data for each variable

	All	Country A	Country B	Country C	Country D	Country E
N	65,194	17,625	5,701	21,900	8,417	11,551
Donor type	0.0	0.0	0.0	0.0	0.0	0.0
Donor age	>0.0	>0.0	>0.0	0.0	>0.0	0.1
Recip age	>0.0	0.0	0.0	0.0	0.0	>0.0
Donor gender	0.1	0.4	0.0	0.0	0.1	0.0.
Recip gender	>0.0	>0.0	0.0	0.0	0.0	0.0
Primary disease	20.1	37.0	15.3	11.8	36.3	0.5
Transplant type	0.0	0.0	0.0	0.0	0.0	0.0
Mismatches at A locus	10.7	6.1	34.8	0.2	0.0	33.8
Mismatches at B locus	10.7	6.1	34.8	0.2	0.0	33.8
Mismatches at DR locus	11.7	6.1	35.0	0.2	0.0	39.2
Total mismatches	11.7	6.1	35.1	0.2	0.0	39.2
Transplant number	>0.0	0.0	0.0	0.0	0.2	0.0
Ischemic time	21.1	8.8	49.3	2.7	88.9	11.4

11.5.2 Results and conclusions from the data analysis

All transplants

Figure 1 shows the total number of kidney transplants provided by each country as part of the pilot. The number of transplants reported ranged between 5,701 and 21,900 reflecting the different levels of transplant activity within each country.

Figure 2 shows the distribution of donor types across countries, which varied significantly ($p<0.0001$). Country B had the largest proportion of living donor transplants and non-heart beating donor transplants at 40.6% and 22.6% respectively. By contrast, country E performed 8.1% living transplants and no non-heart beating transplants.

Figure 1 Number of transplants reported across countries

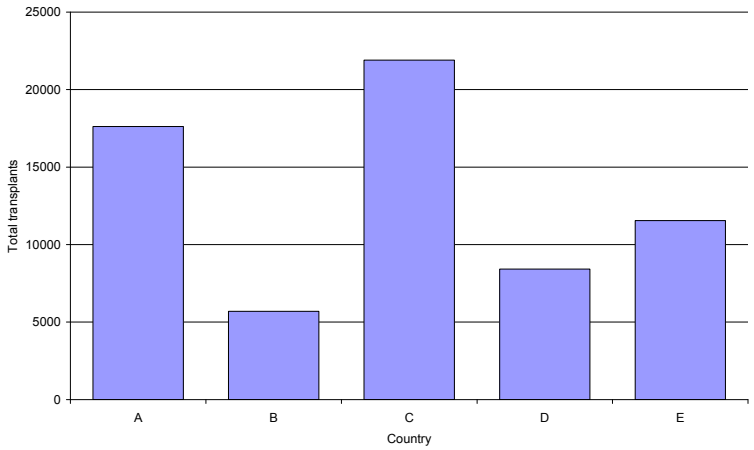
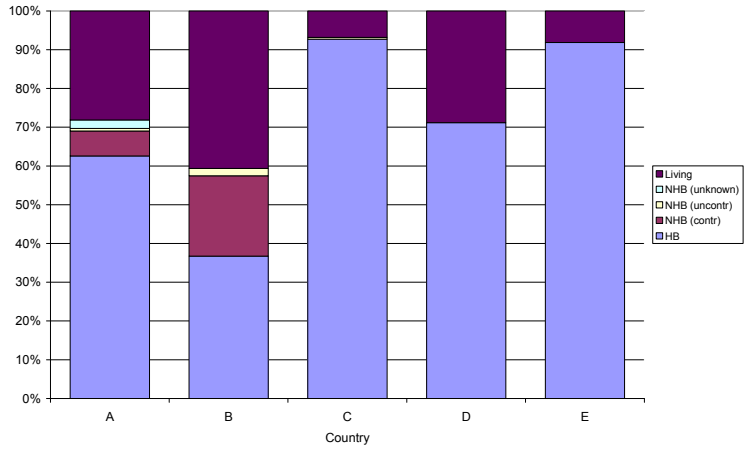


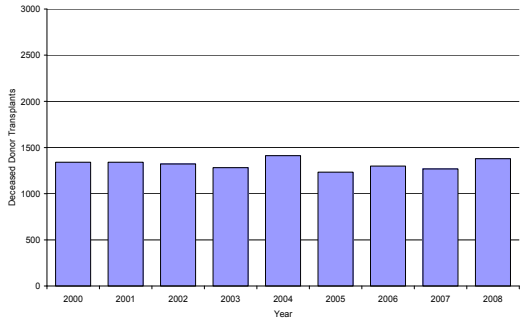
Figure 2 Donor type distribution across countries



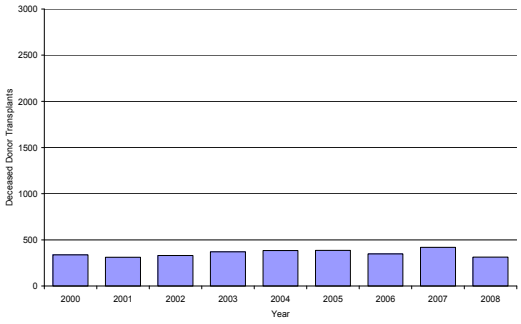
Focusing on adult transplants only, Figure 3 presents the number of deceased donor transplants performed each year in each country, and Figure 4 presents the corresponding information for live donor transplants. The largest number of deceased donor transplants were performed in Country C. Deceased donor transplantation was constant over the time period of the pilot study in Countries A, B and D. Country C saw an increase in transplantation over the years and Country E was unable to provide data for deceased donor transplants performed in 2000 and 2001.

The largest number of living donor transplants were performed in Country A. Countries A, B and C saw rapid increases in living donor transplantation over the time period of the pilot study, with the number of transplants performed in a year more than doubling between 2000 and 2008. Living donor transplants increased more modestly in Country D, and remained relatively static in country E, with no living donor transplant data available for 2000.

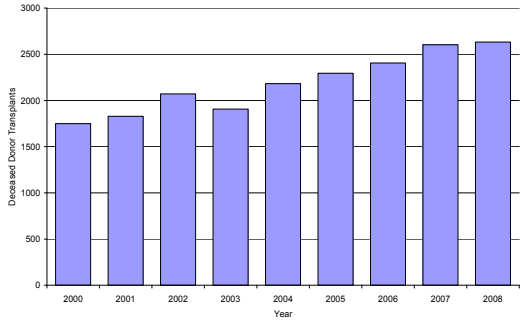
Figure 3 Number of deceased donor transplants by year for each country



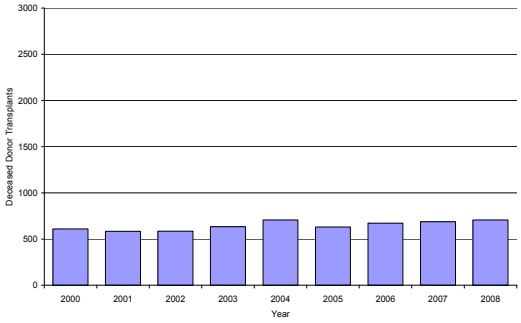
Country A



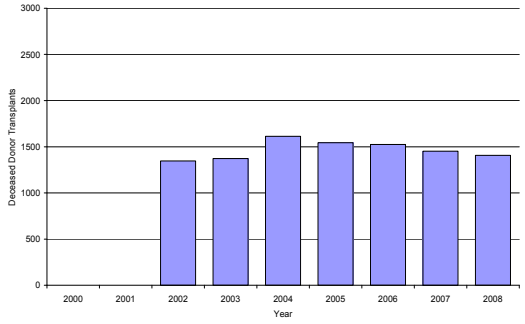
Country B



Country C

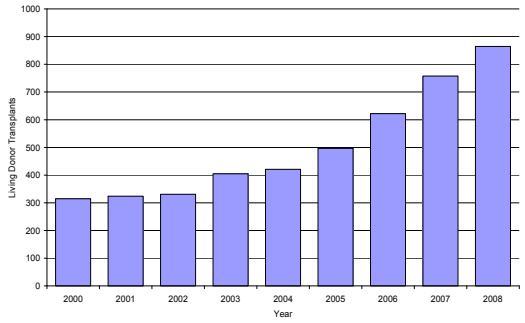


Country D

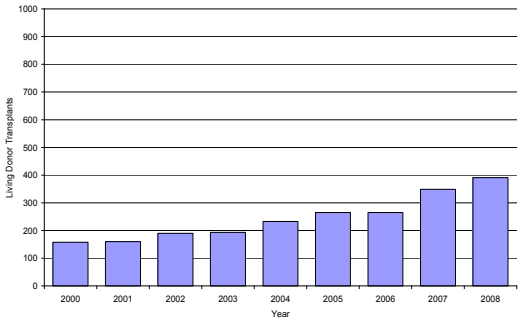


Country E

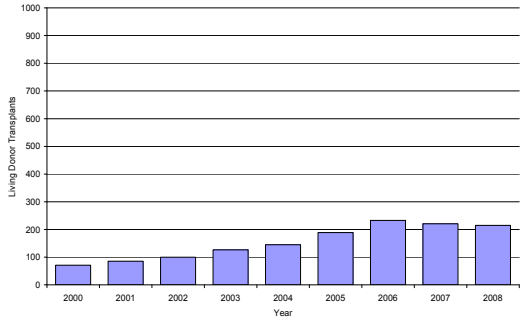
Figure 4 Number of living donor transplants by year for each country



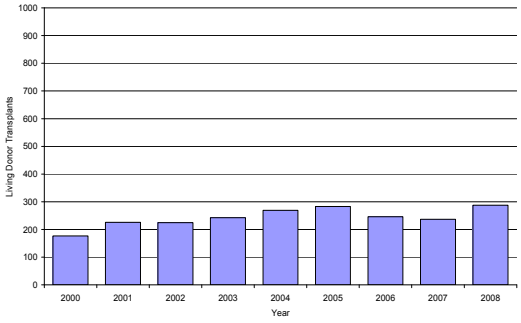
Country A



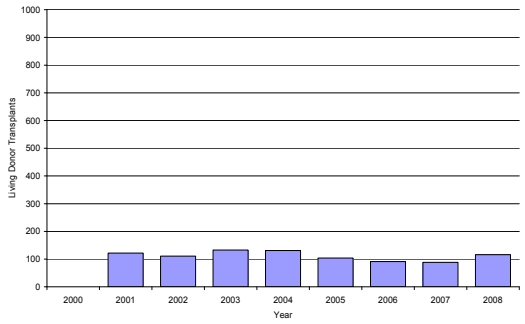
Country B



Country C



Country D



Country E

Adult deceased donor transplants

Table 2 describes the characteristics of all adult deceased donor kidney transplants in each of the five participating countries for known data values only.

Donor type varied significantly between countries with the largest proportion of non-heart beating donor transplants performed in country B (39.9%), while countries D and E only performed heart beating donor transplants.

Mean donor age ranged from 45.0 years in Country A to 49.5 years in Country E, as illustrated in Figure 5, and a one-way ANOVA indicated that this difference was statistically significant.
Similarly, mean recipient age varied significantly between countries, with a minimum of 47.0 years in Country A and a maximum of 51.1 years in Country B, as shown in Figure 6.

Figures 7 and 8 present the donor and recipient gender distribution, respectively, across countries. The majority of donor and recipients were male in all countries, but the proportion of male donors

varied from 51.7% to 61.1% (p<0.0001), and the proportion of male recipients varied from 58.9% to 64.9% (p<0.0001).

Figure 9 presents the distribution of primary diseases across countries, and the distributions differ significantly. Country D transplanted the largest proportion of diabetic patients (17.5%), while in Country E only 1.7% of transplants were for diabetic patients. Countries A and C had very similar primary disease distributions.

The proportion of double kidney transplants performed is shown in Figure 10 and differed significantly between countries, and ranged from 0.4% in Country D to 5.9% in Country E.

Figures 11 to 13 present the mismatch distribution at the A, B and DR loci respectively, while Figure 14 presents the total mismatch scores and Figure 15 presents the proportion of 000 mismatch transplants performed. HLA matching differed significantly between countries, with countries A and B have lower mean mismatch scores than countries C to E. The proportion of 000 mismatch transplants performed also reflected this pattern, accounting for around 15% of transplants in countries A and B, but between 1% and 7% of transplants in the other three countries.

Figure 16 presents the distribution of graft number across countries. This differed significantly across with countries, with Country E performing far less regrafts (5.2%) than the other four countries (all >15%).

Mean ischemia time ranged from 14.9 hours in Country E to 20.2 hours in Country B, as shown in Figure 17, and this difference was statistically significant.

Table 2	Characteristics of adult deceased donor kidney-only transplants						
	All	**Country A**	**Country B**	**Country C**	**Country D**	**Country E**	**p-value**
Donor type							
HB	94.1	86.3	60.1	99.5	100.0	100.0	<0.0001
NHB (contr.)	4.5	9.5	36.5	0.0	0.0	0.0	
NHB (uncontr.)	0.6	1.0	3.4	0.5	0.0	0.0	
NHB (unknown)	0.8	3.3	0.0	0.0	0.0	0.0	
Mean recip. age (years)	48.6	47.0	51.1	48.3	50.7	49.0	<0.0001
Donor gender (%male)	56.5	52.7	51.7	61.1	53.9	54.7	<0.0001
Recip. gender (% male)	62.5	61.9	58.9	61.7	64.1	64.9	<0.0001
Primary disease (%)							
Glomerular	32.1	32.2	21.9	31.1	26.9	38.3	<0.0001
Diabetes	8.1	9.3	6.5	9.4	17.5	1.7	
Polycystic	15.4	17.4	12.7	16.8	16.8	11.7	
Other	44.5	41.2	58.9	42.8	38.8	48.4	
Transplant type (% single kidney)	98.0	99.0	99.4	98.6	99.6	94.1	<0.0001
Mismatches at A locus (%)							
0	23.9	27.3	39.7	19.4	27.5	20.5	<0.0001
1	53.8	55.4	50.2	53.2	52.6	55.6	
2	22.4	17.4	10.1	27.4	19.9	23.8	

Table 2 (cont.) Characteristics of adult deceased donor kidney-only transplants

	All	Country A	Country B	Country C	Country D	Country E	p-value
Mismatches at B locus (%)							
0	16.4	23.2	27.0	12.6	15.2	12.1	<0.0001
1	52.7	62.0	55.5	47.5	49.8	53.9	
2	30.9	14.8	17.6	39.9	35.0	34.0	
2	12.9	4.6	5.2	18.8	17.3	8.9	
Total mismatches (%)							
0	7.2	15.8	14.5	3.1	6.5	1.0	<0.0001
1	8.7	9.4	11.3	7.8	7.2	10.5	
2	22.4	33.2	29.3	15.1	22.1	22.6	
3	27.0	25.3	29.7	25.4	30.1	31.2	
4	24.4	12.1	11.0	33.7	19.1	29.1	
5	8.1	3.2	3.3	11.9	11.3	4.6	
6	2.2	1.0	1.0	3.0	3.8	1.0	
000 mismatch txs (%)	7.1	15.8	14.4	3.1	6.5	0.9	<0.0001
Transplant number (%)							
1	86.4	84.3	82.9	84.3	84.5	94.8	<0.0001
2	11.5	13.1	13.6	13.4	12.5	4.7	
3 or more	2.2	2.6	3.5	2.4	3.0	0.5	
Mean ischemic time (hours)	18.6	19.0	20.2	20.1	17.2	14.9	<0.0001

Figure 5 **Donor age distribution across countries**
Box and whisker plots show the median value, first and third quartiles, and 5th and 95th percentiles

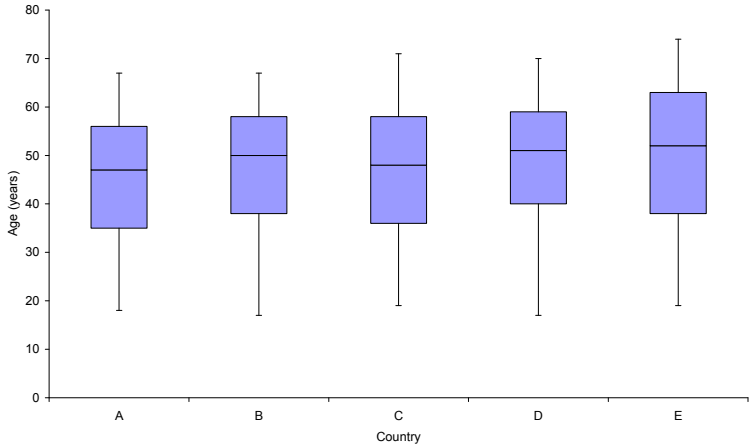


Figure 6 **Recipient age distribution across countries**
Box and whisker plots show the median value, first and third quartiles, and 5th and 95th percentiles

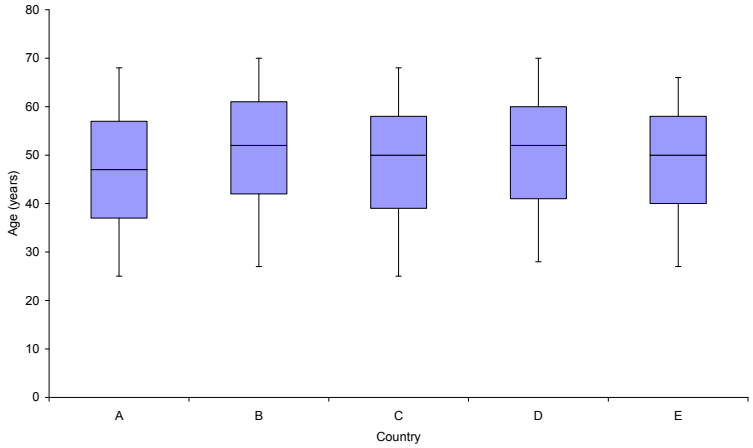


Figure 7 Donor gender distribution across countries

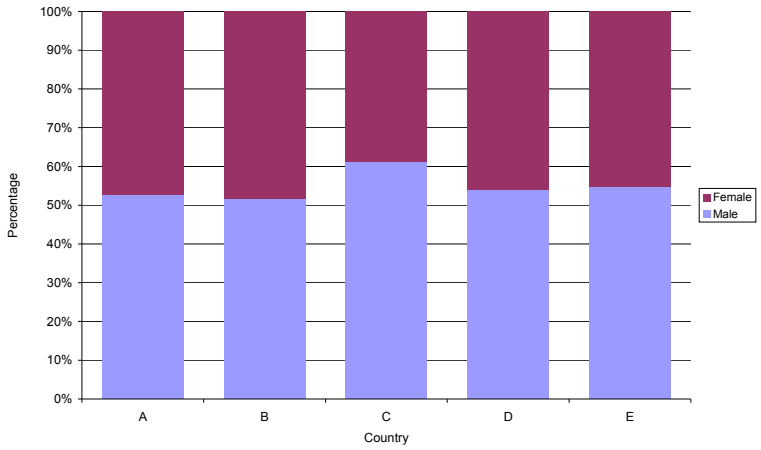


Figure 8 Recipient gender distribution across countries

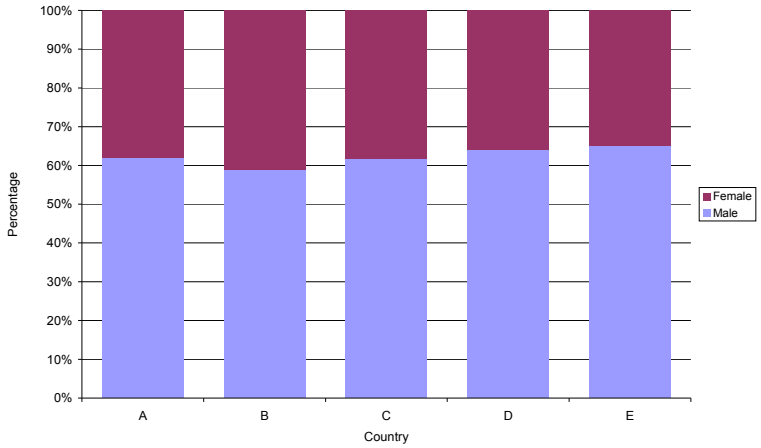


Figure 9 Recipient primary disease distribution across countries

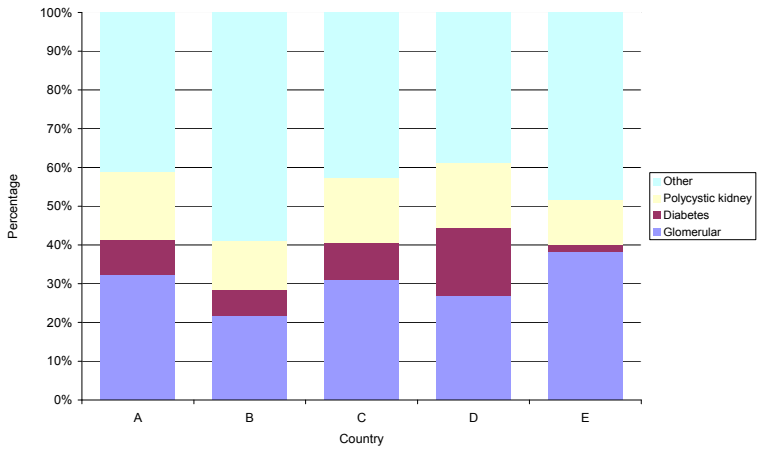


Figure 10 Transplant type distribution across countries

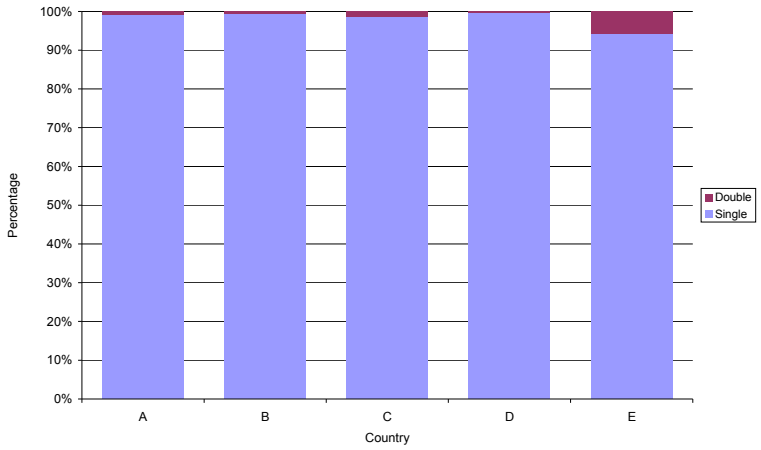


Figure 11 A locus mismatch distribution across countries

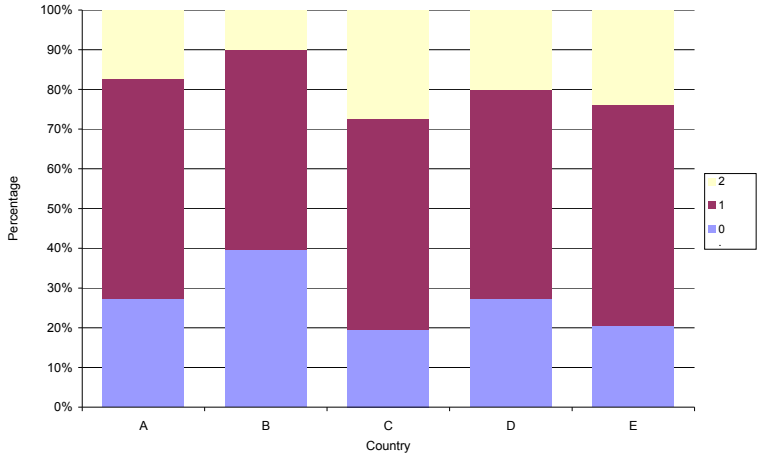


Figure 12 B locus mismatch distribution across countries

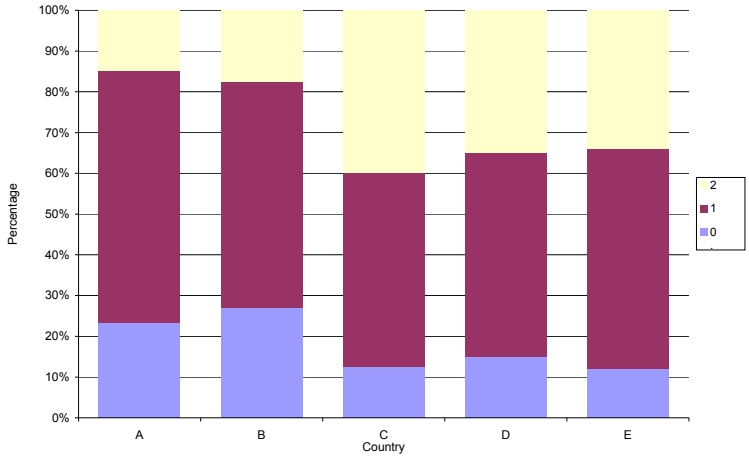


Figure 13 DR locus mismatch distribution across countries

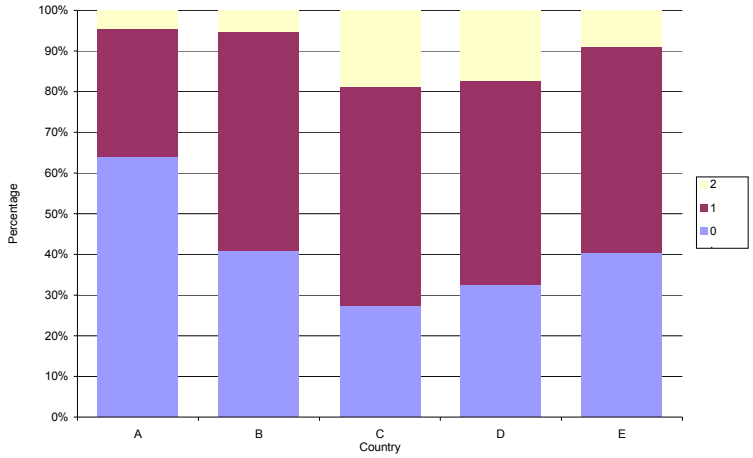


Figure 14 Total mismatch score distribution across countries

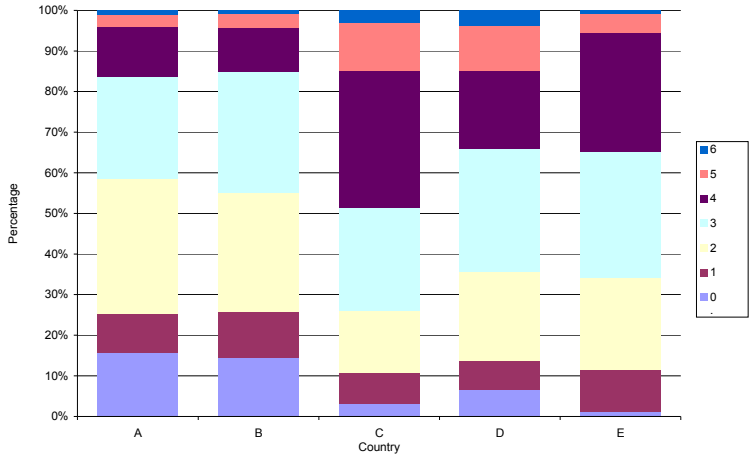


Figure 15 Proportion of 000 mismatch transplants across countries

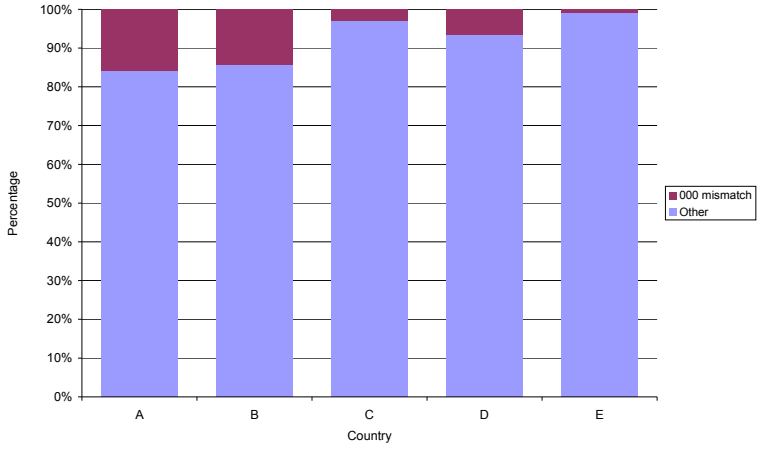


Figure 16 **Transplant number distribution across countries**

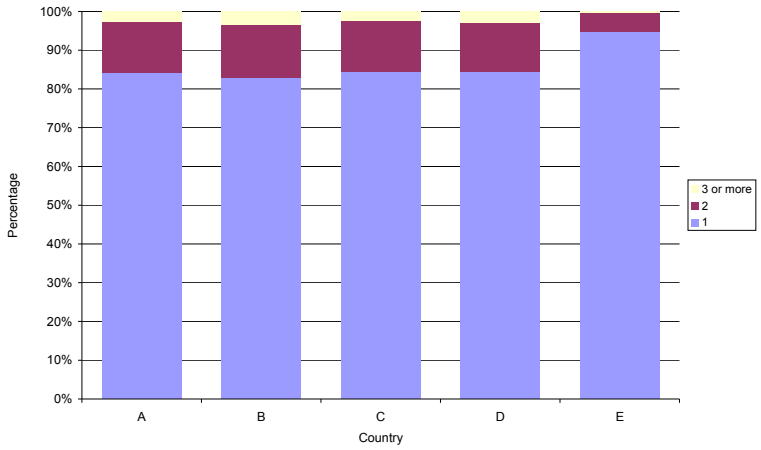


Figure 17 **Ischemic time distribution across countries**
Box and whisker plots show the median value, first and third quartiles, and 5th and 95th percentiles

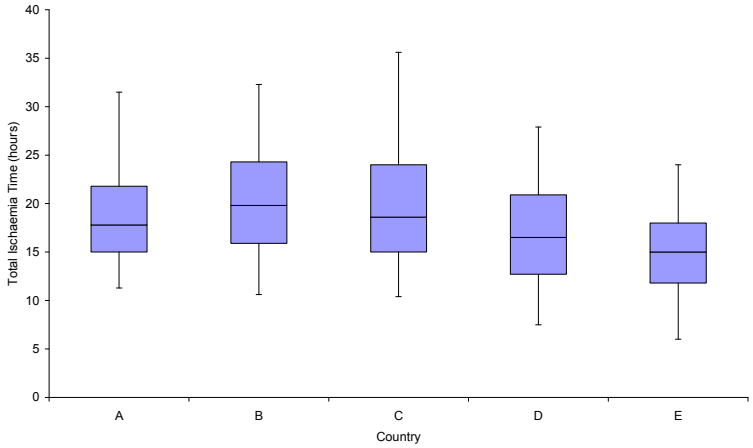


Figure 18 Graft survival following first adult deceased donor kidney transplant

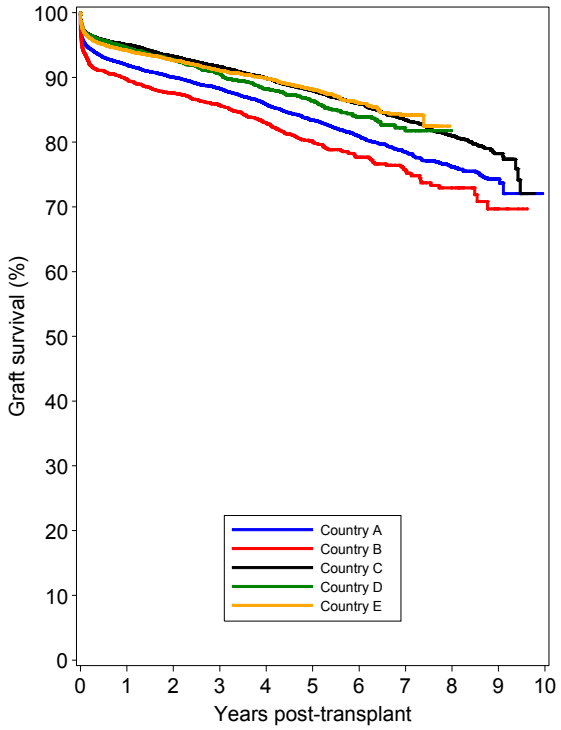


Figure 18 presents long-term graft survival following first adult deceased donor kidney transplant, and table 3 presents the Kaplan-Meier one and five year survival estimates, together with 95% confidence intervals. There is statistically significant evidence of a difference in unadjusted graft survival rates between the five countries, with five-year graft survival ranging from 80.2% in Country B to 88.1% in Country E.

The survival curves diverge very early in the post-transplant period, with countries A and B reporting around 2% of grafts failing on the day of transplant, compared with around 0.4% in the other three countries. Conversely, around 2% of patients are reported alive on the day of transplant with no further follow-up in Counties C to E, while the corresponding figure for countries A and B is 0.4%. This may suggest some difference in data reporting mechanisms when grafts suffer primary non-function.

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	91.9	(91.4, 92.5)	83.4	(82.4, 84.2)
Country B	89.7	(88.5, 90.8)	80.2	(78.2, 82.0)
Country C	95.1	(94.7, 95.4)	87.9	(87.3, 88.5)
Country D	94.6	(93.7, 95.3)	86.4	(84.8, 87.9)
Country E	94.2	(93.7, 94.6)	88.1	(87.3, 88.9)
Log-rank test	p<0.0001		p<0.0001	

Table 4 presents the results of Cox proportional hazards models for five-year graft survival. All candidate risk factors were forced into the model; there was no model building performed. Missing data for categorical variables was incorporated in the analysis by using a separate level of each risk factor, but the hazard ratios are omitted from the table for simplicity.

The “All” column summarizes a model which was applied to all data provided, regardless of country and therefore describes the average influence of each risk factor across all five countries. Donor type, donor age and recipient gender had the strongest negative impact on survival, while double kidney transplants and transplants for polycystic kidney disease had the strongest protective effects. The addition of country to the model was highly statistically significant (p<0.0001), indicating a significant difference in five year graft survival between countries after adjusting for the other risk factors available in the data set.

The individual country columns summarize the effect of each risk factor in that country and were estimated by adding each country*risk factor interaction to the model in turn. The p-value relates to the statistical significance of adding that interaction term to the model, and reflects the level of evidence against the hypothesis that the risk factor has the same influence in all five countries. Interestingly, there is evidence of a differential effect on outcome between countries for donor type, recipient age, primary disease, transplant type and HLA mismatch at all three loci.

Table 4	Cox model for five year graft survival following first adult deceased donor kidney-only transplant						
		Hazard ratios					
	All	Country A	Country B	Country C	Country D	Country E	p-value
Donor type							0.005
HB	1.00	1.00	1.00	1.00	1.00	1.00	
NHB (contr.)	1.58	0.94	1.37	0.94	0.94	0.94	
NHB (uncontr.)	2.15	1.09	2.75	1.14	1.09	1.09	
NHB (unknown)	1.66	1.24	1.24	1.24	1.24	1.24	
Donor age (per 5 years)	1.12	1.13	1.12	1.10	1.20	1.13	0.27
Recip. age (per 5 years)	0.96	0.98	0.98	0.94	1.08	0.98	0.01
Donor gender							0.74
Male	1.00	1.00	1.00	1.00	1.00	1.00	
Female	1.03	0.98	0.91	1.03	1.26	1.02	
Recip. gender							0.36
Male	1.00	1.00	1.00	1.00	1.00	1.00	
Female	1.12	1.11	1.13	1.21	0.87	1.02	
Primary disease							0.007
Glomerular	1.00	1.00	1.00	1.00	1.00	1.00	
Diabetes	1.06	1.01	1.16	1.09	0.75	0.74	
Polycystic	0.70	0.65	0.82	0.70	0.96	0.69	
Other	1.01	0.88	1.09	1.08	0.80	0.94	

Table 4 (cont.) Cox model for five-year graft survival following first adult deceased donor kidney-only transplant

	All	Country A	Country B	Country C	Country D	Country E	p-value
Transplant type							0.03
Single	1.00	1.00	1.00	1.00	1.00	1.00	
Double	0.63	1.19	3.21	0.74	*	0.51	
Mismatches at A locus (%)							0.03
0	1.00	1.00	1.00	1.00	1.00	1.00	
1	0.95	1.01	1.05	0.88	1.34	0.99	
2	0.97	0.98	1.76	0.95	2.31	0.99	
Mismatches at B locus							0.05
0	1.00	1.00	1.00	1.00	1.00	1.00	
1	1.01	1.08	1.09	0.95	1.26	1.03	
2	1.03	1.21	1.57	0.95	2.27	1.30	
Mismatches at DR locus							0.04
0	1.00	1.00	1.00	1.00	1.00	1.00	
1	0.97	1.07	1.18	1.00	1.06	1.19	
2	1.03	1.39	1.07	1.06	3.01	1.47	
Ischemic time (per 5 hours)	1.07	1.08	1.14	1.08	1.02	1.01	0.12

* Hazard ratio could not be estimated due to low number of events in the double kidney transplant group

Adult living donor transplants

Table 5 describes the characteristics of all adult living donor kidney transplants in each of the five participating countries for known data values only.

Mean donor age ranged from 45.7 years in Country C to 51.2 years in Country E, as shown in Figure 19, and a one-way ANOVA indicated that this difference was statistically significant. Similarly, mean recipient age varied significantly between countries, with a minimum of 38.7 years in Country E and a maximum of 45.8 years in Country B, as shown in Figure 20.

Figures 21 and 22 present the donor and recipient gender distribution, respectively, across countries. Male donors were the minority in all countries, but the proportion varied from 28.9% to 45.5% ($p<0.0001$). The majority of recipients were male in all countries, but the proportion varied from 60.0% to 66.9% ($p=0.0002$).

Figure 23 presents the distribution of primary diseases across countries, and the distributions differ significantly. The proportion of patients with glomerular disease ranged from 21.4% in Country B to 51.8% in Country E. In common with deceased donor kidney transplantation, Country D transplanted the largest proportion of diabetic patients (14.0%).

As expected, all living donor kidney transplants in all countries were single kidney transplants.

Figures 24 to 26 present the mismatch distribution at the A, B and DR loci respectively, while Figure 27 presents the total mismatch scores and Figure 28 presents the proportion of 000 mismatch transplants performed. HLA matching differed significantly between countries, with country B having higher mean mismatch scores than the other countries. The proportion of 000 mismatch transplants performed also reflected this pattern, accounting for 17.4% of transplants in Country C, but only 5.4% of transplants in Country B.

Figure 29 presents the distribution of graft number across countries. This differed significantly across with countries, with Country E performing far less regrafts (2.8%) than the other four countries.

Mean ischemia time was not reported for any living donor transplants in Countries D or E, but varied significantly among the other three countries, as shown in Figure 30. Country B appeared to have longer ischemia times.

Table 5 Characteristics of adult living donor kidney-only transplants

	All	Country A	Country B	Country C	Country D	Country E	p-value
Mean donor age (years)	48.0	46.6	50.1	45.7	49.0	51.2	<0.0001
Mean recip. age (years)	42.2	41.3	45.8	39.0	43.8	38.7	<0.0001
Donor gender (%male)	42.3	45.5	43.4	42.3	40.0	28.9	<0.0001
Recip. gender (% male)	62.0	60.0	61.7	62.2	64.4	66.9	0.0002
Primary disease (%)							
Glomerular	34.2	36.2	21.4	35.2	35.8	51.8	<0.0001
Diabetes	7.4	9.3	4.1	4.5	14.0	3.9	
Polycystic	12.8	15.2	12.0	13.2	13.1	6.4	
Other	45.6	39.3	62.6	47.2	37.1	38.0	
Mismatches at A locus (%)							
0	31.8	31.8	21.7	34.3	34.0	26.6	<0.0001
1	53.7	53.9	53.6	52.3	51.3	61.2	
2	14.5	14.4	24.7	13.4	14.8	12.3	
Mismatches at B locus (%)							
0	23.2	23.7	11.6	27.1	23.5	18.8	<0.0001
1	54.8	55.1	50.3	55.2	52.6	60.4	
2	21.9	21.2	38.1	17.6	23.8	20.9	

Table 5 (cont.) Characteristics of adult living donor kidney-only transplants

	All	Country A	Country B	Country C	Country D	Country E	p-value
Mismatches at DR locus (%)							
0	28.8	28.8	19.1	34.0	28.5	25.8	<0.0001
1	54.7	56.0	52.7	52.9	51.1	60.5	
2	16.5	15.2	28.3	13.1	20.4	13.7	
Total mismatches (%)							
0	13.6	13.6	5.4	17.4	15.3	6.9	<0.0001
1	8.1	8.1	5.7	9.0	7.6	8.8	
2	21.5	22.5	17.6	21.1	18.9	24.9	
3	29.6	29.1	25.0	29.4	29.2	35.0	
4	11.6	11.6	19.1	9.9	11.2	12.5	
5	11.2	11.2	17.6	9.7	11.9	8.9	
6	4.5	4.0	9.8	3.6	6.0	2.9	
000 mismatch txs (%)	13.6	13.6	5.4	17.4	15.3	6.9	<0.0001
Transplant number (%)							
1	89.5	87.9	88.8	88.2	91.3	97.2	<0.0001
2	8.7	10.3	9.2	10.0	7.0	2.0	
3 or more	1.8	1.8	2.0	1.8	1.7	0.8	
Mean ischemic time (hours)	2.4	2.4	3.1	2.2	-	-	<0.0001

Figure 19 **Donor age distribution across countries**
Box and whisker plots show the median value, first and third quartiles, and 5th and 95th percentiles

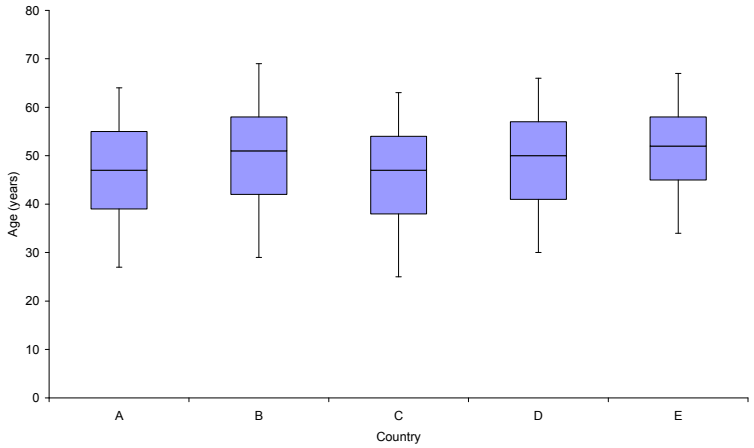


Figure 20 **Recipient age distribution across countries**
Box and whisker plots show the median value, first and third quartiles, and 5th and 95th percentiles

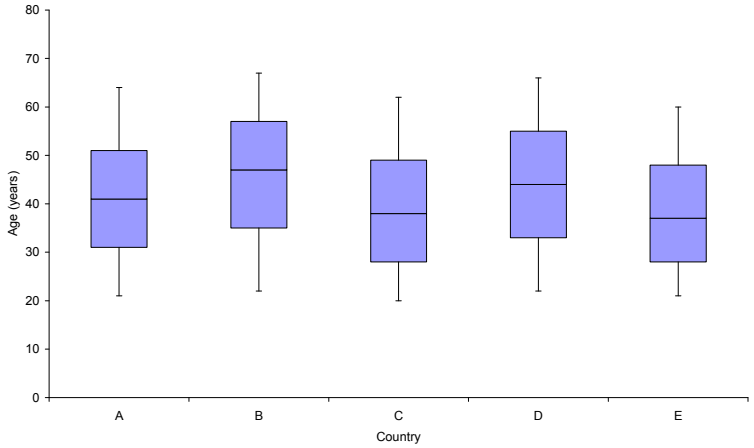


Figure 21 **Donor gender distribution across countries**

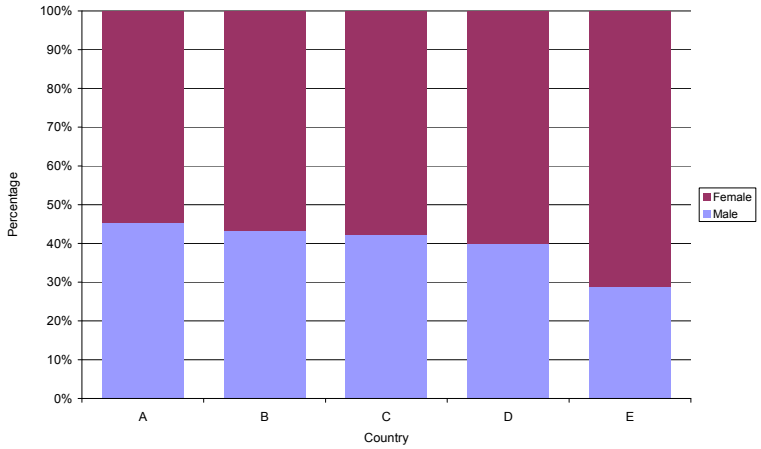


Figure 22 Recipient gender distribution across countries

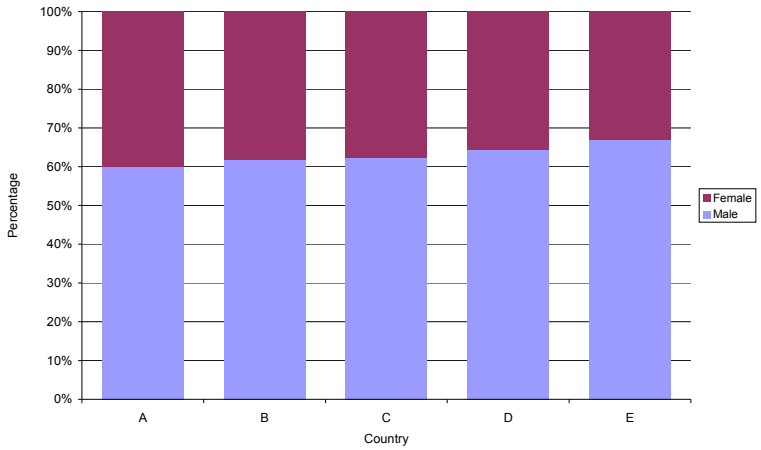


Figure 23 Recipient primary disease distribution across countries

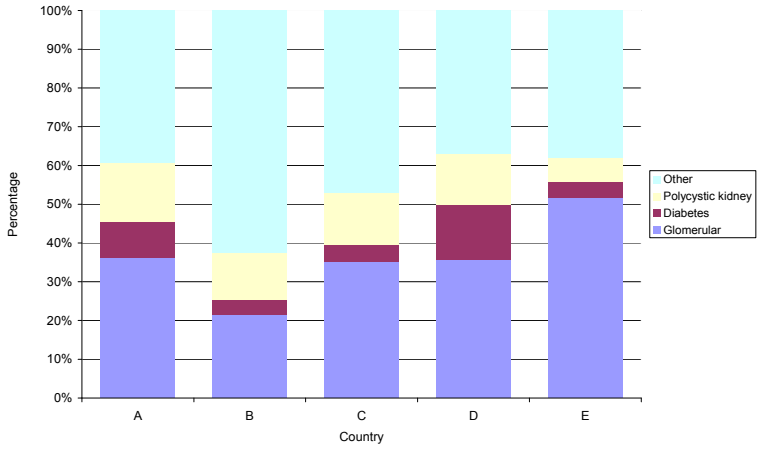


Figure 24 A locus mismatch distribution across countries

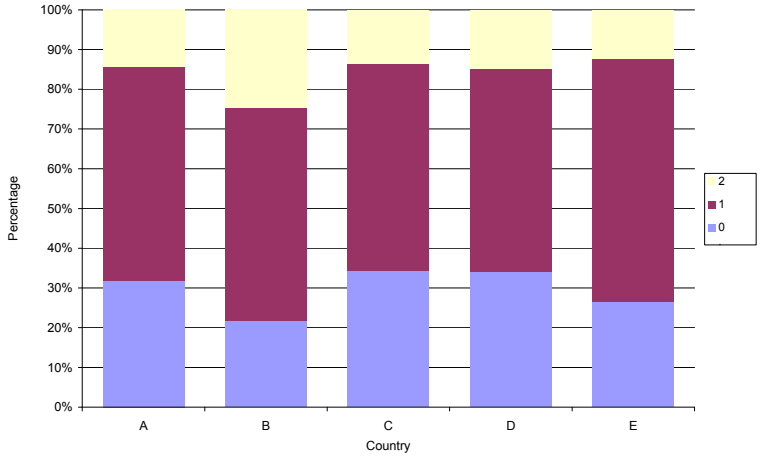


Figure 25 B locus mismatch distribution across countries

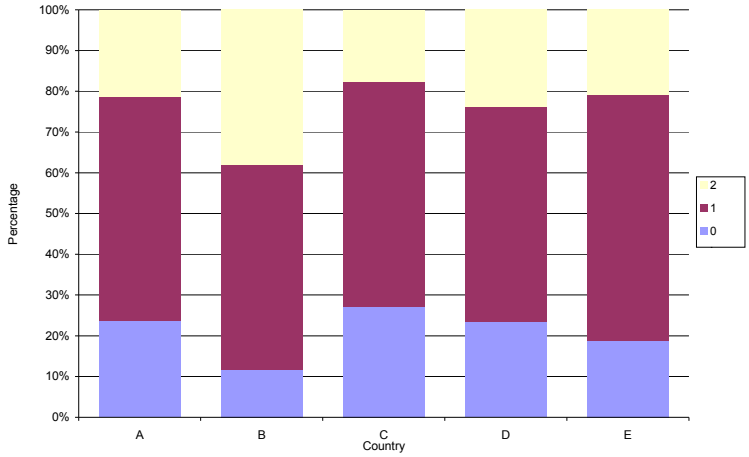


Figure 26 DR locus mismatch distribution across countries

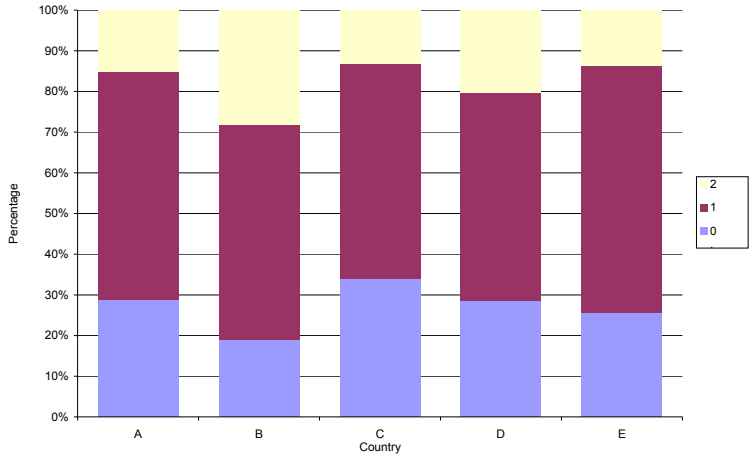


Figure 27 **Total mismatch score distribution across countries**

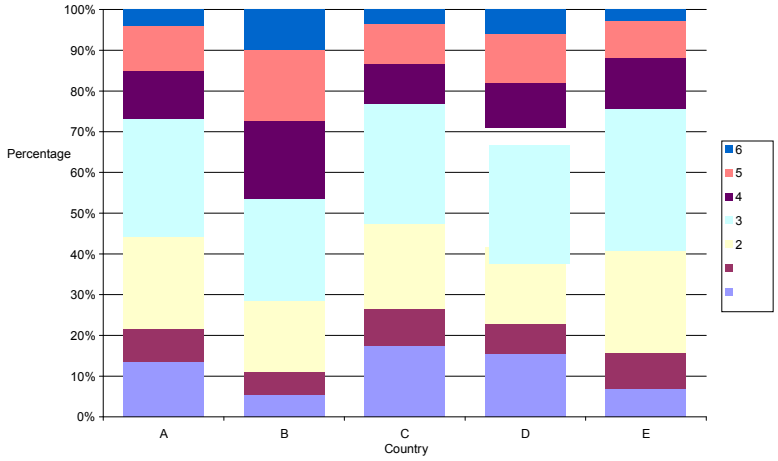


Figure 28 **Proportion of 000 mismatch transplants across countries**

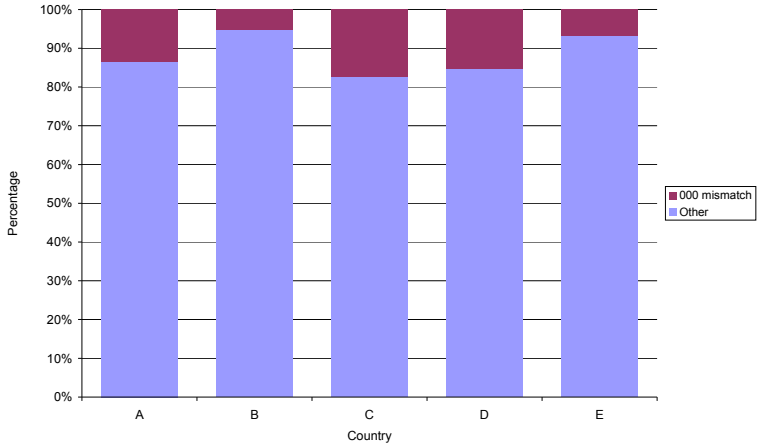


Figure 29 **Transplant number distribution across countries**

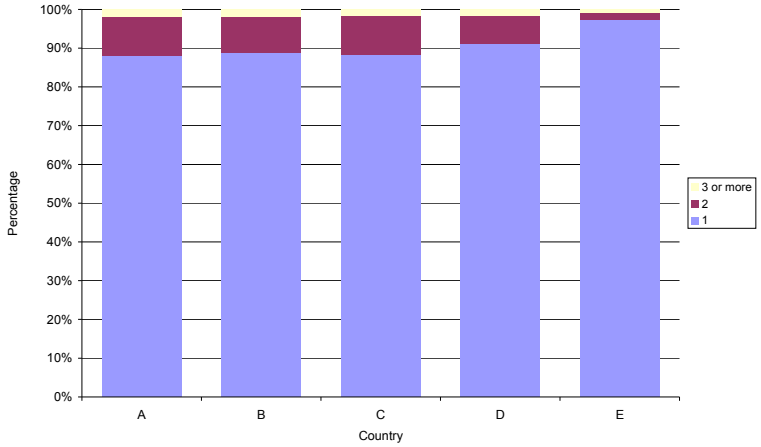


Figure 30 **Ischemia time distribution across countries**
Box and whisker plots show the median value, first and third quartiles, and 5th and 95th percentiles

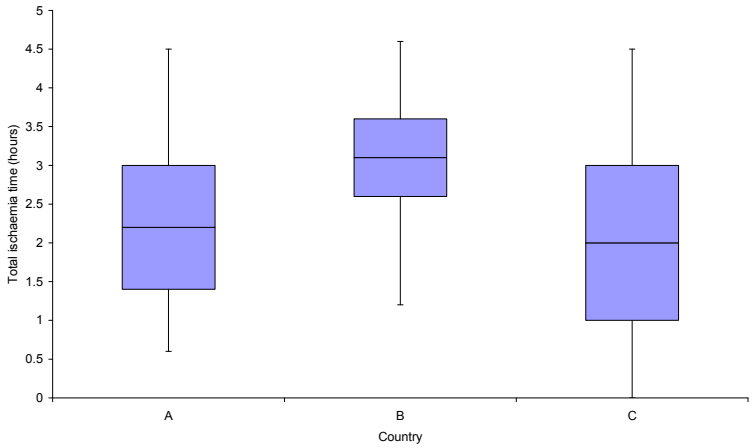


Figure 31 **Graft survival following first adult living donor kidney transplant**

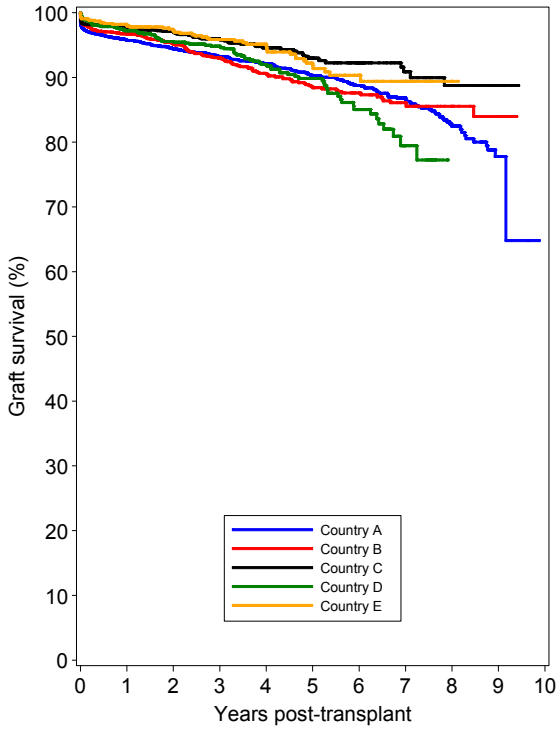


Figure 31 presents long-term graft survival following first adult live donor kidney transplant, and table 6 presents the Kaplan-Meier one and five year survival estimates, together with 95% confidence intervals. There is statistically significant evidence of a difference in unadjusted graft survival rates between the five countries, with five-year graft survival ranging from 88.6% in Country B to 93.0% in Country C.

Table 6	One and five year graft survival estimates following first adult living donor kidney transplant, by country			
	One-year survival estimate	**95% Confidence Interval**	**Five-year survival estimate**	**95% Confidence Interval**
Country A	95.7	(95.0, 96.3)	90.3	(89.1, 91.4)
Country B	96.7	(95.8, 97.4)	88.6	(86.5, 90.3)
Country C	97.7	(96.7, 98.4)	93.0	(90.7, 94.7)
Country D	97.2	(96.1, 98.0)	89.8	(87.1, 92.0)
Country E	98.1	(96.8, 98.8)	92.2	(89.3, 94.4)
Log-rank test	p<0.0001		p=0.002	

Table 7 presents the results of Cox proportional hazards models for five year graft survival. All candidate risk factors were forced into the model; there was no model building performed. Missing data for categorical variables was incorporated in the analysis by using a separate level of each risk factor, but the hazard ratios are omitted from the table for simplicity.

The “All” column summarizes a model which was applied to all data provided, regardless of country and therefore describes the average influence of each risk factor across all five countries. Recipient gender, diabetic primary disease and HLA mismatches at the A locus had the strongest negative impact on survival, while transplants for polycystic kidney disease had the strongest protective effects. The addition of country to the model was highly statistically significant (p<0.0001), indicating a significant difference in five year graft survival between countries after adjusting for the other risk factors available in the data set.

The individual country columns summarize the effect of each risk factor in that country and were estimated by adding each country* risk factor interaction to the model in turn. The p-value relates to the statistical significance of adding that interaction term to the model, and reflects the level of evidence against the hypothesis that the risk factor has the same influence in all five countries. Interestingly, there is evidence of a differential effect on outcome between countries for recipient age, primary disease, ischemia time and HLA mismatches at the A and B loci.

Table 7 Cox model for five year graft survival following first adult living donor kidney-only transplant

	Hazard ratios						
	All	**Country A**	**Country B**	**Country C**	**Country D**	**Country E**	**p-value**
Donor age (per 5 years)	1.09	1.07	1.12	1.16	1.06	1.18	0.56
Recip. age (per 5 years)	0.94	0.88	0.99	1.02	0.88	1.07	<0.0001
Donor gender							0.93
Male	1.00	1.00	1.00	1.00	1.00	1.00	
Female	0.99	0.96	1.14	0.94	0.96	1.06	
Recip. gender							0.84
Male	1.00	1.00	1.00	1.00	1.00	1.00	
Female	1.14	1.22	0.96	1.21	1.11	1.03	
Primary disease							0.02
Glomerular	1.00	1.00	1.00	1.00	1.00	1.00	
Diabetes	1.32	1.04	0.22	1.73	2.10	1.30	
Polycystic	0.83	0.74	0.78	1.22	0.27	*	
Other	1.15	0.89	1.13	1.20	0.82	2.71	

* Hazard ratio could not be estimated due to low number of events

Table 7 (cont.) Cox model for five year graft survival following first adult living donor kidney-only transplant

	All	Country A	Country B	Country C	Country D	Country E	p-value
Mismatches at A locus (%)							0.03
0	1.00	1.00	1.00	1.00	1.00	1.00	
1	1.24	1.06	*	2.65	1.14	1.75	
2	1.32	1.01	*	2.64	1.41	2.43	
Mismatches at B locus							0.01
0	1.00	1.00	1.00	1.00	1.00	1.00	
1	0.95	1.00	0.29	1.09	0.99	0.65	
2	0.94	0.81	1.17	2.66	0.71	0.74	
Mismatches at DR locus							0.23
0	1.00	1.00	1.00	1.00	1.00	1.00	
1	0.84	0.83	0.47	0.76	0.82	1.09	
2	0.94	0.75	1.10	1.30	1.28	0.95	
Ischemic time (per 5 hours)	1.25	1.09	0.94	0.85	-	-	<0.0001

* Hazard ratios could not be estimated due to low number of events

11.6 Limitations and recommendations arising from pilot study

The pilot study was a proof-of-concept exercise to establish whether data from two or more European countries could be successfully collected, combined and analysed. It focused on kidney transplantation over a short time period with a very small set of risk factors. These risk factors were agreed in advance with participating countries and were known to already be collected by several national registries. The precise definitions of each risk factor were not available from Work Package 4 prior to the pilot study, but were defined with agreement from participants in advance. There were minimal exclusion criteria for the data set, to make data submission as straightforward as possible.

There are some important limitations in the pilot study. Firstly, it involved collecting a small set of common variables from a small group of highly motivated European countries with well-established transplant programs and national registries. It did not consider the issues that may arise when collecting data from countries with less established transplant programs, nor with larger or more complex data sets which were harder to define. The pilot study also did not test the legal or functional requirements for a European Registry.

Despite this simple design and these limitations, the pilot study highlighted a number of issues, and hence provided much useful information about the practicalities of sharing data across European countries.

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. This issue is being addressed by Work Package 2 on Dissemination.

Some countries were unable to provide data for the full time period of the study. The European Registry would need to be flexible enough to cope with incomplete data sets.

Data submission

For the pilot study data submission was recommended to be a csv file with password protection sent via e-mail, but as described in section 4.4, none of the countries participating in the pilot study fully met this requirement. Data submission mechanisms for the European Registry will therefore need to be carefully considered. Clearly data must be transmitted securely and in alignment with all legal requirements in this area, but the method of transmission must also be simple and user-friendly to ensure the optimum levels of adherence.

The pilot study included all kidney transplants performed over an eight year period and the data set included fourteen variables. The largest file submitted had around 22,000 records and was easily handled as an e-mail attachment, but the European Registry would expect much larger data sets to be submitted and so this should also inform the data submission mechanism.

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. The output of Work Package 4 is therefore crucial in order to define each question clearly and in a way that allows maximum participation from across Europe.

One country indicated that they were unable to distinguish between graft failure and deaths with functioning graft effectively, particular in the early post-operative 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, and on occasion, required significant manipulation. Participating countries must therefore be aware of the work required from them in order 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.

Data handling

The pilot study was a relatively small scale exercise, with the final data set only including 65,000 records and eighteen variables. The data could therefore easily be stored on the hard-drive of a standard computer, and manipulated and analysed using a standard software package.

The European Registry would be anticipated to hold much more data than this, and so robust data storage mechanisms need to be established to ensure security of the data and optimum performance of any queries or analyses performed. Similarly, the analysis software chosen needs to be capable of handling extremely large data sets.

The data manipulation required in the pilot study to amalgamate data from across countries and then perform analysis, was fairly extensive. While improvements in the data submission process and definition of the data set should reduce this, there is an expectation that the European Registry would require some central staffing with the necessary skills and dedicated time to address these issues.

Analysis

The pilot study demonstrated that interesting analysis can be performed on data from several European countries. Missing data was a significant issue for some countries and some variables. The definition of fields in a European Registry data set therefore must have clear coding for missing data. It may also be necessary for some key fields to be mandatory in order to provide the key information for all participating countries without the potential biases associated with missing data. The output of Work Package 7 on quality will also be relevant here, as the European Registry will need to optimize the quality of data received.

Those analysing the data must be competent statisticians with a thorough understanding of the many aspects of statistics that relate to the management and analysis of registry data. This includes knowledge of statistical modelling and methods for handling missing values, as well as methods for managing, summarizing and presenting data. It is therefore recommended that the central European Registry staff includes one or more experienced statisticians.

11.7 Conclusions

The pilot study provided a great deal of useful information to inform the design of a European Registry. A relatively small data set was collected from five EFRETOS partner countries, and successfully combined and analysed. However, the process was not always straightforward and highlighted several issues. In particular:

- countries without national registries are likely to find participation in a European Registry challenging;
- stakeholders within countries must be well informed and supportive of the European Registry's aims and support data submission;
- the definition of fields in the European Registry must be highly detailed and give guidance on how existing coding structures should be mapped to any new categorization used by the registry;
- the selection of fields for the basic data set must take account of the availability of those items in existing national registry data sets;
- participating countries must commit sufficient time to preparation of the data set to this pre-specified format and must follow any data security requirements specified by the European Registry;
- central registry staff will be required to manipulate and analyse the data received;
- missing data is common and must be treated appropriately in any analysis.

Through taking account of these issues, and the points that arise in other work packages of the EFRETOS project, a sound foundation will be laid for a European Registry.

Overview of principles and recommendations for creating a European Registry

The aim of this Deliverable is to give a general overview of the main issues involved in the creation of a pan-European Registry. The main points of principle and recommendations that are set out below summarize material that has been presented in the following Deliverable:

Deliverable D4: First outline of the report on the use of a registry of registries (May 2010)

This Deliverable should be referred to for more detailed supporting material.

This European Registry will be a "registry of registries". In some countries national or supranational registries already exist, in others these registries still have to be developed. This will lead to different challenges. Where registries already exist, adaptations might be necessary to allow cooperation with the European Registry. Countries that do not have a registry yet need to build it up and cooperation with the European Registry might develop in a stepwise approach starting with the delivery of a minimum data set and later extension of the cooperation. These aspects are taken into account in the following document that is organized as follows:

- summary of the data sets that will form the European Registry;
- major considerations for the collection, storage and updating of data from different countries;
- Development and maintenance of the data base, procedures for disseminating summary data, and the resources required for the European Registry;
- Composing of a list of the main recommendations for the creation and continuation of a European Registry.

This Deliverable presents a preliminary report on the overview of principles and recommendations for creating a European Registry and is as such subject to change as additional information becomes available from on-going surveys and discussions.

12 Key points and Recommendations

12.1 The European Registry data set

The European Registry is designed to hold activity and outcome data on the transplantation of solid organs. As explained in Deliverable D4, there will be a **basic data set** that all countries that contribute to the European Registry must ultimately provide on a regular basis. This data set consists of all variables that are acknowledged to be of importance for a comprehensive evaluation of transplant outcomes. The data items encompass information on the donor, the transplant candidate, the early and late organ function, post-transplant morbidity and mortality. Selection of relevant items was performed by organ specific teams of European experts, guided by the European Society of Organ Transplantation (ESOT). The selected items were subsequently scrutinized whether they could be classified as either a basic or an expanded data set item. Finally a definition for the data items was drafted.

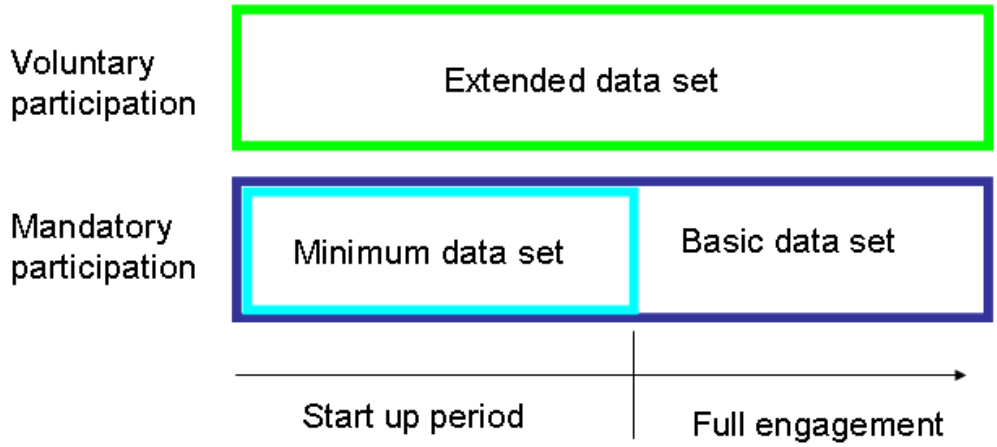


Figure 1. The three types of data sets for the European Registry.

We recognize that some countries will be in the early stages of developing a national registry, and may not be able to provide all the data in the basic data set from the start. Accordingly, we have agreed on a subset of the basic data set, i.e. the **minimum data set** that must be provided by each participant from the date when they become a contributor to the European Registry. The variables that feature in the basic data set that are additional to those in the minimum mandatory data set must be provided to an agreed timescale by each contributor. Upon the start of the collaboration between a country and the European Registry an agreement on this transition period will be made. Countries that want to continue to participate in the European Registry will be requested to mandatory deliver all data described in the basic data set.

We have further recommended that the European Registry should seek to collect an **expanded data set** that will, for example, facilitate detailed studies on outcomes in patients suffering from rare diseases or conditions, to provide an evidence base that will inform clinical decision making. Contributors to the European Registry will not be required to deliver data on all variables in the expanded data set. However, all participating countries will be encouraged to provide these data to inform regional studies of transplant issues of clinical importance. It is expected that once a national registry has agreed to provide values of a particular variable to the European Registry, the data submitted will be as complete as possible.

The data items and their definitions that feature in the minimum mandatory, and basic data set are described in the following Deliverable:

Deliverable D7: Report on a dedicated data dictionary (October 2010)

Definitions for the expanded data set will have to be developed and agreed upon whenever data items are introduced to the expanded data set

Complementary information will be provided in Deliverable D10, related to safety items and definitions.

12.2 Data collection and validation

12.2.1 Data collection

Data are expected to be uploaded from the national or supranational registries to the European Registry on a regular basis, either annually or six monthly. The format will be tightly specified, but in a way that contributors will find it straightforward to follow, and will not preclude contributions from national registries with less advanced computing facilities. The data items are to be delivered according to standard definitions and formats and exclusively in the English language. These requirements already preclude the possibility for countries to deliver a simple extract from their national registry.

Although the European Registry will expect data to be submitted in a pre-defined manner, it is anticipated that a variety of formats for the submission of data will be used in the early stages of the European Registry's establishment. So as not to delay the incorporation of data into the European Registry, data may initially be accepted in the form of a spreadsheet, a csv (comma separated values) file, or other agreed formats. However, contributing countries will be expected to adhere to a common format for data submission when the European Registry becomes established. Upon the start of the collaboration between a country and the European Registry an agreement on the transition period till data have to be delivered in the common format will be made.

The medium term goal would be for data to be uploaded using the internet. An early task for the European Registry will be to develop mechanisms and protocols for this, including the introduction of appropriate levels of security for data transmission.

The definition and format of each data item to be submitted as part of the basic or expanded data sets has been defined in great detail in the data dictionary (Deliverable D7), and we will expect every participant to adhere to these formats. A country that intends to participate in the European Registry will have to show commitment for this wish of European harmonization, expressed by growing adherence to the required standard formats. Experience with the pilot study described in Deliverable D4 (Chapter 4) suggests that this adherence might not be achievable in the early stages. This will inevitably lead to correspondence between data contributors and the European Registry to resolve inconsistencies, and a "translation table" will be needed to convert submitted data into the format required by the European Registry. However, we expect that the required formats for data submission will be obtained after an initial 'settling in' period.

12.2.2 Quality Assurance

In order to ensure that the quality of the data that are submitted to the European Registry is maintained, a quality assurance system is essential. Details of the types of quality assurance processes are described in Deliverable D4 (Chapter 7); the final certification system will be described in D12. Before a data set has been uploaded to the European Registry, these data will need to be checked for consistency and adherence to format in the uploading process, duplicate observations will need to be identified and eliminated, unlikely or impossible combinations of values will need to be queried, and checks for comparability between time periods will be necessary. To allow this, once a data set has been submitted to the European Registry, it will be placed in a holding area while these checks are carried out, and any errors are resolved with the data contributor. The rules that govern the

ultimate step leading to the uploading of a patient's record to the European Registry depend on the data items. Identifiers will only need to be checked for duplicity and format adherence, while clinical parameters will also require checks for consistency. Only when all quality assurance checks are passed these clinical data items will be uploaded to the European Registry itself.

In order to facilitate an effective quality assurance system, countries participating in the European Registry will need to be able to communicate in English and respond to data queries in a timely fashion.

When the European Registry has become established, various stakeholders will be using the data for particular analyses and for the production of summary information. This work may lead to the identification of errors in the data set that have not been picked up at the time the original data were uploaded. However, the quality assurance procedures described in the previous section should mean that the number of changes needed to the uploaded registry data will be small.
Once an initial set of data has been submitted for a particular patient, updates will be needed to take account of increased follow-up times, during which patient may have died or grafts failed. This will also provide the opportunity to update entries by adding values that were missing at the time of initial uploading. This information has to be provided on a regular basis, so that the European Registry does not become out of date, and so there will need to be a planned schedule for the correction and updating of data. Each time the record for a particular patient is amended, we suggest that the complete record - including the previous static items - for that patient is resent to the European Registry for uploading. This procedure will further safeguard the quality of the submitted data as a check with historical data can be performed. It is further recommended that updated versions of the registry data set are issued every six months. Notice that this interval refers to calendar months and not the six month interval after transplantation

12.3 Development and maintenance

After the establishment of the European Registry the data collected will be used by various stakeholders for particular analyses and for the production of summary information. In this process it might become evident that data fields have to be added, removed or adapted.
In addition it has to be considered that the area of organ transplantation is fast moving, with a steady flow of new treatment regimens and new approaches to patient care. As a consequence of these two factors the variables in the basic and expanded data sets will change over time. Some variables in the data set may cease to be important while others that are not included may be required. It will therefore be necessary for the data set that underpins the European Registry to be kept under review.

12.4 Technical requirements

The European Registry will need to host a relational data base with the necessary hardware and software to provide a reliable, resilient and secure registry. It will also need to host a web site to promote communication about the European Registry and to facilitate web based data uploads from participating countries. There is also a requirement for online reporting of patient and graft survival rates, online interactive tables and data download, all on a per participating country basis. Data security will be paramount. Individual data access accounts will ensure data availability at appropriate access levels, i.e. a particular transplant program will have access to all of its own data, but restricted access to the full European data set. Detailed specifications for each of these items will need to be devised. Information on the technical requirements for the European Registry is summarized in Chapter 6 of Deliverable D4.

12.5 Management resources

The European Registry needs to be organized in such a way as to ensure that as many countries as possible are able to contribute to the basic data set.

Because of this, in the early stages of the creation of the European Registry, a larger number of staff will be needed. These staff will be engaged in a greater degree of data cleansing than is likely to be needed once the European Registry becomes more firmly established, they will be handling different formats of data submission, and dealing with any lack of compliance with data definitions and formats as described above. In the longer term, a certain rhythm will have to be developed, with participating countries being better acquainted with the instructions on how data are to be supplied. Fewer staff will then be needed for data uploading. However, since it is expected that some countries will join the European Registry after it has been established, the European Registry will need to have the resources available to facilitate new contributors.

The report on the use of a registry of registries (Deliverable D4) envisages that there will be a Management Board that is ultimately responsible for the design and function of the European Registry, and a Review Committee that will oversee the day to day operation of the Registry (see Chapter 5 of Deliverable D4). Staff to ensure successful data submission and perform data analysis will be required, along with IT staff to maintain the registry systems and support a helpdesk function. Corporate services will need to be provided to support the work of the Management Board and Review Committee, as well as the personnel and financial requirements of the fulltime Registry Staff.

12.6 Communications strategy

One of the first steps would be to create a publicly accessible web site for the European Registry. This web site will contain much of the general information about the aims, content and function of the European Registry. The web site will also need to have an area that is restricted to named individuals in contributing countries, and accessible by personal log in.

It is important that contributors to the registry are regularly informed about developments. This will include information on countries contributing, general information on the uploading and quality assurance functions, studies based on data in the European Registry that have been agreed by the Review Committee, summaries of points discussed at meetings of the Management Board, staff news and so on. The most appropriate format for this would be through the web site, but with e-mail alerts as new material is added or the content revised.

Data in the basic data set will also need to be summarized and reported on a regular basis, perhaps six monthly. Some guidance on the summary data that may be provided through the web site is given in Deliverable D4 (Chapter 3). Here it is suggested that the number of transplants is given for each calendar year for each type of organ donor and by country. In addition, there should be graft and patient survival rates at 1, 3 and 5 years for each organ, separately for adults and paediatric patients. Unadjusted or adjusted survival curves might also be presented for each country. One of the early tasks for the Management Board will be to develop and agree the format of these summary data.

One of the main reasons for establishing a European Registry is that it will enable researchers from the contributing countries to have access to data for specific audits or research studies. A mechanism for promoting such requests will also need to be established. We strongly recommend that all such proposals are discussed by the Review Committee that will be set up for this purpose. In due course, it should be possible to download certain summary data from the web site.

12.7 Main Recommendations

The detailed description of the design and function of the European Registry in Deliverable D4, and this summary of the requirements for creating the European Registry have produced a number of recommendations. These are summarized below.

Recommendation 1
National or supranational registries on organ transplantation should be established in all countries. The structure of these registries should allow data delivery to the European Registry.

Recommendation 2
Besides collection of data on waiting list and transplant activities, data on outcome of transplanted patients should be collected. National legislation ensuring that transplant programs report on a mandatory and regular basis on outcome of their patients would facilitate the data collection and reporting process.

Recommendation 3
The necessary funding for setting up and maintaining this national registry should be made available by the competent authorities.

Recommendation 4
Although the format of the required data set will be tightly specified, flexibility will be needed 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.

Recommendation 5
After data have been submitted to the European Registry, quality assurance procedures should be performed before data are uploaded to the Registry itself.

Recommendation 6
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.

Recommendation 7
A relational database will be required to accommodate the data and web site produced that will allow data submission through the internet.

Recommendation 8
Regular reports that summarize the data held in the European Registry will need to be produced and disseminated.

Recommendation 9
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.

Recommendation 10
In the early stages of the formation of the European Registry, a greater number of staff will be needed for setting up the Registry and accepting the first submissions of data from participating countries, but there will be a continuing need for staff to facilitate the uploading of data from countries that join the Registry at a later stage.

A European Registry that is developed and managed in line with these recommendations will be a great asset to the international transplant community.

13 Surveys

13.1 Survey on functionality

Survey on Functionality of the post-transplant registry

Country	
Organ Exchange Organization	
Filled in by name e-mail telephone	
Date	

Please mail your answers of the survey to:
jsmits@eurotransplant.org or
Fax to 0031 71 579 00 57 to the attention of
Dr. J. Smits
EFRETOS project coordinator

ORGANIZATION

Question 1 Do you have a national organization responsible for collecting post-transplant follow-up data?
Answer 1 Yes/No If Yes, all follow-up data are collected at a national level by ….. (name of the organization).

Question 2 Is this organization required by the ministries of health to collect follow-up data?
Answer 2 Yes/ No If No, please explain

Question 3 What are the specific tasks of this organization?
Answer 3 Data collection Y/N Reporting of outcome data Y/N Auditing of centres Y/N If Yes to any of the above, please provide details

Question 4 What type of staff work at this organization? (data entry person, data manager...)
Answer 4

Question 5 Do you have a registry that contains all organ transplant registrations?
Answer 5

Question 6 Does the national registry have a registry review board? (i.e. a committee that controls the use of the registry)
Answer 6

Question 7 How is this registry review board organized? (e.g. organ specific delegates, chosen delegates, legal-ethical experts, representatives of the ministry)
Answer 7

Question 8 What are the tasks of this registry review board?
Answer 8

Question 9 When did the national registry start?
Answer 9 Year the registry started: Date of first transplant registered

DATA COLLECTION

Question 10 How do you request for follow-up data? (multiple options are possible)
Answer 10 □ by mail / fax □ by e-mail □ by automatic e-mail □ by automatic e-mail, generated by a schedule □ triggered by login procedure with a schedule □ other, please explain……

Question 11 Is it voluntary or mandatory for centres to report follow-up data to the national registry?
Answer 11 Please explain, as some data might be mandatory and others voluntary.

Question 12 Do you have data collection targets? (e.g. 80% of follow-up forms should be returned within two months of their due date)
Answer 12 Yes/No If Yes, please give details

DATA DELIVERY

Question 13 How are data delivered to you? (multiple options are possible)
Answer 13 □ paper questionnaires □ on site data collection by study nurses □ on line data entry by centres □ local follow-up system with data upload of pre-defined data set □ free delivering in all kinds of formats and modes (.xls, .dat, paper, USB, etc.) □ other, please describe…

Question 14 When are data delivered? (multiple options are possible)
Answer 14 □ upon request at appointed fixed time points (e.g. 3m,1y, nth year) □ upon request for specific projects □ continuous without request no fixed time points □ other, please describe

DATA MANAGEMENT

Question 15 What kind of actions do you take to improve the quality of the data? (e.g. by data cleaning)
Answer 15 □ manual data management □ automatic data management □ no action, please explain

Question 16 At what time points do you perform data quality controls?
Answer 16 □ in the uploading/data entry and saving phase □ in the analysis phase □ other, please explain

Question 17 Do you make use of quality indicators that induce reminders for follow-up? (e.g. if the delivered data have missing values for 80% of a factor, do you then send out the questionnaire again)
Answer 17.

REGISTRY DATA

Question 18 Do you have a fixed format for the variables stored in the registry?
Answer 18. □ Yes, go to Q 19 □ No, go to Q 20

Question 19 Give your standard format for each of the variables requested in the EFRETOS pilot study
Answer 19 - Donor type (deceased, living), e.g. Categorical 'Cad' and 'Liv' - Age recipient, e.g. date of birth dd.mm.yyy or age numerical - Gender of recipient - Age donor - Gender of donor - Primary disease of recipient, e.g. ICD-10 or SNOMED - HLA Mismatch data, e.g. 1 or 001 or HLA-A MM=0, HLA-B MM=0, HLA-DR MM=1 - Ischemia time - Date of transplant - Date of graft failure - Date of death

Question 20 How do you register the follow-up data? (multiple options are possible)
Answer 20 □ at organ level □ at transplant level □ at patient level

Question 21 In case you receive an organ from another OEO, do you register the donor number from the other OEO or only your own donor registration number? (e.g. organ from the UK and used for transplantation in ET, ET stores the ET donor number and not the NHSBT donor number, no name) (multiple options are possible)
Answer 21 □ donor number own organization □ donor number other OEO □ other, please explain

Question 22 In case an organ from your own OEO is used for transplantation in another OEO, do you register the recipient/transplant number from the other OEO? (e.g. organ from ET and used for transplantation in the UK, ET stores the ET donor number, pt. name, gender and date of birth, date of transplant; and creates an ET recipient and transplant number but no identifying number from NHSBT) (multiple options are possible)
Answer 22 □ transplant/recipient number own organization □ transplant/recipient number other OEO □ other, please explain

Question 23 If one of the patients on your waiting list is transplanted outside your country/organization, do you keep track of this patient?
Answer 23 Yes/No If Yes, please give details

Question 24 Do you have a system to identify double registration on the waiting list across OEOs?
Answer 24 Yes/No If Yes, please give details.

Question 25 Do you have a system to identify double registration of a transplant across OEOs?
Answer 25 Yes/No If Yes, please give details

Question 26 Can you describe the data flow from time of data uploading/ data entry to the analysis data base**?**
Answer 26

Question 27 Do you have a separate analysis data base?
Answer 27 Yes/No If Yes, go to question 28, else to 29

Question 28 How often do you refresh your separate analysis data base?
Answer 28

ANALYSIS

Question 29 What kind of quality indicators do you use?
Answer 29 □ none, all data that are delivered are taken up in the analysis □ only centres that fulfil specific criteria are taken up in the analysis, please specify □ only data that fulfil specific criteria are taken up in the analysis, please specify

Question 30 Level of access to the registry data (multiple options are possible)
Answer 30 □ a centre has full access to all of her own data, on request □ a centre has full access to all of her own data at any time □ a centre has full access to all data in the registry, on request (e.g. for specific projects) □ a centre has full access to all data in the registry □ a centre has access to own data but only in aggregated format □ a centre has access to all data but only in aggregated format

Question 31 How are data from the registry disseminated? (multiple options are possible)
Answer 31 □ Annual Report on paper □ Annual Report as pdf □ Interactive tables on-line □ Kaplan-Meier curves on-line □ Slide kit □ Data extract □ Other, please specify

13.2 Survey on technical aspects

Technical Survey EFRETOS

Country	
Organ Exchange Organization	
Filled in by name e-mail telephone	
Date	

Please send your answers of the survey to:
jsmits@eurotransplant.org or
Fax to 0031 71 579 00 57 to the attention of
Dr. J. Smits
EFRETOS project coordinator

Because of the technical aspects of the questions, it could be helpful for you to hand over this questionnaire to the IT-staff of your organization.

If you have any questions, please do not hesitate to contact:
Murk Schaafsma
phone: +31 71 5 795 794
e-mail: m.schaafsma@eurotransplant.org

Question 1 Please describe the functions of your follow-up system for data entry / uploading
Answer 1 - Who enters the follow-up data? > the centres / external users: yes / no > your organization on the basis of paper questionnaires: yes / no > other, please explain - Do you use data entry screens? > yes / no > if yes, please specify (per organ, per transplant, per recipient, per time point): - Do you upload files from other systems? > yes / no > if yes: what kind of files (CSV, XML, other): what kind of reply files do you offer - Other, please specify:

Question 2 If you offer your users schedules for collection of follow-up data, please describe the process. (paper / electronic by e-mail / electronic work lists and so on)
Answer 2

Question 3 How do you store your follow-up data? (in a relational data base, file system, XML, object data base)
Answer 3

Question 4 Please describe the architecture of your **hardware** used in follow-up data collection
Answer 4 - Data base server(s) > hardware : > operating system : - Application server(s) > hardware : > operating system : - Other: *It could be helpful to add a drawing of the architecture*.

Question 5 Please describe the architecture of your **software** used in follow-up data collection. (including the name and version of the data base used)
Answer 5 Data base system(s): Application server system: If you do not have an application server please specify your user interface: The software is developed in (what language(s)), see also question 8: *It could be helpful to add a drawing of the architecture*

Question 6 Is your follow-up data collection system a system separated from your system for day today business for organ allocation? If yes, please describe and see also question 7
Answer 6

Question 7 Does your follow-up system have interfaces with other systems within your organization?
Answer 7 Yes/No If Yes, which layers (data layer, user interface layer, other)?

Question 8 Please describe the architecture for the software development; (open source) programming language(s), layers, development tools, etc.
Answer 8 *It could be helpful to add a scheme, especially in case you use different layers in your software architecture*.

Question 9 Business rules; where are the business rules of your follow-up system located (in the data entry screens, in the data base, as the second layer, in the web service, in the file up-load)? When the (same) business rules are located in different places, please specify.
Answer 9

Question 10 If you use a separate environment for analysis purposes, please describe the technical architecture. (servers, data base, tools, etc.)
Answer 10 *Please specify name, version.* *It could be helpful to add a drawing of the architecture*

Question 11 If you offer your users on-line analysis tools please describe the technical architecture. (server, tools, your own software, etc.)
Answer 11 *Please specify name, version.* *It could be helpful to add a drawing of the architecture*

Question 12 Are there national standards / regulations on information security management in health, based on ISO 27799:2008?
Answer 12 Yes/No If Yes, please explain

Question 13 Are all registry related IT tasks subcontracted or performed internally?
Answer 13

13.3 Survey on legal issues

Country	
Organ Exchange Organization	
Filled in by name e-mail telephone	
Date	

Please mail your answers of the survey to:
jsmits@eurotransplant.org or
Fax to 0031 71 579 00 57 to the attention of
Dr. J. Smits
EFRETOS project coordinator

ORGANIZATION

Question 1 Do you have a national/regional organization/institution responsible for collecting post-transplant follow-up data?
Answer 1 Yes/No If Yes, all follow-up data is collected at a national or at regional level by ….. (name of the organization).

Question 2 Is there any legal obligation behind the systematic of collection on post-transplant follow-up data? (E.g. laid down in transplantation act, hospital act; mandatory provision for quality management). Please provide the text of this regulation (in English)!
Answer 2 Yes/No If Yes, do you still obtain (informed) consent by the patient (transplant recipient?). Please provide your consent form if existent! If No, do you obtain (informed) consent by the patient (transplant recipient?). Please provide your consent form if existent!

Question 3 Do you have a national registry for the collection of post-transplant follow-up data?
Answer 3 If Yes, what is the name of the organization/institution tasked with managing this registry?

Question 4 Please specify the kind of information which is collected/stored in your registry. If available please provide us with a copy of the data collection form or electronic mask
Answer 4

Question 5 In what way (identifiable / coded/ anonymized) is the information stored in the registry?
Answer 5 Please specify

Question 6 Does your national transplantation act contain provisions on data protection? What are the relevant provisions for data collection in the context of organ transplantation in your data protection act? Are there any exemptions foreseen for medical research and epidemiology?
Answer 6 Yes/No If Yes, please specify these exemptions?

USE AND DISCLOSURE OF DATA REGISTRY

Question 7 What is the specific purpose of the data collection as specified in Answer 4?
Answer 7

Question 8 Do you also collect donor data en do you have the possibility to correlate it to recipient data?
Answer 8

Question 9 Which organizations provide the data to the registry?
Answer 9

Question 10 Is the data published?
Answer 10 Yes/No If Yes, in what way?

Question 11 Who has access to the data in the registry?
Answer 11

Question 12 Is the data transferred to other organizations? (e.g. international registries such as CTS) or individuals?
Answer 12 Yes/No If Yes, in what form and on what legal basis?

Question 13 For what purpose is the data provided to other organizations and/or individuals?
Answer 13

Question 14 Are the patients made aware of any disclosures of their data to third parties?
Answer 14 Yes/No If Yes, in what way?

Question 15 How long is data stored in the registry? If there is a difference between identified, coded and anonymized data please specify.
Answer 15

DATA PROTECTION AND SECURITY

Question 16 Does your registry have a data protection policy that covers all aspects of the processing of personal data?
Answer 16 Yes/No If Yes, please specify or provide the text in English.

Question 17 **Do the security procedures include measures to safeguard the integrity of the data and of its processing?**
Answer 17 Yes/No If Yes, please specify.

RIGHT OF ACCESS

Question 18 Is there a clear procedure for dealing with access requests?
Answer 18 Yes/No If Yes, please provide information.

Question 19 A European wide registry would require the assignment of a unique European identification number for each recipient. Would your national legislation allow the use of a European identification number?
Answer 19 Yes/No

13.4 Survey on quality issues

Data Quality Survey WP7

Country	
Organ Exchange Organization	
Filled in by name e-mail telephone	
Date	

Please send your answers of the survey to:
carlo.decillia@iss.it or
Fax to +390649904101 to the attention of
Dr C.De Cillia
WP7 responsible for CNT

Question 1 Do you collect data on?
- The donation process Yes/ No - The transplant process Yes/ No - The follow-up of transplant recipients Yes/ No

Question 2 Does the registry hold patient identifiable information? (e.g. name, date of birth, place of birth,…)
Answer 2 Yes/ No

Question 3 At which level are donation data being collected? (multiple options possible)
Answer 3 - individual donation unit Y / N - regional registry Y / N - national registry Y / N - otherwise, please explain

Question 4 At which level are transplant data being collected? (multiple options possible)
Answer 4 - individual transplant unit Y / N - regional registry Y / N - national registry Y / N - otherwise, please explain

Question 5 Is it mandatory by national authorities to collect post-transplant outcome data?
Answer 5 Y/N

Question 6 Are the data contributors financially reimbursed?
Answer 6 Yes/No If Yes, please give details

Question 7 Is there a national authority towards which outcome data have to be reported?
Answer 7 Yes/No If Yes, please give details

Question 8 Are the outcome data used by national authorities for monitoring?
Answer 8 Yes/No If Yes, please give details

Question 9 Are the outcome data used for publications?
Answer 9 Yes/No

Question 10 At what time points are data collected (every six months, annually, other)?
Answer 10

Question 11 Is it compulsory to register data?
Answer 11 - donor data Y / N - recipient data Y / N - transplant procedure data Y / N - post-transplant outcome data Y / N

Question 12 Who is entitled to access the data base?
Answer 12

Question 13 Who is entitled to use the data?
Answer 13

Question 14 Is there a system in place for obtaining follow-up data when it is due?
Answer 14 Yes/No If yes, please explain.

Question 15 Do you perform a check on the data format at time of upload or data entry? (i.e. a check right number of variables in the right sequence and with the expected format e.g.: integer, date, string etc...)
Answer 15 Yes/No If yes, please explain.

Question 16 Do you perform a check on internal consistency at time of upload or data entry? (i.e. a check for right "coding" of each variables ,e.g. variable GENDER have to contain only "M" and "F" for "Male" and "Female", in addition to a check for compatibility of different variable combination e.g. "Paediatric Flag"=yes with right "Age" value below 18 years)
Answer 16 Yes/No If yes, please explain.

Question 17 Do you perform a check on duplicate records?
Answer 17 Yes/No If yes, please explain.

Question 18 Do you perform a check on accuracy? (i.e. a check for age negative or > 200 years)
Answer 18 Yes/No If yes, please explain.

Question 19 Do you perform a check on reliability? (i.e. a check on reproducibility , data on 2005 transplants received in 2007 have to be comparable to data on 2005 transplants received in 2008)
Answer 19 Yes/No If yes, please explain.

Question 20 Is there a check on completeness of the data set? (i.e. a check that all performed transplants are recorded in the registry)
Answer 20 Yes/No If yes, please explain.

Question 21 Is there a check on completeness of the outcome data? (i.e. a check on percentage of patients with e.g. 1 year of follow-up)
Answer 21 Yes/No If yes, please explain.

Question 22 Is there a check on completeness of covariate information? (i.e. a check on filling rate of variable on patients information e.g. age)
Answer 22 Yes/No If yes, please explain.

Question 23 Is there a check for systematic omissions?
Answer 23 Yes/No If yes, please explain.

Question 24 Do you use quality indicators for data contributors? (e.g. filling rate of variable collected)
Answer 24 Yes/No If yes, please explain.

Question 25 Do you require minimal standards of quality for your data contributors?
Answer 25 Yes/No If yes, please explain.

Question 26 Are all consecutive transplants delivered by the data contributors? (i.e. data on every transplant performed in your country)
Answer 26 Yes/No If yes, please explain.

Question 27 Do you perform periodically audits at the transplant centres?
Answer 27 Yes/No If yes, please explain.

Question 28 What types of audits take place? (e.g. on site with external or internal commission)
Answer 28 Please explain.

Question 29 Do you verify data that were previously supplied during these audits? (i.e. a check on transplant data collected by the transplant centre)
Answer 29 Yes/No If yes, please explain.

13.5 Survey on safety management systems

13.5.1 Part 1: Non-standard risk donors

1 ARE DONORS WITH ACUTE INTOXICATION AS DIRECT OR INDIRECT CAUSE OF DEATH OR CHRONIC INTOXICATION USED FOR ORGAN TRANSPLANTATION IN YOUR COUNTRY?

1.1 If available, please provide a definition for acute intoxication as direct or indirect cause of death:
1.2 If no, is there any legal and/or technical provision precluding the use of these donors? Please specify the legal and/or technical provision and the source:
1.3 If affirmative, is there any technical document/guideline applied for the use of organs from these donors?
1.4 If affirmative, please specify the conditions agreed upon for the use of organs from these donors:

	CONDITIONS
General recommendation	
Amanita Phalloides	
Antidepressants	
Barbiturics	
Benzodiacepins	
Carbon Monoxide	
Cocaine	
Cyanur	
Ethylenglycol	
Extasis	
Hydrocarburs	
Isoniacide	
Methanol	
Neuroleptics	
Organophosphorade pesticides	
Paracetamol /Acetaminophen	
Plumb	
Other	

1.5 Is there any specific assessment related to the moment of donation / transplantation and to the follow-up of the recipients transplanted from such donors?

If affirmative, please specify below:

	Yes	**No**	**NA**
Graft survival			
Cause of graft loss			
Attributability of graft loss to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Patient death			
Cause of patient death			
Attributability of recipient death to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		

	Yes	No	NA
Any other safety problem after transplantation	Named as: Is severity recorded? What the criteria for considering severe a certain condition? How is it graded? Is attributability recorded? What are the criteria for assessing attributability? How is it graded?		

If affirmative, how long is the specific post-transplant follow-up assessment performed?

2. ARE DONORS WITH A PRESENT HISTORY OF NON-CNS MALIGN NEOPLASIA USED FOR ORGAN TRANSPLANTATION IN YOUR COUNTRY?

2.1 If no, is there any legal and/or technical provision precluding the use of these donors? Please specify the legal and/or technical provision and the source.
2.2 If affirmative, is there any technical document/guideline applied for the use of organs from these donors?

If affirmative, please specify the conditions agreed upon for the use of organs from these donors

	CONDITIONS
General Recommendations	
Renal adenocarcinoma	
Prostate adenocarcinoma	
***In situ* Carcinoma**	
Non melanoma skin cancer	
Others	

2.3 Is there any specific baseline (donors and recipients) and follow-up assessment for recipients transplanted from these donors?
If affirmative, please specify below:

	Yes	**No**	**NA**
Donor: histological type of tumour	Please provide classification		
Donor: size of primary tumour			
Donor: histological severity of the tumour	Please provide classification		
Donor: location of the tumour	Please provide classification		
Donor: date of diagnosis of the tumour			
Donor: treatment (Surgery, Radiotherapy, Chemotherapy…)			
Graft survival			
Cause of graft loss			

Attributability of graft loss to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Recipient death			
Cause of recipient death			
Attributability of recipient death to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Tumour transmission	Please provide information on definition applied for tumour transmission		
Any other safety problem after transplantation	Named as: Is severity recorded? What the criteria for considering severe a certain condition? How is it graded? Is attributability recorded? What are the criteria for assessing attributability? How is it graded?		

If affirmative, how long is the specific post-transplant follow-up assessment performed?

3. ARE DONORS WITH A PAST HISTORY OF NON-CNS MALIGN NEOPLASIA USED FOR ORGAN TRANSPLANTATION IN YOUR COUNTRY?

3.1 If no, is there any legal and/or technical provision precluding the use of these donors? Please specify the legal and/or technical provision and the source.
3.2 If affirmative, is there any technical document/guideline applied for the use of organs from these donors?
3.3 If affirmative, please specify the conditions agreed upon for the use of organs from these donors.

	CONDITIONS
General conditions	
Renal adenocarcinoma	
Prostate adenocarcinoma	
Breast cancer	
Lung cancer	
Colon cancer	
Others	

3.4 Is there any specific baseline (donors and recipients) and follow-up assessment for recipients transplanted from these donors?

If affirmative, please specify below:

	Yes	No	NA
Donor: histological type of tumour	Please provide classification		
Donor: size of primary tumour			
Donor: histological severity of the tumour	Please provide classification		
Donor: extension of the tumour	Please provide stage (TNM?)		
Donor: location of the tumour	Please provide classification		
Donor: time free of disease	Defined as		
Graft survival			
Cause of graft loss			
Attributability of graft loss to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Recipient death			
Cause of recipient death			
Attributability of recipient death to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Tumour transmission	Please provide information on definition applied for tumour transmission		
Any other safety problem after transplantation	Named as: Is severity recorded? What the criteria for considering severe a certain condition? How is it graded? Is attributability recorded? What are the criteria for assessing attributability? How is it graded?		

If affirmative, how long is the specific post-transplant follow-up assessment performed?

4. ARE DONORS WITH A PRESENT HISTORY OF CNS NEOPLASIA USED FOR ORGAN TRANSPLANTATION IN YOUR COUNTRY?

4.1 If no, is there any legal and/or technical provision precluding the use of these donors? Please specify the legal and/or technical provision and the source.

4.2 If affirmative, is there any technical document/guideline applied for the use of organs from these donors?

4.3 If affirmative, please specify the conditions agreed upon for the use of organs from these donors.

	CONDITIONS
WHO grade I	
WHO grade II	
WHO grade III	
WHO grade IV	

4.4 Is there any specific baseline (donors and recipients) and follow-up assessment for recipients transplanted from these donors?

If affirmative, please specify below:

	Yes	No	NA
Donor: histological type of tumour			
Donor: treatment received			
Graft survival			
Cause of graft loss			
Attributability of graft loss to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Recipient death			
Cause of recipient death			
Attributability of recipient death to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Tumour transmission	Please provide information on definition applied for tumour transmission		
Any other safety problem after transplantation	Named as: Is severity recorded? What the criteria for considering severe a certain condition? How is it graded? Is attributability recorded? What are the criteria for assessing attributability? How is it graded?		

If affirmative, how long is the specific post-transplant follow-up assessment performed?

5. ARE DONORS WITH A PAST HISTORY OF CNS NEOPLASIA USED FOR ORGAN TRANSPLANTATION IN YOUR COUNTRY?

5.1 If no, is there any legal and/or technical provision precluding the use of these donors? Please specify the legal and/or technical provision and the source.

5.2 If affirmative, is there any technical document/guideline applied for the use of organs from these donors?

5.3 If affirmative, please specify the conditions agreed upon for the use of organs from these donors.

	CONDITIONS
WHO grade I	
WHO grade II	
WHO grade III	
WHO grade IV	

5.4 Is there any specific baseline (donors and recipients) and follow-up assessment for recipients transplanted from these donors?

If affirmative, please specify below:

	Yes	No	NA
Donor: histological type of tumour			
Donor: treatment received			
Donor: time free of disease	Defined as:		
Graft survival			
Cause of graft loss			
Attributability of graft loss to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Recipient death			
Cause of recipient death			
Attributability of recipient death to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Tumour transmission	Please provide information on definition applied for tumour transmission		
Any other safety problem after transplantation	Named as: Is severity recorded? What the criteria for considering severe a certain condition? How is it graded? Is attributability recorded? What are the criteria for assessing attributability? How is it graded?		

If affirmative, how long is the specific post-transplant follow-up assessment performed?

6. ARE DONORS WITH A POSITIVE SEROLOGY FOR HCV (ANTI-HCV POSITIVE DONORS) USED FOR ORGAN TRANSPLANTATION IN YOUR COUNTRY?

6.1 If no, is there any legal and/or technical provision precluding the use of these donors? Please specify the legal and/or technical provision and the source.
6.2 If affirmative, is there any technical document/guideline applied for the use of organs from these donors?
6.3 If affirmative, please specify the conditions agreed upon for the use of organs from these donors.
6.4 Is there any specific baseline (donors and recipients) and follow-up assessment for recipients transplanted from these donors?
If affirmative, please specify below:

	Yes	No	NA
Donor: Anti-HCV antibodies			
Donor: NAT			
Donor: HCV genotype			
Donor: Anti-HCV treatment			
Recipient: Anti-HCV antibodies	Baseline: Post-transplant (provide timeline)		
Recipients: NAT	Baseline: Post-transplant (provide timeline)		
Recipient: HCV genotype	Baseline: Post-transplant (provide timeline)		
Graft survival			
Cause of graft loss			
Attributability of graft loss to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Recipient death			
Cause of recipient death			
Attributability of recipient death to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Biochemical liver profile	Baseline: Post-transplant (provide timeline)		
Liver histology	Baseline: Post-transplant (provide timeline)		
Any other safety problem after transplantation	Named as: Is severity recorded? What the criteria for considering severe a certain condition? How is it graded? Is attributability recorded? What are the criteria for assessing attributability? How is it graded?		

If affirmative, how long is the specific post-transplant follow-up assessment performed?

7. ARE DONORS WITH A POSITIVE HBs ANTIGEN USED FOR ORGAN TRANSPLANTATION IN YOUR COUNTRY?

7.1 If no, is there any legal and/or technical provision precluding the use of these donors? Please specify the legal and/or technical provision and the source.
7.2 If affirmative, is there any technical document/guideline applied for the use of organs from these donors?
7.3 If affirmative, please specify the conditions agreed upon for the use of organs from these donors.
7.4 Is there any specific baseline (donors and recipients) and follow-up assessment for recipients transplanted from these donors?

If affirmative, please specify below:

	Yes	No	NA
Donor: HBsAg			
Donor: Anti-delta			
Recipient: HB status baseline	HBsAg: Anti-HBc: Anti-HBs:		
Recipient: HB status after transplantation (provide schedule)	HBsAg: Anti-HBc: Anti-HBs:		
Biochemical liver profile	Baseline: Post-transplant (provide timeline)		
Liver histology	Baseline: Post-transplant (provide timeline)		
Graft survival			
Cause of graft loss			
Attributability of graft loss to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Recipient death			
Cause of recipient death			
Attributability of recipient death to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Any other safety problem after transplantation	Named as: Is severity recorded? What the criteria for considering severe a certain condition? How is it graded? Is attributability recorded? What are the criteria for assessing attributability? How is it graded?		

If affirmative, how long is the specific post-transplant follow-up assessment performed?

8. ARE DONORS WITH A POSITIVE ANTI-HBc USED FOR ORGAN TRANSPLANTATION IN YOUR COUNTRY?

8.1 If no, is there any legal and/or technical provision precluding the use of these donors? Please specify the legal and/or technical provision and the source.
8.2 If affirmative, is there any technical document/guideline applied for the use of organs from these donors?
8.3 If affirmative, please specify the conditions agreed upon for the use of organs from these donors.
8.4 Is there any specific baseline (donors and recipients) and follow-up assessment for recipients transplanted from these donors?

If affirmative, please specify below:

	Yes	No	NA
Donor: HB status	HBsAg: Anti-HBc: Anti-HBs		
Recipient: HB status baseline	HBsAg: Anti-HBc: Anti-HBs:		
Recipient: HB status after transplantation (provide schedule)	HBsAg: Anti-HBc: Anti-HBs:		
Biochemical liver profile	Baseline: Post-transplant (provide timeline)		
Liver histology	Baseline: Post-transplant (provide timeline)		
Graft survival			
Cause of graft loss			
Attributability of graft loss to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Recipient death			
Cause of recipient death			
Attributability of recipient death to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Any other safety problem after transplantation	Named as: Is severity recorded? What the criteria for considering severe a certain condition? How is it graded? Is attributability recorded? What are the criteria for assessing attributability? How is it graded?		

If affirmative, how long is the specific post-transplant follow-up assessment performed?

9. **ARE DONORS WITH RISK FACTORS FOR VIRAL INFECTIOUS DISEASES USED FOR ORGAN TRANSPLANTATION IN YOUR COUNTRY?**

9.1 Please provide your definition for risk factors for viral infectious disease.
9.2 If no, is there any legal and/or technical provision precluding the use of these donors? Please specify the legal and/or technical provision and the source.
9.3 If affirmative, is there any technical document/guideline applied for the use of organs from these donors? Please specify.
9.4 Is there any specific follow-up assessment for recipients transplanted from these donors?
If affirmative, please specify below:

	Yes	No	NA
Donor serology	Specify		
Donor NAT	Specify		
Donor risk factor			
Recipient: serology baseline	Specify		
Recipient serology post-transplant	Specify		
Recipient NAT post-transplant	Specify		
Graft survival			
Cause of graft loss			
Attributability of graft loss to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Recipient death			
Cause of recipient death			
Attributability of recipient death to the type of donor	Please provide the criteria and the procedure applied for assessing the attributability		
Tumour transmission	Please provide information on definition applied for tumour transmission		
Any other safety problem after transplantation	Named as: Is severity recorded? What the criteria for considering severe a certain condition? How is it graded? Is attributability recorded? What are the criteria for assessing attributability? How is it graded?		

If affirmative, how long is the specific post- transplant follow-up assessment performed?

10. ARE DONORS WITH EMERGENT INFECTIOUS DISEASES (TROPICAL DISEASES INCLUDED) USED FOR ORGAN TRANSPLANTATION IN YOUR COUNTRY?

10.1 Please provide the list of diseases defined as emergent in your country.

	Yes	No	NA
HTLV I /II			
Chagas disease			
Malaria			
Other (specify)			

10.2 If no, is there any legal and/or technical provision precluding the use of these donors? Please specify the legal and/or technical provision and the source.

10.3 If affirmative, is there any technical document/guideline applied for the use of organs from these donors? Please specify.

10.4 Is there any specific follow-up assessment for recipients transplanted from these donors?

If affirmative, please specify below:

If affirmative, how long is the specific post- transplant follow-up assessment performed?

11. FINAL QUESTIONS:

11.1 Is there any other condition to be considered as non-standard high risk donor?
11.2 Who collects the information above?
11.3 Who manages centrally the information above?
11.4 How long has your system for follow-up assessment of recipients transplanted from non-standard risk donors been in place?

13.5.2 Part 2: Vigilance systems in organ donation and transplantation

Abbreviations:
AR: Adverse Reaction
SAR: Serious Adverse Reaction
AE: Adverse Event
SAE: Serious Adverse Event

1. **ARE AR / SAR ARISING IN THE RECIPIENTS AFTER ORGAN TRANSPLANTATION REPORTED IN YOUR COUNTRY?**

If you have a particular terminology and/or definition of adverse reaction/serious adverse reaction, please provide:

2. **ARE AR / SAR ARISING IN THE ORGAN LIVING DONOR THAT MIGHT BE RELATED TO THE DONATION PROCEDURE REPORTED IN YOUR COUNTRY?**

3. **ARE AE / SAE AT ANY STAGE OF THE ORGAN DONATION AND TRANSPLANTATION PROCESS REPORTED IN YOUR COUNTRY?**

If you have a particular terminology / definition of AE / SAE, please provide:

4. **IS THERE ANY LEGAL PROVISION FOR THE REPORTING AND/OR MANAGEMENT OF THESE AR / SAR and AE / SAE?**

If affirmative, please specify.

5. **IS THERE ANY SPECIFIC PROTOCOL IN PLACE FOR THE REPORTING AND/OR MANAGEMENT OF THESE AR / SAR and AE / SAE?**

If affirmative, please specify (please facilitate the protocol in writing if possible)

6. **REGARDING THE REPORTING OF AR / SAR and AE / SAE:**

6.1. Is there any trigger (signal) for the detection of the case?
If affirmative, please provide information on triggers. What information is reported?

- Person reporting /centre /contact details
- Organ transplanted
- Date of detection
- Type of reaction
- Date of finalization
- Severity (specify classification)
- Attributability to the donor/ donation/transplantation. Specify classification.
- Actions taken

6.2. Is there any particular form used?
If affirmative, please provide
6.3. Is there any maximum time pre-established for reporting?
If affirmative, please specify:
6.4 What format (electronic / paper) is applied for the reporting of this information?
6.4. Who is responsible for reporting?
6.5. To whom is the case reported?

7. **REGARDING THE MANAGEMENT OF AR / SAR and AE / SAE:**

7.1. Who is responsible for the management?
7.2. Is there any protocol in place for the management?
7.3. What is included under the concept of “management”? Please select with an “X” all that apply:

Investigation / Evaluation	
Re-assess severity / attributability	
Follow-up assessment	
Raise conclusion	
Propose corrective or preventive measures	
Implement corrective or preventive measures	
Completion of a report	
Maintenance of the records	
Statistical analyses	

7.4. Who finds out whether there are other recipients or not?
7.5. Who searches for the other recipients, if any?
7.6. Who communicates the situation to other authorities / physicians?
7.7. Who decides whether the other recipients should be communicated or not?
7.8. What are the criteria for the communication of the situation to patients?
7.9. Who communicates the problem to other affected recipients?
7.10. Is traceability from donor to recipient and backwards possible?
If affirmative, how is traceability ensured?
7.11. Is data protection and confidentiality ensured?

8. IS THIS SYSTEM LINKED TO OTHER VIGILANCE AND SURVEILLANCE SYSTEM (I.E. CELLS AND TISSUES, BLOOD AND BLOOD DERIVATIVES, MEDICINES….)?

If affirmative, please specify.

9. IS THERE A PERIODIC REPORT ON AR / SAR and AE / SAE PRODUCED WITHIN YOUR COUNTRY?

9.1. If affirmative who prepares this report?
9.2. How often is this report expected to be delivered?
9.3. To whom is this report delivered?
9.4. What are the statistical indicators foreseen to be provided by your report?

10. COULD YOU PROVIDE INFORMATION ON AR / SAR and AE / SAE ARISING IN SOLID ORGAN RECIPIENTS AND REPORTED/MANAGED IN YOUR COUNTRY DURING THE LAST SIX MONTHS?

14 References

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[22]. Directive 95/46/EC of the European Parliament and of the Council on the protecting of individuals with regard to the processing of personal data and on the free movement of such data. http://ec.europa.eu/justice_home/fsj/privacy/docs/95-46-ce/dir1995-46_part1_en.pdf

EFRETOS COLLABORATING ORGANISATIONS

Deutsche Stiftung Organtransplantation (DSO) - DE
Nederlandse Transplantatie Stichting (NTS) - NE
Autoridade para os servicos de sangue e de transplantacao (ASST) - PT
Transplantations Coordinating Centre (KST) - CZ
The Hellenic Transplantation Society (EOM) - GR
Polish Transplantation Society (Poltranspant) - PL
SlovakTransplant (ST) - SK
Slovenija Transplant - SL
Universitair Medisch Centrum Groningen (UMCG) - NL
University of Padua - IT

For further information
contact: **efretos@eurotransplant.org**

EFRETOS PARTNER ORGANISATIONS

Eurotransplant International Foundation (ET) - NL
Centro Nazionale Trapianti (CNT) - IT
European Society for Organ Transplantation (ESOT)
NHS Blood and Transplant (NHS) - UK
Organizaciòn Nacional de Trasplantes (ONT) - ES
Agence de la Biomédecine (ABM) - FR
ScandiaTransplant - NO

www.efretos.org

European Framework for the Evaluation of Organ Transplants **EFRETOS** Project

The **EFRETOS** Project is co-funded by the European Commission Grant Number 20081101

THE EFRETOS PROJECT

EFRETOS is a 2-year project funded under the Public Health Program of the European Commission.
The general objective of this project is to provide a common definition of terms and methodology to evaluate the results of organ transplantation, by promoting a European registry on transplant outcomes, building on the currently operational or future national and regional registries.
This project will allow a comprehensive view on the quality and safety in solid organ transplantation in Europe, will gauge actual versus expected outcome and evaluate best practices to promote the health and safety standards in all member states. The registry would allow to have a tool for evaluating outcomes of the use of expanded criteria donors or even new treatment methods and drugs.

SPECIFIC OBJECTIVES

To achieve the general objective the main actions are: developing a common data dictionary, defining a methodology and delineating legal, functional and technical requirements for registry management. Furthermore a safety management program closely monitoring risks associated with the use of special categories of donors will be designed. Finally, a quality assurance procedure is to be described.
Specific objectives of the project include:

- The design of the specifications of the European registry;
- The agreement on common definitions of terms and methodology to evaluate the results of transplantation across Europe;
- The promotion of a registry or network of registries on the follow-up of organ recipients;
- To monitor health of patients who have undergone transplantation of organs;
- To set up a quality assurance system for obtaining high quality data on transplantation outcomes

TASK 1: Development of data dictionary

The aim of this task is to develop a data dictionary with clear definitions of all the variables to be included in the registry that all partners (current registries) in Europe can agree on as being the best possible. For this task:
A complete overview of all variables and data definitions currently used by organizations in Europe will be constructed;

- Groups of European experts in the transplantation field will be set up for the different organs;
- A required "minimum" and optional "expanded" data set of variables to be recommended for collection in the registry will be proposed by the experts and decided upon by the consortium
- The data dictionary will describe individual variables and define the data set that will allow risk-benefit analyses in organ donation and transplantation.
- Building on the outcome of the overview and recommendations described under the first task, existing definitions will be discussed and, if acceptable, confirmed.

TASK 2: Methods and legal and technical requirements

The objective of this second task is twofold: to develop methods for analyzing outcomes on organ transplantations and to propose an organizational structure and legal, functional and technical requirements for this future registry of registries.
Once a common data set and method of analysis have been agreed, data for individual countries will be obtained where possible. This will be done in compliance with all data protection and confidentiality frameworks, and in particular shall not involve the transmission of person identifiable information.

TASK 3: Safety management

The objective of this task is to develop a common safety management procedure. Specific objectives are:

- to review the current available information on criteria applied to transplanted organs from donors with specific conditions in the participating European countries, the technical conditions required, the legal issues, as well as on the risks/problems related to their use;
- to provide a set of recommendations on the use of such organs;
- to develop recommendations for a harmonized system for organ vigilance in organ transplantation, incorporating legal, functional and technical requirements for the management of this system (broad European level)

TASK 4: Quality assurance

The objective of this last task is to set up a quality assurance system for obtaining high quality data on transplantation outcomes.
A consensus document identifying an agreed quality assurance methodology will be worked out for a best practice of quality assurance of transplant outcome, data collection, production pathways and auditing methods.
The definition of quality indicators for organ transplantation is a prerequisite for increasing quality of health in this field. Ensuring the quality of data that are used for assessing transplant outcome is pivotal in this process, as quality assurance of registry data allows comparative analysis.
This work will finally lead to a common shared methodology for assessing the quality of post-transplant outcome, the validation of these data sources and their handling.

Brussels, 17 May 2011

EFRETOS Symposium

UNIFYING DATA COLLECTION CREATING NEW KNOWLEDGE

Health Programme 2008-2013 Together for Health

The EFRETOS project is co-funded by the European Commission (Grant number 20081101)

EFRETOS Symposium

UNIFYING DATA COLLECTION - CREATING NEW KNOWLEDGE

Invitation

The EFRETOS project board kindly invites you to the symposium 'Unifying data collection - creating new knowledge'. During the EFRETOS project, experts from all over Europe joined forces to create a European Framework for the Evaluation of Organ Transplants. Their efforts led to a common definition of terms and a data dictionary, methodology to evaluate the results of organ transplantation, an overview of legal and technical requirements, and systems for safety management and quality assurance. At the symposium the most important results will be presented.

Participants

With a variety of presentations the EFRETOS symposium will not only be of interest for scientists, researchers and medical professionals, but also for politicians and policy makers, patients and representatives of organizations in the field of organ transplantation.

The program

The EFRETOS symposium will grant you a brief glimpse at the future of post-transplant data collection in Europe. Keynote speakers will shed their light on potential benefits, share their experiences and present their views on a Registry of registries. Reception is at 10.00 am, the program starts at 10.30 am and around 4.00 pm a get-together will round-up the symposium.

Registration

To attend, please send an e-mail with your name and profession to *efretos@eurotransplant.org*. Attendance is free of charge for invitees and members of the transplant community.

Information

For further information please contact EFRETOS project secretary Ms. Maaike van Hennik, T (+31) 71 5795 795, M *m.hennik@eurotransplant.org*.

agence de la biomédecine

ONT
ORGANIZACIÓN NACIONAL DE TRASPLANTES

Centro Nazionale Trapianti

Preliminary program

10.30 hours **Welcome note**
Dr. Angelika Schlunck, director of the Representation of the Free State of Bavaria to the EU

10.35 hours **Opening**

10.50 hours **The benefits of a Registry of registries**
From different perspectives, four speakers will shed their light on the benefits. ***Stefaan Van der Spiegel***, representing DG Sanco, explains the EU perspective. ***James Neuberger***, medical director NHSBT, handles the institutional point of view. ***Rutger Ploeg***, president ESOT, voices the scientists' opinion. ***Mark Murphy***, vice-president CEAPIR, gets into the benefits for patients.

12.10 hours **The EFRETOS project and its results (1)**
Project leader ***Arie Oosterlee***, general director Eurotransplant, gives an overview of EFRETOS and the structure of the project. ***Jacqueline Smits***, senior biostatistician Eurotransplant, explains the challenge of creating a common data dictionary.

12.45 hours **Lunch break**

13.30 hours **Lessons from transplant registries already in place**
Alessandro Nanni Costa, director CNT, discusses the national registry in place in Italy. ***Maureen McBride***, director of research UNOS, shares what can be learned from the experiences of UNOS.

14.10 hours **The EFRETOS project and its results (2)**
Dave Collett, director statistics NHSBT, presents the methodology and functional requirements of one European Registry. ***Daniela Norba***, legal advisor DSO, recounts the legal requirements. ***Rosario Marazuela***, medical officer ONT, introduces the subject of safety and organ vigilance.

15.10 hours **Time to look ahead**
Frank Delmonico, president elect TTS, draws conclusions: what has been accomplished and what will it take to put words into action? All former speakers join in to discuss how to proceed towards a Registry of registries.

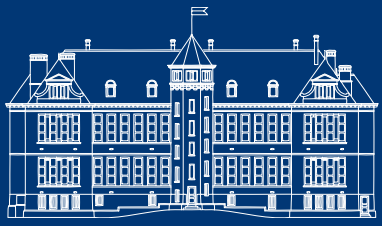
16.00 hours **Closing, followed by a get-together**

EUROTRANSPLANT

SCANDIA TRANSPLANT

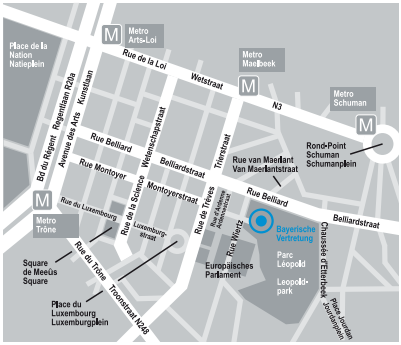
ESOT

NHS Blood and Transplant



The EFRETOS symposium takes place in the charming Representation of the Free State of Bavaria to the EU in Brussels, a stone's throw away from the European Parliament. The Representation of the Free State of Bavaria to the EU kindly supports the symposium.

Address Rue Wiertz 77, 1000 Brussels, tel. +32 (0)2 237 4811



European Framework for the Evaluation of Organ Transplants

Links

Work packages

- WP1 - Project Management
- WP2 - Dissemination of the project
- WP3 - Evaluation of the Project
- WP4 - Development of data dictionary
- WP5 - Methods and legal and technical requirements
- WP6 - Safety management
- WP7 - Quality assurance

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American Journal of Kidney Diseases

American Journal of Transplantation

British Medical Journal

Critical Care Nurse

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Layman's brochure

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Efretos Symposium

- Invitation EFRETOS Symposium May 17, 2011

Events calendar

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Journal of the American Medical Association

Medline

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Nature

Nephrology, Dialysis & Transplantation

Reuters Health

Science

Scientific American

The Journal of Immunology

The Lancet

The New England Journal of Medicine

Transplant Information

Transplant International

Transplant News

Organ Exchange Organizations

Agence de la Biomédecine

Czech coordinating centre (KST)

Eurotransplant International Foundation

Hellenic National Transplant Organization - EOM

Lithuanian Bureau of Organ Transplantation

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Organizaçäo Portuguesa de Transplantaçäo

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Swiss Transplant

bultransplant.bg

Hungarian National Blood Transfusion Service (HNBTS

Deutsche Stiftung Organtransplantation - DSO

UKtransplant

Other Useful Links

American Board of Transplant Coordinators (ABTC)

American Society of Nephrology

American Society of Transplant Surgeons (ASTS)

American Society of Transplantation

Association of Organ Procurement Organizations (AOPO)

CenterSpan

Euroliver Foundation

European Liver Transplant Registry

European Society for Organ Transplantation (ESOT)

European Transplant Coordinators Organization (ETCO)

International Society of Heart and Lung Transplantation (ISHLT)

International Transplant Coordinators Society (ITCS)

International Transplant Nurses Society (ITNS)

LifeSource

North American Transplant Coordinators Organization (NATCO)

Organ Donation (USA)

The Transplantation Society

Transweb

U.S. Renal Data System

European Framework for the Evaluation of Organ Transplants

Contact us

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Telephone: 0031-71 5795 795

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