The Effect of Differing Kidney Disease Treatment Modalities and Organ Donation and Transplantation Practices on Health Expenditure and Patient Outcomes

Final Public Report

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I. Executive Summary

Chronic Kidney Disease (CKD) is the cause of substantial morbidity and mortality and results in major burden to both, individual patients and society as a whole. It has been estimated that about 10% of the population in Europe is affected by CKD and the number of patients is expected to grow as the prevalence of typical risk factors for CKD, such as diabetes and hypertension, is still increasing. CKD is divided into five stages, with stage I describing normal kidney functioning but evidence of kidney damage up to stage V representing kidney failure [KDIGO 2012]. Already from its early stages on, CKD is associated with an increased risk of complications.

Patients who reach stage V of CKD, which is also referred to as end stage kidney disease (ESKD), are in need of a renal replacement therapy (RRT). RRT modalities include hospital-based or home-based haemodialysis or peritoneal dialysis or transplantation from a living or from a deceased donor. It is common to all forms of RRT that they are complex and expensive.

Among Europe, there is a great variability in the use of RRT modalities (Figure 1). The extent of this variability gives reason to believe that not all patients with ESKD receive the most appropriate treatment. Apart from the actual impact on individual patients, this also represents a considerable burden for health care systems.

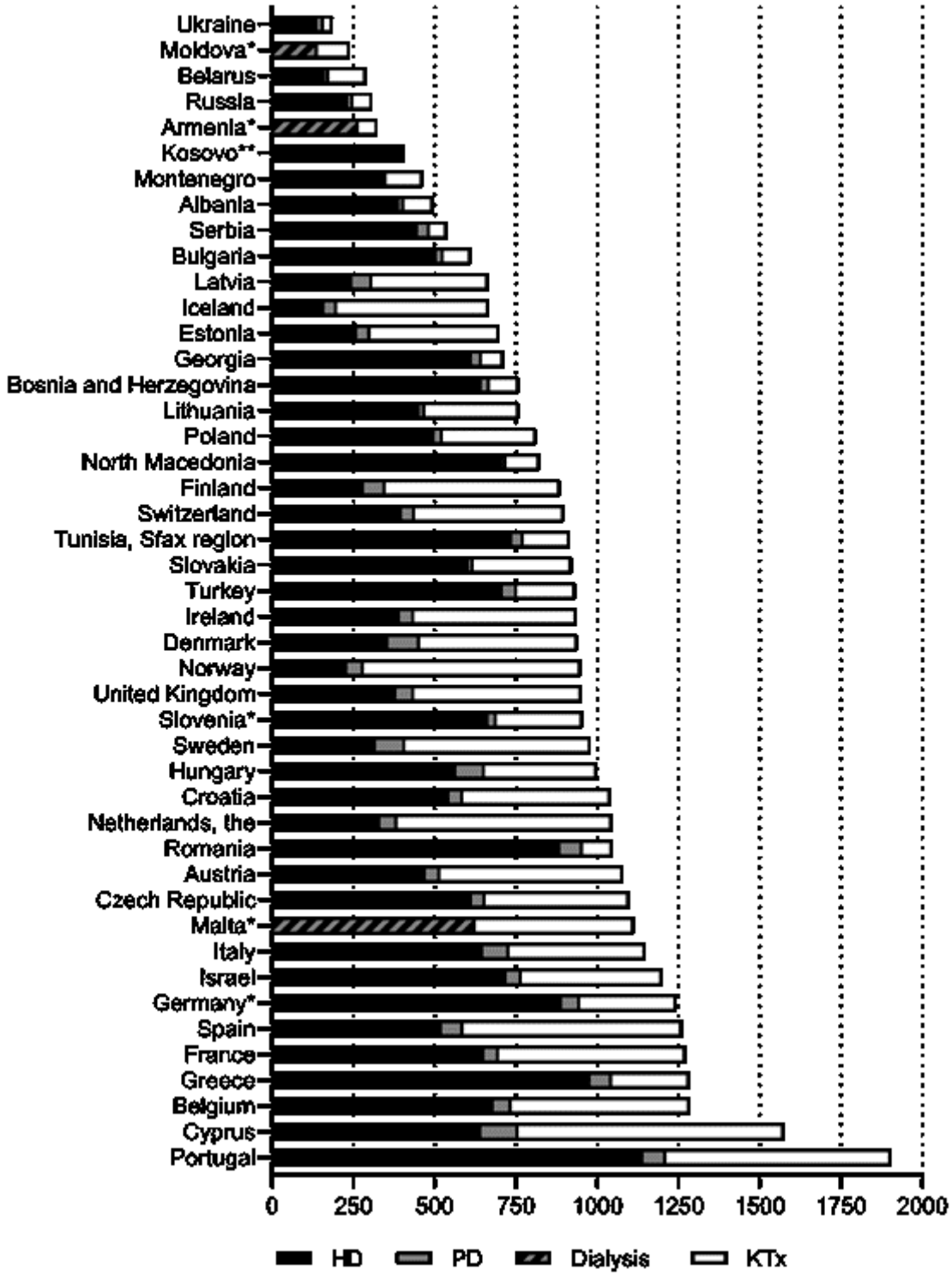

Figure 1: Prevalence per million population by treatment modality on 31 December 2016
(no data was available from Cyprus, Malta and Luxembourg)

In accordance with the values set in the EU-Health Strategy "Together for Health", the key objective of European Pilot Project EDITH (The Effect of Differing Kidney Disease Treatment Modalities and Organ Donation and Transplantation Practices on Health Expenditure and Patient Outcomes) was to lay grounds for providing equal access to good quality healthcare throughout the European Union. In order to achieve this goal, the 48-months project aimed to identify reasons for existing variations in

CKD management as well as to obtain information on long-term kidney transplant outcomes as well as long-term health outcomes of living kidney donors.

EDITH was subdivided into six closely interlinked work packages and involved nine partner organisations from all over Europe:

- Deutsche Stiftung Organtransplantation (DSO) – Germany, project coordination
- Országos Vérellátó Szolgálat (OVSz) – Hungary, project dissemination
- Ministarstvo zdravlja Republike Hrvatske (MoHRC) – Croatia, project evaluation
- Academisch Medisch Centrum (AMC) on behalf of European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) – The Netherlands, WP4
- Istituto Superiore di Sanità – Centro Nazionale Trapianti (ISS-CNT) – Italy, WP4
- Nederlandse Transplantatie Stichting (NTS) – The Netherlands, WP5
- Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) – Spain, WP5 with Hospital Clinic Barcelona (HCB) as affiliated entity
- Eurotransplant International Foundation (ET) – The Netherlands, WP6
- National Health Service Blood and Transplant (NHSBT) –UK, WP6

WP4 Treatment modality choices, outcomes and costs for end-stage kidney disease

An analysis of the epidemiology and costs of different RRT modalities and conservative management was performed to fill existing knowledge gaps regarding the management of ESKD in Europe and countries bordering the Mediterranean Sea. The analysis included an assessment of 1) the frequency of the various treatment modalities for ESKD; 2) factors that influence the choice of those treatment modalities by patients and doctors; 3) the impact of treatment modality choices on health outcomes like patient survival and quality of life, and 4) the impact on health care budgets.

WP4's results deliver starting points for improvements and for harmonizing the availability of ESKD treatment across the EU.

WP5 Establishment of registries to follow-up living donors

Living donor follow-up registries, that support lifelong data collection at fixed intervals of time, are considered necessary to ensure the highest possible protection of the living donor. Corresponding provisions are requested in the EU-Directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation.

As the benefit of a registry strongly depends on the volume of its recorded data, a supranational registry is seen as a valuable opportunity to derive evidence-based answers in an adequate time frame. A European Living Donor Registry (ELDR) has been developed, comprising of a database, a web-based application supporting both direct data entry and file upload, a data download facility, and a report facility complying with all legal requirements. WP5's ELDR not only provides transparent information on living organ donation and transplantation activities, it also allows to identify risk factors for living donors.

WP6 Establishment of follow-up registers for kidney transplant recipients

Comprehensive data on outcomes following kidney transplantation is essential for evaluating the quality and safety of organ donation and transplantation and helps to enhance the development of organ allocation schemes. Additional information on the quality of life of transplant recipients enables to evaluate the benefits of transplantation even more broadly.

Based on recommendations of the previous EU project „European Framework for Evaluation of Organ Transplants" (EFRETOS), a European Kidney Recipient Registry (EKRR) has been developed that

combines data from different Member States. By including also information regarding the quality of life of the transplanted patient, WP6's EKRR provides necessary information in order to adjust the process of organ donation and transplantation, for instance in donor and patient selection and kidney allocation.

Conclusions and recommendations

The EU Health Programme, a main instrument used by the European Commission to implement the EU Health Strategy, defines the facilitation of access to better and safer healthcare for Union citizens as one of its major objectives. The Pilot Project EDITH has contributed to this objective as it suggests ways to fill existing knowledge gaps in order to reduce inequalities and to reach an alignment of procedures and practices in the treatment of CKD as well as organ donation and transplantation. With regard to the living donor registry, EDITH also supported the successful implementation of EU policies (Figure 2).

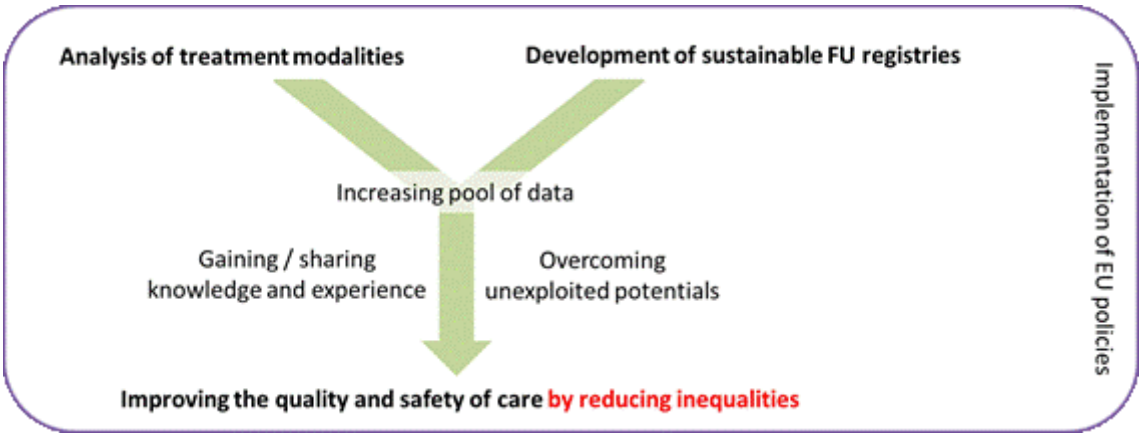

Figure 2: EDITH's long term effects

The sharing of knowledge and good practices is considered a key contributor to increase the overall quality of healthcare across the EU. While data on organ donation and transplant activities in European countries are readily available and published annually, similar data on donor and recipient variables and their impact on transplant outcomes are lacking in many countries. Such information – especially when combined European wide – would allow optimizing the use of scarce organs as well as the overall benefits of organ transplantation, primarily reflected in patients' survival rate and quality of life. In addition, also a timely identification of associated risk factors would be possible, so that adverse appearances in both, transplant recipients and living donors could be managed and preventive strategies and health policies be developed.

In order to fully exploit the potentials of a European data pool on organ donation and transplantation, European Member States are advised to

- ensure national data collection and data delivery to the European transplant registries
- actively support and engage in the continuous development and governance of the European registries
- promote the application of experts to the different posts described in the governance structure of the EDITH registries.

Different institutions such as national transplant organisations, organ exchange organisations and professional associations support the continuation of efforts to establish European transplant registries. The larger the volume of data on transplantation, the more accurate conclusions and appropriate strategies can be drawn and implemented at national and EU level.

II. Description of the Pilot Project EDITH

II.1. Background and objectives

II.1.1 Background

Chronic diseases affect the sufferer over a long period of time and generally progress slowly. Some of them – cardiovascular diseases, cancer, chronic respiratory or kidney diseases, diabetes, mental illness – represent leading causes of mortality. To efficiently address the challenge of chronic diseases, an integrated, horizontal approach is essential – involving all the relevant levels, from communities to policy makers. The EU promotes a comprehensive approach to tackling the chronic disease burden in Europe, for example by efficiently addressing major risk factors (smoking, alcohol abuse, unhealthy diet & lack of physical activity), systematically integrating policy and action to reduce inequalities in health, or improving older people's health and quality of life and the efficiency of care systems through initiatives such as the European Innovation Partnership (EIP) on Active & Healthy Ageing [EU policies]. The reflection process on chronic diseases also brings together the Member States and the Commission to coordinate efforts to respond to the challenges of chronic diseases.

Among chronic diseases, chronic kidney diseases (CKD) are important diseases, often 'silent' but with huge costs for the patients (in terms of quality of life and life time) and for the society in general. It is estimated [EKHA 2015] that one in 10 Europeans have at least one symptom of existing CKD, such as the presence of protein in the urine – an indicator of reduced kidney function. And an estimated 90% of these individuals are unaware they have early-stage CKD, as they experience few or no symptoms. Nevertheless, from its early stages onwards, CKD is associated with an increased risk of complications and death, to a large extent attributable to an ensuing cardiovascular event. Diabetes is the leading cause of kidney disease, followed by high blood pressure (hypertension). The prognosis faced by patients with CKD is linked with the effects of these other diseases. Although progress has been made in recent years, end-stage renal disease still kills more people each year than breast or prostate cancers or even road traffic accidents. Globally there was an 82% increase in the number of deaths from CKD between 1990 and 2010.

Patients who eventually reach end-stage kidney disease need renal replacement therapy (RRT) via dialysis or kidney transplantation. Data from the European Renal Association- European Dialysis and Transplant Association (ERA-EDTA) Registry shows that the prevalence of people on RRT across Europe increased by 3.3 % from 2011 to 2012 to reach 716.7 per million population. They are different types of renal replacement therapies: for dialysis hospital-based or home-based haemodialysis or peritoneal dialysis, and transplantation from a living or from a deceased donor. The type of therapy chosen will depend on the clinical status of the patient, but also of the options available in his/her environment, as well as of orientations proposed by the treating physicians. For some patients reaching end-stage kidney disease, neither dialysis nor transplantation can be envisaged, because of the patients' own choice or due to their poor clinical condition.

The costs for treating CKD are important. The most commonly prescribed form of dialysis in EU Member States, hospital-based haemodialysis alone costs up to €80,000 per year per patient. Moreover, this does not take into account the lost productivity caused when CKD interferes with time at work, or prevents patients from working altogether. In general, it is estimated that RRT consumes 2% of overall healthcare expenditure in Europe, for only 0.1% of the population. The total 'direct' cost of RRT across Europe is unknown, but one estimate puts it at up to €15 billion per year. There are additional healthcare costs of co-interventions needed to sustain RRT and to treat its

complications, indirect costs associated with the time patients are absent from work while undergoing treatment, and ancillary costs such as transportation to and from the clinic. These figures also exclude the medical costs incurred before patients reach end-stage CKD – a population estimated to be around 100 times larger than the population on RRT. Moreover, choices of a type of renal replacement therapy are not always the best adapted to the patients' needs.

Amongst renal replacement therapies, it has been demonstrated [EUMoH 2012] that kidney transplantation, in particular from living donors, offers the best results in terms of health outcomes for the transplanted patient, often avoiding dialysis (while it is also possible and necessary to ensure the best possible screening and protection of the living donors), but also in terms of cost-effectiveness; thus enabling to best treat more patients in need. Health Ministers confirmed in December 2012 in their Council Conclusions that "organ transplantation is considered to be the most cost-effective treatment for end-stage renal failure" [Consilium 2018].

In the European Union, organ donation and transplantation is an issue tackled by Member States, but also at EU level. The Commission adopted in 2007 a "Communication on organ donation and transplantation" and the undertaken impact assessment identified major policy challenges for organ donation and transplantation. These included 1) ensuring the quality and safety of human organs, 2) increasing organ availability and 3) enhancing the efficiency and accessibility of transplantation systems in the EU. A public consultation demonstrated wide support for EU initiatives in this field.

In December 2008, the Commission adopted a proposal for a Directive that defines quality and safety requirements for human organs, and an Action Plan [EU policies] for improving co-operation between Member States in this field. The directive 2010/53/EU on standards of quality and safety of human organs intended for transplantation [Directive 2010/45/EU] was adopted by the European Parliament and the Council on 7 July 2010. It provides for the appointment of Competent Authorities in all Member States, for authorisation of procurement and transplantation centers and activities, for traceability systems, as well as for the reporting of serious adverse events and reactions. The deadline for Member States to transpose the requirements of the Directive was 27 August 2012.

While Directive 2010/53/EU applies a generic approach for all types of human organs intended for transplantation (no specific considerations for kidneys, or livers, or lungs etc.), the Article 15 on quality and safety aspects of living donation deserves to be mentioned in this call, as it is particularly relevant for kidney transplants from living donors: "1. Member States shall take all necessary measures to ensure the highest possible protection of living donors […]. 2. Member States shall ensure that living donors are selected on the basis of their health and medical history, by suitably qualified and trained or competent professionals. Such assessments may provide for the exclusion of persons whose donation could present unacceptable health risks […]. 3. Member States shall ensure that a register or record of the living donors is kept […; 4. They] shall endeavour to carry out the follow-up of living donors and shall have a system in place […] in order to identify, report and manage any event potentially relating to the quality and safety of the donated organ, and hence of the safety of the recipient, as well as any serious adverse reaction in the living donor that may result from the donation." In addition to this quality and safety aspects in the EU legislation, the EU Action Plan on organ donation and transplantation states that EU "Member States should to increase organ availability, promote living donation programme following best practices" (objective 2) and therefore "support registers of living donors" (priority action 3). The development of such registers, and of methodologies to apply for such registers, has been supporting by a Working group of national experts on Living Donation and has also been co-funded, via the EU Health Programme and other EU funding mechanisms, in several projects, for example EULID, ELIPSY, the LIDOBS and the ELPAT Conferences and most recently the Joint Action ACCORD (Work package 4, building upon previous projects). In addition, EU-funded Research projects relating to kidney diseases or transplantation will

be valuable for this pilot project, for example POSAT, COPE, DIREKT; Kidney Injury, Technology, OLDIAS and SCOPE.

Another important aspect of organ transplantation in general and of kidney transplantation in particular is the follow-up of transplanted patients. Indeed, it is not worth transplanting patients if they do not survive the transplant procedures and also if they do not have a good, or at least improved quality of life after transplantation. In addition, the collection of post-transplant results can offer findings on the mid- and long-term only if done in a consistent and comprehensive manner, via commonly defined methodologies. In its recital 24, Directive 2010/53/EU mentions that "the collection of relevant post-transplantation data is needed for a more comprehensive evaluation of the quality and safety of organs intended for transplantation. Sharing such information between Member States would facilitate further improvement of donation and transplantation across the Union." Under its Objective 5 (improving quality and safety), the EU Action Plan on organ donation and transplantation also recognises the need for the "evaluation of post-transplant results", its Priority Action 9, with two actions: action 9.1. "develop common guidelines of terms and methodology to evaluate the results of transplantation", and action 9.2. "develop a register or network of registers to follow up organ recipients". Action 9.1. has been implemented via the EU funding of the international collaborative project EFRETOS13 (European Framework for the Evaluation of Organ Transplants). It is proposed to implement Action 9.2. via the present pilot project, building upon the results, methodologies and terms delivered in the EFRETOS project.

II.1.2 General Objective of the project

In accordance with the values set in the EU-Health strategy "together for health", the key objective of EDITH was to lay grounds for providing equal access to good quality health care throughout Europe. With a focus set on CKD, the alignment of treatment modalities as well as the access to transplantation was seen as an essential precondition. In order to achieve the overall objective, the project wanted to examine the effect of differing kidney disease treatment modalities and organ donation and transplantation practices on health expenditure and patient outcomes. The project's three main priority areas were

1. the assessment of the different treatment modalities for chronic kidney diseases (haemodialysis, peritoneal dialysis (hospital-based or home-based), transplantation from deceased donors and living donors, conservative management) used currently in the different EU Member States and associated countries; the frequency of choice of each of the available options, the factors influencing the treatment choice, the impacts in terms of health and costs, both at patient's level and societal level;
2. the establishment by EU Member States of registries to follow-up living donors, as required under Article 15 of Directive 2010/53/EU, following the methodology and data set already defined in the EU-funded Joint Action ACCORD; solutions should be proposed for each Member State to fulfill its legal obligation, while international data sharing should also be put in place for Member States interested;
3. the establishment of follow-up registers for transplant recipients, at minima at national levels and possibly also at European level, following the methodologies and recommendations already formulated and tested, for example via the EU-funded project EFRETOS.

II.1.3 Specific objectives of the project

#	Title	Indicators	WP
1	Assess the frequency of different treatment modalities for end-stage kidney disease (ESKD) in the different EU Member States and associated countries	Analysis of the frequency (both incidence and prevalence) of treatment modalities (haemodialysis (including its subtypes home haemodialysis, haemofiltration and haemodiafiltration), peritoneal dialysis and renal transplantation from living and deceased donors)	WP4
2	Analysis of the factors influencing the choice of treatment modalities by patients and doctors	Report on factors influencing the choice of treatment modalities by patients and doctors, including information derived from the literature and results from surveys among patients and doctors	WP4
3	Analysis of the impact of treatment modality choices on health outcomes like quality of life and patient survival	Report on impact of treatment modality choice on health outcomes	WP4
4	Evaluation and analysis of impact of different treatment options for CKD on costs	Report on the current practices in CKD – financial impact	WP4
5	Identify participating countries for the European Living Donor Registry (ELDR)	Report on outcomes of questionnaire about willingness to participate among EU Member States	WP5
6	Description of the functional design of the ELDR	Report on the ELDR specifications (dataset, functional and technical requirements)	WP5
7	Description of the governance structure of the ELDR	Report on governance organization for the ELDR (and data request handling)	WP5
8	Provide functional and technical advice to support national initiatives to set up or further develop living donor registries	Report on support given during the course of the project to different national organizations and initiatives	WP5
9	Setting up a European Living Donor Registry including long-term living donor follow-up data delivery to ELDR	Realization of an ELDR including technical management	WP5
10	Proposal for achieving sustainability of the Europeans Living Donor Registry	Recommendation report for a sustainable ELDR including calculation of costs to continue the ELDR after the project and recommendations for future financing, based on outcomes of a questionnaire among EU countries (especially objective 5)	WP5
11	Identify needs of Member States in regard to setting up a national follow-up registry of kidney transplant outcomes	Report on status of existing national kidney follow up registries, their content and requirements for future development	WP6
12	Agree on a data set that specifies the variables that should feature in a national registry and produce the corresponding data dictionary, closely following the work accomplished in the EFRETOS project	Report on variables that need to feature in a national transplant registry Report on technical needs, reporting requirements and IT to provide adequate data collection methods and recommendations on incorporation of a sound legal basis for patient consent	WP6
13	Description of the functional design of national and supranational follow-up registries	Report on the functional design of national and supranational follow-up registries.	WP6

#	Title	Indicators	WP
14	Establish a European transplant registry from combining data from Member States and demonstrate how this can benefit transplant practice across Europe including Support of the building of national follow-up registries by member states, with the possibility of international data sharing	Realization of a European transplant registry including technical management	WP6
15	Design a governance structure that enables a sound and sustainable basis for the registry	Report on governance, organisation, publication policies and data sharing policy for European Registry	WP6
16	Carrying out a study in as many Member States as possible on the quality of life of kidney transplant recipients, and determine the potential for including such data in a national registry	Report on the design and implementation of a Quality of Life tool for kidney transplant recipients.	WP6
17	Proposal for achieving sustainability of the European Kidney Transplant Follow-up Registry	Report on plans for the sustainability of National and European transplant registries	WP6

II.1.4 Targeted groups

EDITH had a wide range of target groups. In the first place of course the patients themselves and the corresponding patient organizations, because all treatment options and their impact that were discussed and analysed in this project, can have an immediate impact on the patients. That was also the reason why the patient groups were actively involved in all work packages looking at the preferences of the patients and the impact of the different treatment options on the quality of life of the patients. The results of the project are not only informative for the patients, but will most probably also very practically influence the treatment options and choices for the patients, at least in the long run.

The medical community was another important target group, especially the healthcare professionals involved in the treatment of patients with CKD as well as healthcare professionals working in the field of organ donation and transplantation. The results of the data, reports and analyses provided by the different registries involved in this project can have an immediate impact on evidence based decision making regarding the treatment choices that are offered to individual patients with end-stage organ failure. The most important aspect of a large data base is, that the analyses has not only a general but also a possible patient-specific impact, because the conclusions that can be drawn from the data of the registry also allow to develop recommendations for tailored treatment of patients with specific comorbidities and risk factors. This target group was taken into consideration on two levels, regarding their practical work in patient care within hospitals and transplant centres and regarding their scientific activities within professional associations.

Further target groups were the health ministries, national competent authorities and delegated bodies, because the results of the project might have direct impact on policy making and financial decision making. To this end also the health insurance systems of the different member states can benefit from the medical analyses but also the related aspects of the financial implications of the different treatment options. Together it was expected that this can contribute to the harmonization of the treatment options in the EU and other countries.

II.2. Project structure

II.2.1 Consortium

Deutsche Stiftung Organtransplantation (DSO) - Coordinating organisation
Deutsche Stiftung Organtransplantation (DSO) is the national organ procurement organization responsible for coordinating post-mortem organ donation in Germany (see §11 TPG). Its tasks and responsibilities are settled in an agreement with its contracting authorities, the German Medical Association, the National Association of Statutory Health Insurance Funds and the German Hospital Federation.

Hungarian National Blood Transfusion Service (OVSZ)
The Hungarian National Blood Transfusion Service – Országos Vérellátó Szolgálat (OVSZ) serves as national centralized provider of blood component products to the hospital sector in Hungary and is responsible for strategic planning, management, training and advisory activities in health policy decision making for the field of preparative and clinical transfusiology. The Organ Coordination Office (OCO) – Szervkoordinációs Iroda (SzI) as department of the OVSZ is responsible for all Hungarian organ and tissue procurement coordination.

Ministarstvo zdravlja Republike Hrvatske – Ministry of Health Republic of Croatia (MoHRC)
The Institute for Transplantations and Biomedicine is an organization unit of the Ministry performing the tasks of planning, coordination and monitoring the implementation of measures for ensuring availability and safety of biological materials for the purpose of medical treatment. The institute plans, prepares, coordinates and monitors the implementation of the National Transplantation Programme.

Academisch Medisch Centrum (AMC)
on behalf of European Renal Association – European Dialysis and Transplant Association (ERA-EDTA).

In this project the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry will be represented by the Academic Medical Centre Amsterdam (AMC). The ERA-EDTA and AMC have a longstanding and successful collaboration on this European registry for kidney patients treated by dialysis or transplantation.

Istituto Superiore di Sanità - Centro Nazionale Trapianti (ISS-CNT)
The National Institute of Health (ISS) is a public technical and scientific body of the Italian NHS, under the control of the Ministry of Health. Italian National Transplant Centre (CNT) is a technical body of the Ministry of Health, it was set up under the Law n. 91 of 1999 and it is located at the ISS where it performs its activities as a department of the same body.

Nederlandse Transplantatie Stichting (NTS)
The Dutch Transplant Foundation is a Competent Authority according to European Directive 2010/45/EU. The foundation was set up to mediate in obtaining, characterizing and transporting organs as well as in assigning the organs to a suitable recipient.

Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)
The Consorci Institut D'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) is a public research centre dedicated to translational research in the field of biomedicine. Hospital Clínic de Barcelona (HCB) – affiliated entity to IDIBAPS – is a university tertiary hospital located in Barcelona.

Eurotransplant International Foundation (ET)
The Stichting Eurotransplant International Foundation is a non-profit international organisation that facilitates allocation and cross border exchange of deceased donor organs for its members: Austria,

Belgium, Croatia, Germany, Hungary, Luxembourg, the Netherlands and Slovenia. In this international collaborative framework, the participants include all transplant hospitals, tissue typing laboratories and hospitals where organ donations take place.

National Health Service Blood and Transplant (NHSBT)

NHS Blood and Transplant is a Special Health Authority in England and Wales, accountable to the Department of Health. The organisation is responsible for the supply of safe blood to hospitals in England, and for the supply of tissues and solid organs to hospitals across the UK. Specific responsibilities include promoting blood, tissue and organ donation to the public, managing the supply of blood to hospitals in England, managing organ transplantation in the UK, managing the British Bone Marrow Register, and working with hospital colleagues to promote the safe and appropriate use of blood.

Table 1: EDITH's project partner

WP	Applicant organisation name	Country
1	Deutsche Stiftung Organtransplantation (DSO)	DE
2	Hungarian National Blood Transfusion Service (OVSZ)	HU
3	Ministarstvo zdravlja Republike Hrvatske – Ministry of Health Republic of Croatia (MoHRC)	HR
4	Academisch Medisch Centrum (AMC) on behalf of European Renal Association – European Dialysis and Transplant Association (ERA-EDTA)	NL
4	Istituto Superiore di Sanità - Centro Nazionale Trapianti (ISS-CNT)	IT
5	Nederlandse Transplantatie Stichting (NTS)	NL
5	Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)	ES
6	Eurotransplant International Foundation (ET)	NL
6	National Health Service Blood and Transplant (NHSBT)	UK

II.2.2 Work packages

WP1 Coordination

WP 1 was dedicated to the coordination of the project, including the technical, administrative and financial management. The specific objectives of WP 1 were:

- to promote an efficient implementation of all tasks within the project
- to monitor the actions of every WP and their alignment to the overall objectives
- to support all partners in carrying out their project-related tasks
- to accompany decision processes on issues that might affect the achievement of the overall objectives of the project and provide assistance in the implementation of sound, long-term solutions
- to provide an effective management of common activities of the EDITH consortium
- to ensure an efficient administrative and financial management of the project, including the provision of reports and other required documentation
- to maintain the communication of the EDITH consortium with the European Commission representatives and the Project Officer

WP2 Dissemination

The role of Work Package 2 was to ensure that the project, its outcomes and deliverables were made known to all relevant target groups and stakeholders. The specific objectives of WP 2 were:

- to develop a unique visual appearance of the project
- to identify all relevant target groups and to develop a concise dissemination plan
- to inform all target groups about the project, its overall objectives, goals and development
- to promote the outcomes and results of the project

WP3 Evaluation

Work Package 3 aimed to ensure that the project was implemented as planned. Specific objectives were:

- Monitoring and evaluation of the partnership (communication, commitment, leadership, meeting organisation, etc.), the process (milestones, achievement of objectives, etc.) and the products (reports, websites, etc.)
- Evaluation of the action's effectiveness, the achievement of objectives and the impact of outcomes

WP4 Treatment modalities choices, outcomes and costs for end-stage kidney disease

Objectives of WP4 were

- To assess the frequency of different treatment modalities for end-stage kidney disease (ESKD) in the different EU Member States and associated countries;
- To determine the factors influencing the choice of those treatment modalities by patients and doctors;
- To determine the impact of treatment modality choice on health outcomes like quality of life and patient survival;
- To evaluate the impact of treatment modality choice on health care budgets

WP5 Establishment of registries to follow-up living donors

WP5 aimed to support the establishment of registries to follow-up living kidney donors, in line with Article 15 of Directive 2010/53/EU. This WP supported MS in building up their national systems to follow-up living donors as well as the development and implementation of a common, supranational tool to share data.

WP6 Follow-up registry for transplant recipients

This work package was build on the work of the EFRETOS project. Aim was to facilitate a consistent and comprehensive collection of data in EU Member States through national kidney follow-up registries and to enable a European Kidney Transplant Registry to be established.

Table 2: EDITH's work packages

WP	Title	Description
1	Coordination of the project	Actions undertaken to manage the project and to make sure that it is implemented as planned
2	Dissemination of the project	Actions undertaken to ensure that the results and deliverables of the project will be made available to the target groups
3	Evaluation of the project	Actions undertaken to verify if the project is being implemented as planned and reaches the objectives
4	Assessment of different treatment modalities for CKD	Preparation of an overview on different treatment modalities for CKD focusing on: - a comparison, from a micro- and macro-economic perspective, of the various treatment modalities for CKD in EU Member States and associated countries (Iceland, Norway, Turkey, Switzerland) - factors that influence the selection of those modalities in Member States and associated countries (Iceland, Norway, Turkey, Switzerland) - factors that influence the treatment choice from the patients' or doctors' perceptive - impact of treatment choice on healthcare budgets

WP	Title	Description
5	Establishment of registries to follow-up living donors	Establishment of an operational tool (register) to follow-up living donors (kidney). The basic registry tool will support MS in building up their national systems. Additionally, an option for international data sharing is foreseen. Such operational tool will be based on the experience learned and recommendations formulated by previous EU-funded projects (e.g. ACCORD). It will contribute to ensure the quality and safety aspects required by EU legislation in the field of organ donation and transplantation and it will serve the whole transplant community, as learnings from such registers will enable to propose better indications for (future) patients on transplant waiting lists.
6	Establishment of follow-up registers for transplant recipients	Establishment of an operational supranational tool (register) to follow-up transplant recipients. Such operational tool will be based on the experience learned and recommendations formulated by previous EU-funded projects (e.g. EFRETOS). It will contribute to ensure the quality and safety aspects required by EU legislation in the field of organ donation and transplantation and it will serve the whole transplant community, as learnings from such registers will enable to propose better indications for (future) patients on transplant waiting lists.

II.2.3 Timeline

The project was originally scheduled to last 36 months, from 01.01.2017 to 31.12.2019. During the runtime of the project, two requests for an extension of the duration have been submitted and approved. In the end, the duration of the project was 48 months, from 01.01.2017 to 31.12.2020.

The first amendment was filed in May 2019. The extension became necessary as many partners reported significant delays in at least one deliverable. According to the partners, the entry into force of the General Data Protection Regulation (GDPR) has led to uncertainties among the European Member States regarding the correct interpretation of new requirements. Accordingly, several countries expressed reservations about EDITH's chosen approaches on international data collection. These reservations affected both, the conduction of pan-European surveys (WP4) as well as the development of registries (WP5, WP6).

The second amendment was filed in April 2020 as a result to the challenges due to the coronavirus pandemic after many partners stated that they only had limited capacities to implement the actions required for EDITH's closure. The second extension of the project duration was supposed to enable a

proper finalisation of the technical work, including the collection of more data in the database and the implementation of foreseen dissemination measures.

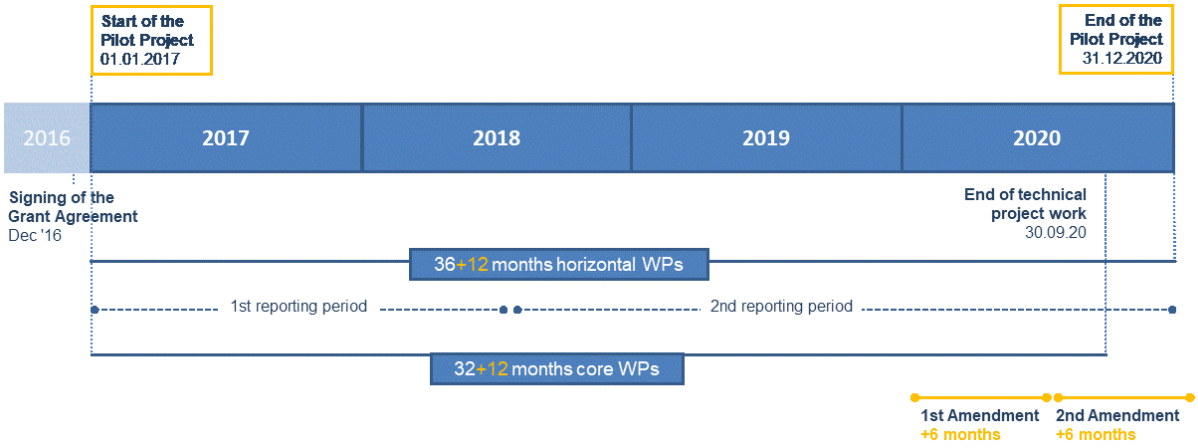

Figure 3: timelineof the Pilot Project EDITH

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CKD Evaluation and Management – KDIGO

Treatment modalities choices, outcomes and costs for End Stage Kidney Disease

Frequency of end-stage kidney disease treatment modalities

I. Report on the frequency of dialysis, kidney transplantation and comprehensive conservative management for end-stage kidney disease patients in Europe (D4.1)

Responsible partner: AMC
Document. Deliverable D4.1 18112020_DEF of 18.11.2020

I.1. Activity goals

The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry collects data on renal replacement therapy (RRT) via national and regional renal registries in Europe and countries bordering the Mediterranean Sea [ERA-EDTA Registry Annual report 2018]. Data for the year 2016 were received from 36 European Union (EU) Member States and non-EU countries. When leaving out Israel and Tunisia, the 34 participating European countries cover a general population of 677.3 million people, representing 80.5% of the general population located in the European continent. Each year, the ERA-EDTA Registry provides an overview of the frequency and outcomes of dialysis and kidney transplantation in the ERA-EDTA Registry Annual Report [ERA-EDTA Registry Annual report 2018], in a scientific paper summarizing the annual report [Kramer 2018] and other scientific papers.

Notwithstanding the possibility for the ERA-EDTA Registry of publishing an extensive overview on the number and outcomes of dialysis and kidney transplantation in Europe, currently the ERA-EDTA Registry does not receive data from all countries in Europe. Also, in contrast to RRT, the frequency of comprehensive conservative management (CCM) is unknown in most European countries although this treatment has become an alternative for RRT in elderly patients with multi-morbidity and poor prognosis [Kurella Tamura 2016].

As part of the EDITH project, in this deliverable we aim to provide a more extensive overview of the frequency of dialysis and kidney transplantation in the different European countries than the one currently available, by using ERA-EDTA Registry data supplemented by data from other sources. In addition, the EDITH Nephrologist survey was used to estimate the frequency of CCM for patients in individual European countries.

I.2. Methods

Annex 1 provides an overview of all sources used to determine the frequency of RRT, kidney transplantation and CCM as treatment for patients with end-stage kidney disease (ESKD) by country. Countries considered to be part of both Europe and Asia (Armenia, Georgia, Russia and Turkey) were also included, as well as Israel and Tunisia because they provided 2016 data to the ERA-EDTA Registry.

I.2.1 Data collection on renal replacement therapy

ERA-EDTA Registry data

National and regional renal registries that sent individual patient data and aggregated data on the year 2016 to the ERA-EDTA Registry were included. The details of methods of data collection and data processing have been described elsewhere [ERA-EDTA Registry Annual report 2018].

All national and regional renal registries contributing individual patient data to the ERA-EDTA Registry followed national legislation with regard to ethics committee approval and patient informed consent.

Expansion of aggregated data collection

Within the EDITH project, the ERA-EDTA Registry (Amsterdam UMC, location AMC) invited contact persons in all EU Member States and non-EU countries that do not provide data to the ERA-EDTA Registry yet to encourage them to provide data to the Registry in the future. Until now, Kosovo managed to provide data for the first time to the Registry during the EDITH project. It is not unexpected that due to short time period and the huge effort needed to build a renal registry other countries were not able to provide data yet. However, current activities in the contacted countries provide hope that data delivery from some of these countries will start within the next 2-5 years. Among other activities, one member of the Registry staff visited the Luxembourg Society for Nephrology on 27 November 2018 to advise them on building up a renal registry. After the EDITH project, we will continue to make efforts to add new countries to the ERA-EDTA Registry.

In addition, under the umbrella of the EDITH project, the table for collection of aggregated data on both incidence and prevalence has been extended by additionally requesting:

- data by both age group and sex
- treatment modality on day 1 (not only on day 91)

These additional data give the opportunity to examine potential sex differences by age group as well as the type of treatment modality at the start of RRT (which was already possible for countries providing us with individual patient data). The new template for data collection has already been sent to the renal registries.

Other sources

- Incidence and prevalence of RRT
  For countries not providing data to the ERA-EDTA Registry other sources were used to determine the frequency of RRT, i.e. insurance data (Germany) [Potthoff 2017], the United States Renal Data System (USRDS) report (Hungary, Israel) [United States Renal Data System 2016], personal communication (Cyprus, Ireland), Newsletter Transplant (Armenia, Malta, Moldova) [Newsletter Transplant 2018], the Eurotransplant annual report (Germany, Luxembourg and Slovenia) [Eurotransplant International Foundation 2016], a scientific paper on the results of a survey among nephrologists (Kosovo, Montenegro, Slovenia) [van der Tol 2019], and a scientific paper on the results of a survey among representatives of Eastern European countries on the International Society of Nephrology (ISN) Regional Board (Montenegro) [Spasovski 2019] (see Annex 1).
  For some countries, frequency data were incomplete and in that case we received estimates on the incidence (Germany and Hungary) and prevalence of dialysis (Armenia, Malta and Moldova).
- Number of transplants performed
  The Global Observatory on Donation and Transplantation (GODT) data were used to obtain the number of kidney transplants performed in Armenia, Germany, Hungary, Ireland, Italy (entire country), Malta, Montenegro, Moldova, and Slovenia [Global Observatory on Donation and Transplantation]. Data from Luxembourg were obtained from the Eurotransplant annual report [Eurotranpslant International Foundation 2016].

Definitions on the frequency of RRT

The incidence of RRT on day 1 was defined as the number of patients starting RRT in 2016 and expressed per million of general population (pmp). The RRT modality specific incidence pmp was also examined on day 91 after the start of RRT, mainly because some patients receive hemodialysis for a short period while preparations are made for peritoneal dialysis. The prevalence of RRT was defined

as the number of patients on RRT at 31 December 2016. Both the prevalence of RRT and the number of transplants performed in 2016 were expressed pmp.

As general population data, we used the midyear population of 2016 as provided by Eurostat [http://ec.europa.eu/eurostat/data/database] for countries sending individual patient data to the ERA-EDTA Registry. Exceptions to this rule were Austria, Bosnia and Herzegovina, Spanish regions, United Kingdom for which we received population data from the country itself. For countries providing aggregated data to the ERA-EDTA Registry, we used population data as provided by the national registry. For countries not providing data to the ERA-EDTA Registry in 2016, we used the midyear population of 2016 as provided by Eurostat.

I.2.2 Data collection on comprehensive conservative management

EDITH Nephrologist survey

As part of the EDITH project, the ERA-EDTA Registry administered an online EDITH nephrologist survey among European nephrologists and kidney transplant surgeons. The survey was publicly accessible from March 14, 2019 until May 19, 2019. The survey received a waiver from the Medical Ethical review committee of the Amsterdam University Medical Center (UMC), location AMC (W18_279#18.323). Results from respondents from countries for which additional ethical approval was not needed, or from countries where additional approval was received before the start of the survey, were included in the final analysis. As a consequence, no data could be reported on Albania, Iceland, Lithuania, Luxembourg, Montenegro, and Portugal. All respondents provided online informed consent before completing the survey.

The section of the survey dealing with CCM was completed by nephrologists only. CCM was defined as "planned holistic patient-centred care for patients with stage 5 chronic kidney disease (CKD) who require RRT but do not receive this. It includes interventions to delay the progression of kidney disease, shared decision making, active symptom management, detailed communications including advanced care planning, psychological support, social and family support and cultural and spiritual domains of care". It should be noted that CCM does not include "choice-restricted conservative care" for patients in whom resource constraints prevent or limit access to KRT. The survey included two questions on the frequency of CCM in 2018. The first question asked for an estimation of the percentage of patients in the clinic who were offered CCM instead of RRT, in case the patient had a level of renal function on which the nephrologist would normally start RRT (of note, this is not equal to the incidence of CCM as patients may not accept the offer). The second question concerned an estimation of the percentage of ESKD patients in the clinic who received CCM (further indicated as prevalence of CCM).

Global Kidney Health Atlas

In addition, the Global Kidney Health Atlas (GKHA) as an ISN led initiative launched an international survey in 2016-2018 aiming at identifying gaps of kidney care worldwide that may contribute to develop strategies to close these gaps of care. One section of this survey covers information on the frequency of conservative kidney management in 46 European countries, presented for Europe as a whole by region (Western Europe, Eastern and Central Europe, and Newly Independent State (NIS) countries and Russia). Although this part of the survey is not published (yet) in the "regular" GKHA report, the authors of GKHA wrote a report for the European commission on conservative kidney management in patients with end-stage kidney disease living in Europe (GKHA Report 2019].

I.2.3 Analyses

Summary statistics on the frequency of RRT were calculated for all participating countries providing data on the incidence and prevalence of haemodialysis, peritoneal dialysis, and kidney

transplantation as well as data on kidney transplant rates. As Israel and Tunisia are not part of Europe, they were not included in the summary statistics. The summary statistics were therefore based on 28 countries (44.7% of the population participating in this study).

For some countries (Armenia, Germany, Malta, Moldova and Slovenia), we did not have information on the prevalence of patients with a functioning kidney graft and therefore estimated this prevalence. To this end, using data from 36 European countries, we developed a regression formula describing the relationship between kidney transplantation rates and the prevalence of kidney transplanted patients.

For the analyses on the frequency of CCM in each country, we calculated the mean and standard deviation as well as the median and interquartile range of the percentages of CCM as provided by nephrologists. In the figures, we present the results of countries with at least five survey respondents. The frequency of RRT and CCM are presented as unadjusted results. Analyses were performed using SAS software version 9.4 [SAS Institute Inc.].

I.3. Results

Following figures show a map of Europe with the incidence of RRT on day 1 (Figure 4), prevalence of RRT (Figure 5), kidney transplantation rate (Figure 6), median estimated percentage of patients who were offered CCM (Figure 7), and the median estimated prevalence of CCM (Figure 8) in all participating countries. More details on the frequency of RRT and CCM are described below.

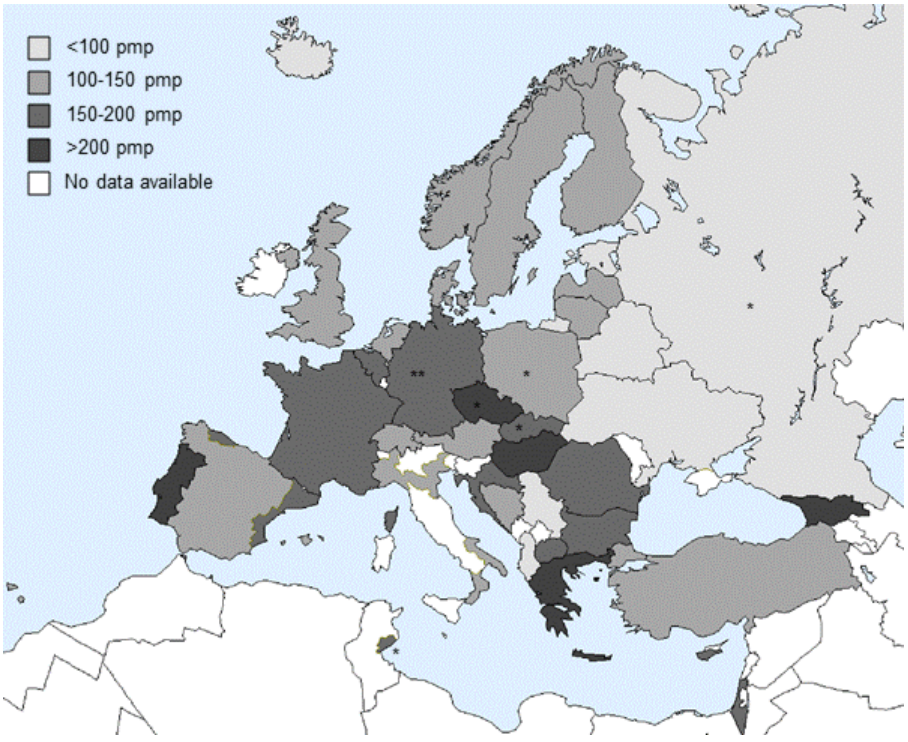

Figure 4: Incidence of renal replacement therapy for end-stage kidney disease per million population on day 1 in 2016.

* Countries with incidence data on dialysis patients only (Czech Republic, Poland, Russia, Slovakia, Tunisia (Sfax region))
# Country with incidence data on dialysis and pre-emptive deceased donor kidney transplanted patients only (Germany)

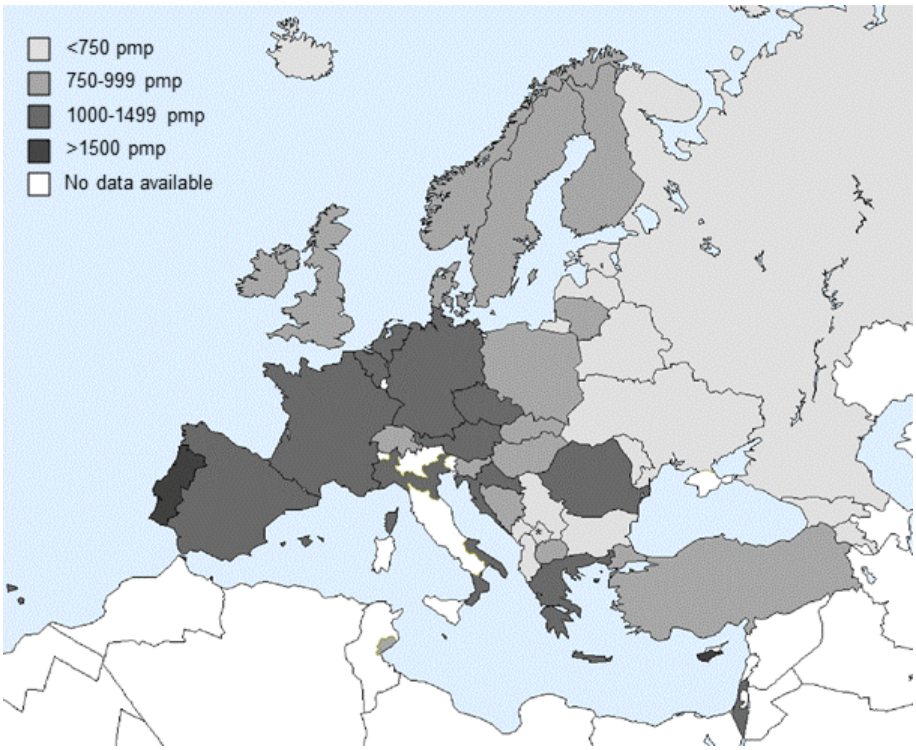

Figure 5: Prevalence of renal replacement therapy for end-stage kidney disease per million population on 31 December 2016

* Country with prevalence data on dialysis patients only (Kosovo)

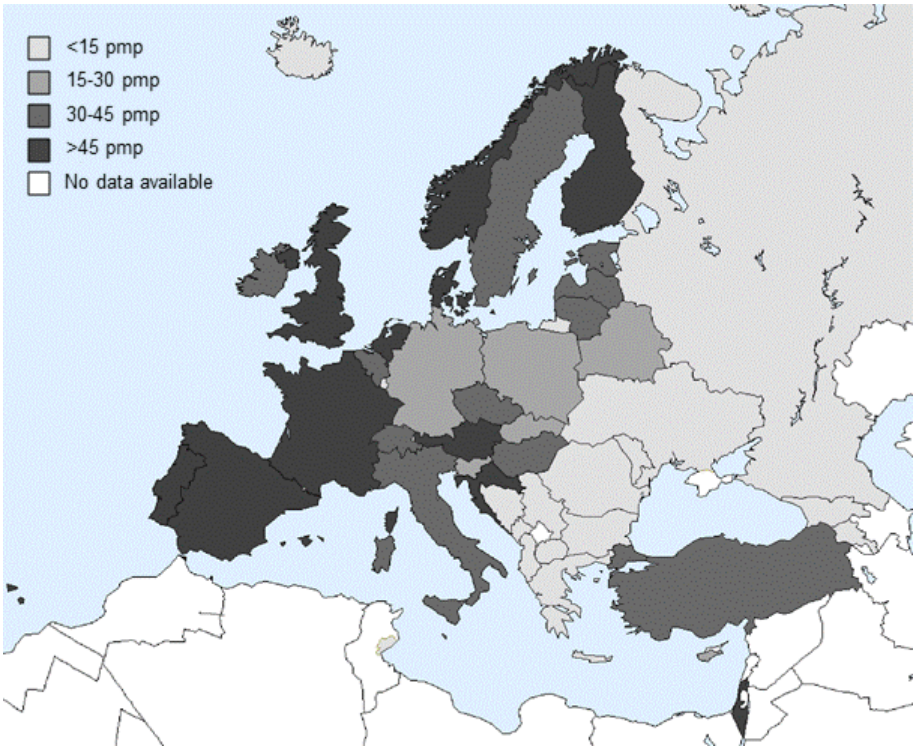

Figure 6: Kidney transplants performed in per million population in 2016

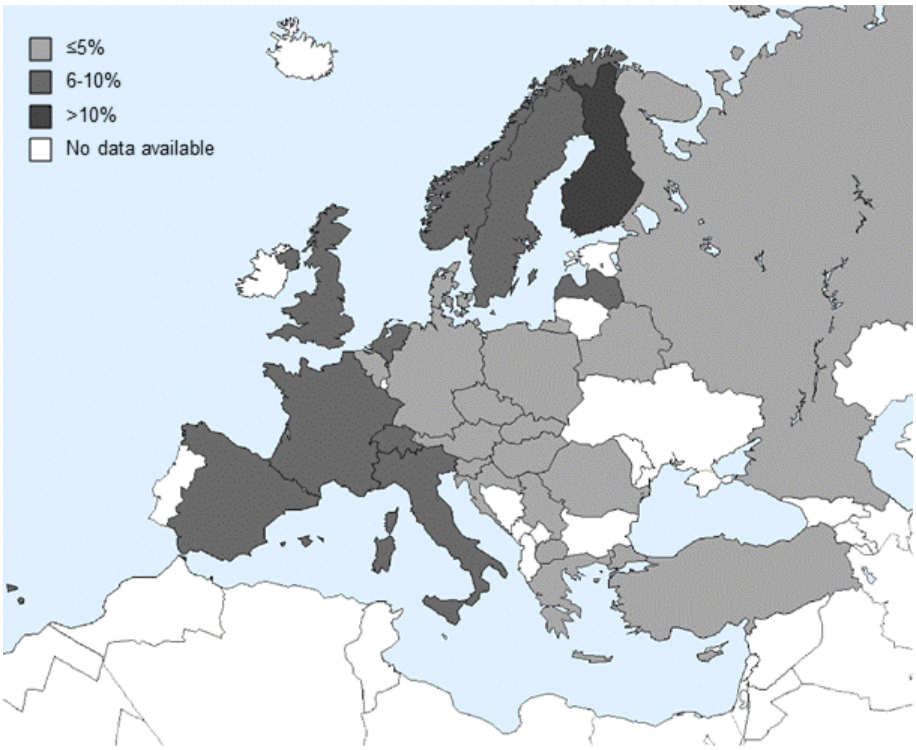

Figure 7: Median proportion of patients with end-stage kidney disease in the clinic who were offered comprehensive conservative management in 2018

Only countries with at least 5 respondents are included.

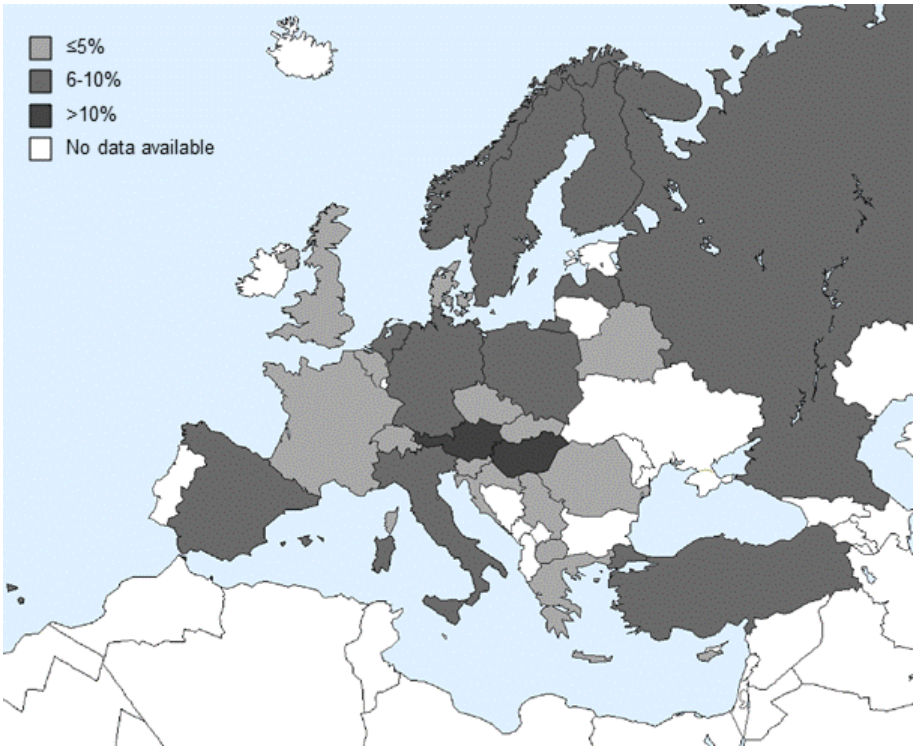

Figure 8: Median proportion of patients with end-stage kidney disease who received comprehensive conservative management in 2018

Only countries with at least 5 respondents are included.

I.3.1 Incidence of RRT

In 2016, 97.996 patients in 39 countries commenced RRT for ESKD. Figure 9 provides the incidence of RRT by treatment modality for all countries. The RRT incidence was highest in Greece (251 per million population [pmp]), Czech Republic (243 pmp), and Portugal (236 pmp), whereas it was lowest in Ukraine (29 pmp), Russia (59 pmp) and Belarus (62 pmp). Please note that for Czech Republic, Poland, Russia, Tunisia (Sfax region) and Slovakia we were unable to obtain data on pre-emptive kidney transplantation and therefore used the incidence of dialysis instead. The highest rate of preemptive kidney transplantation was reported by the Netherlands (17 pmp) followed by Turkey (15 pmp) and Norway (12 pmp).

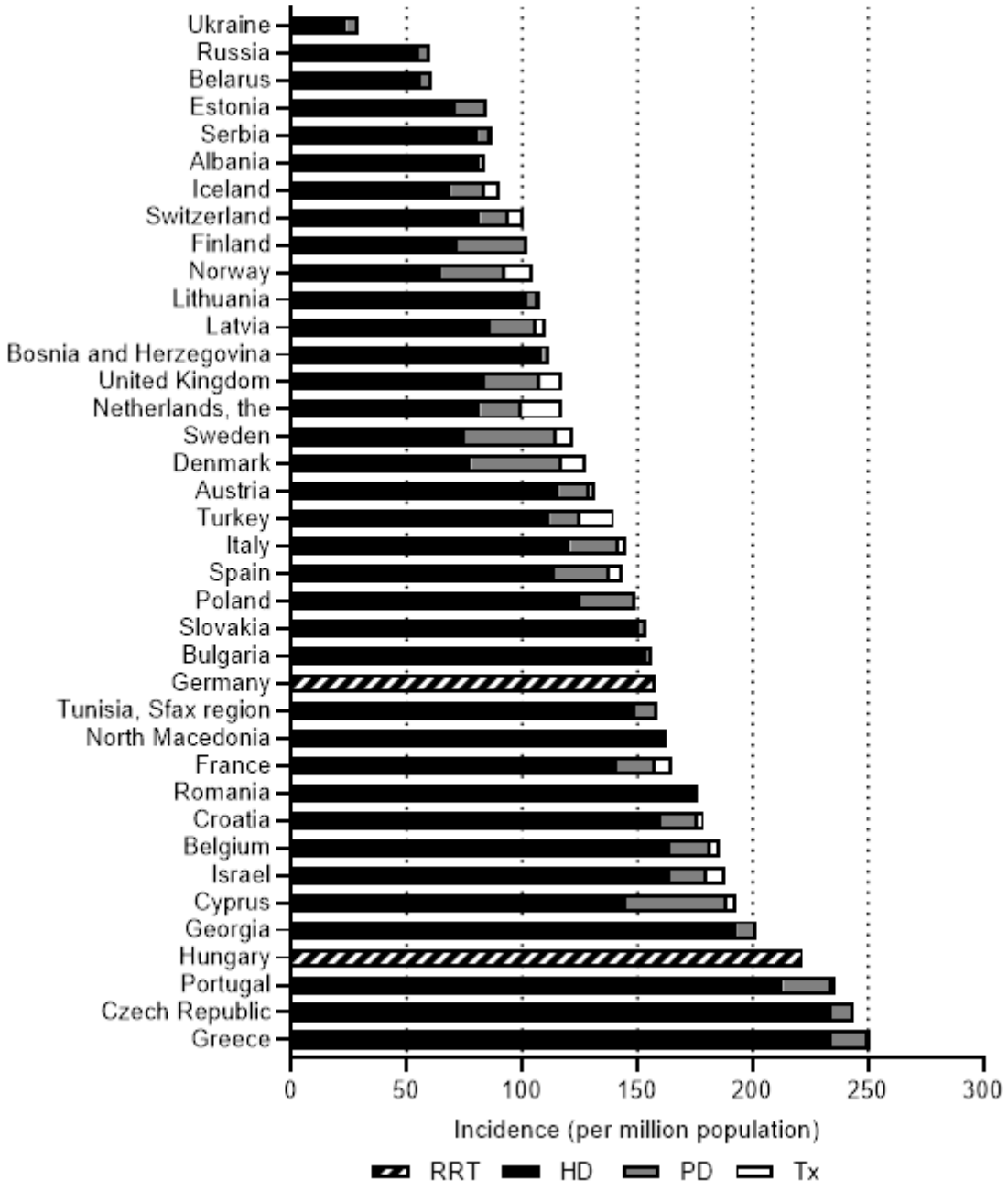

Figure 9: Incidence of RRT for ESKD per million population by treatment modality on day 1 in 2016

Abbreviations used; RRT: renal replacement therapy; ESKD: end-stage kidney disease; HD: hemodialysis; PD: peritoneal dialysis; Tx: kidney transplantation.

Figure 10 provides the incidence of RRT by treatment modality on day 91. The incidence of hemodialysis was highest in Greece (208 pmp) and Portugal (199 pmp) whereas for peritoneal dialysis it was highest in Cyprus (41 pmp), Sweden (38 pmp) and Denmark (37 pmp).

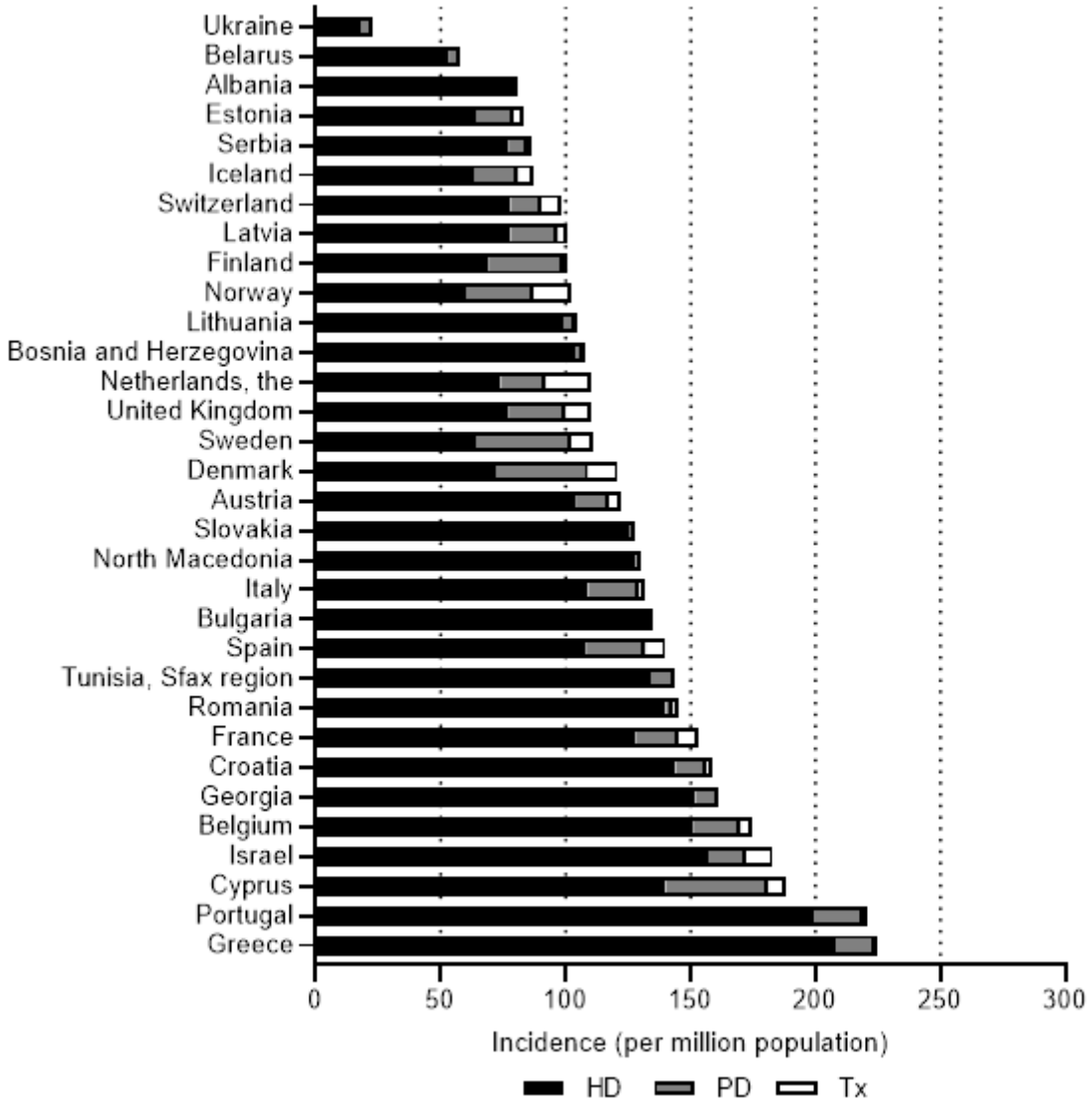

Figure 10: Incidence of RRT for ESKD per million population by treatment modality on day 91 in 2016

Abbreviations used; RRT: renal replacement therapy; ESKD: end-stage kidney disease; HD: hemodialysis; PD: peritoneal dialysis; Tx: kidney transplantation

I.3.2 Prevalence of RRT

On 31 December 2016, 690.173 patients in 45 countries received RRT for ESKD. Figure 11 provides the prevalence of RRT by treatment modality. By far the highest prevalence of RRT was seen in Portugal (1906 pmp) followed by Cyprus (1575 pmp) and Belgium (1286 pmp).

The prevalence of center hemodialysis was highest in Portugal (1143 pmp), Greece (979 pmp) and Romania (887 pmp), and that of home hemodialysis was highest in Denmark (28 pmp), Finland (25 pmp) and the United Kingdom (20 pmp). It should be noted that in many countries home hemodialysis was not reported or did not exist. The prevalence of peritoneal dialysis was highest in

Cyprus (114 pmp), Denmark (97 pmp) and Sweden (90 pmp). The prevalence of patients with a functioning kidney graft was highest in Cyprus (817 pmp), Portugal (693 pmp) and Spain (672 pmp). It was lowest in Ukraine (27 pmp), Serbia (52 pmp) and Armenia (estimated 58 pmp).

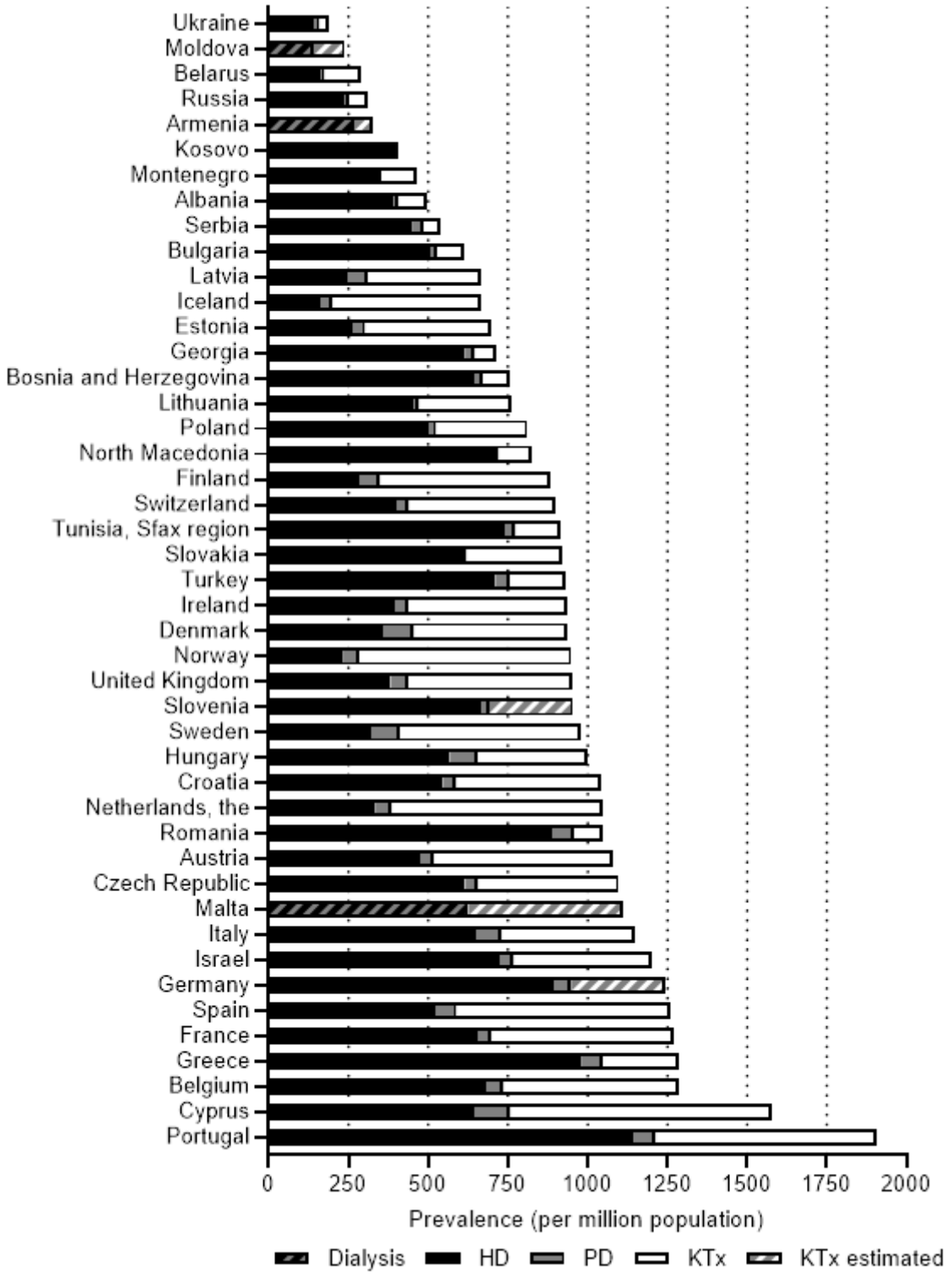

Figure 11: Prevalence of RRT for ESKD per million population by treatment modality on 31 December 2016

Abbreviations used; RRT: renal replacement therapy; ESKD: end-stage kidney disease; HD: hemodialysis; PD: peritoneal dialysis; Tx: kidney transplantation.

I.3.3 Kidney transplants

In 2016, 26.008 kidney transplantations were performed in 44 countries. Figure 12 provides the number of kidney transplants performed by country. The countries with the highest kidney transplantation rates were Spain (64 pmp) followed by the Netherlands (59 pmp) and France (54 pmp). Of note, in Spain, the majority of kidney transplants were from deceased donors (57 pmp) and only some from living donors (7 pmp), whereas in the Netherlands a small majority of kidney transplants were from living donors (33 pmp) and the rest from deceased donors (25 pmp). The lowest number of kidney transplants were performed in Luxembourg (0 pmp), Armenia (2 pmp) and Montenegro, North Macedonia and Ukraine (all 3 pmp).

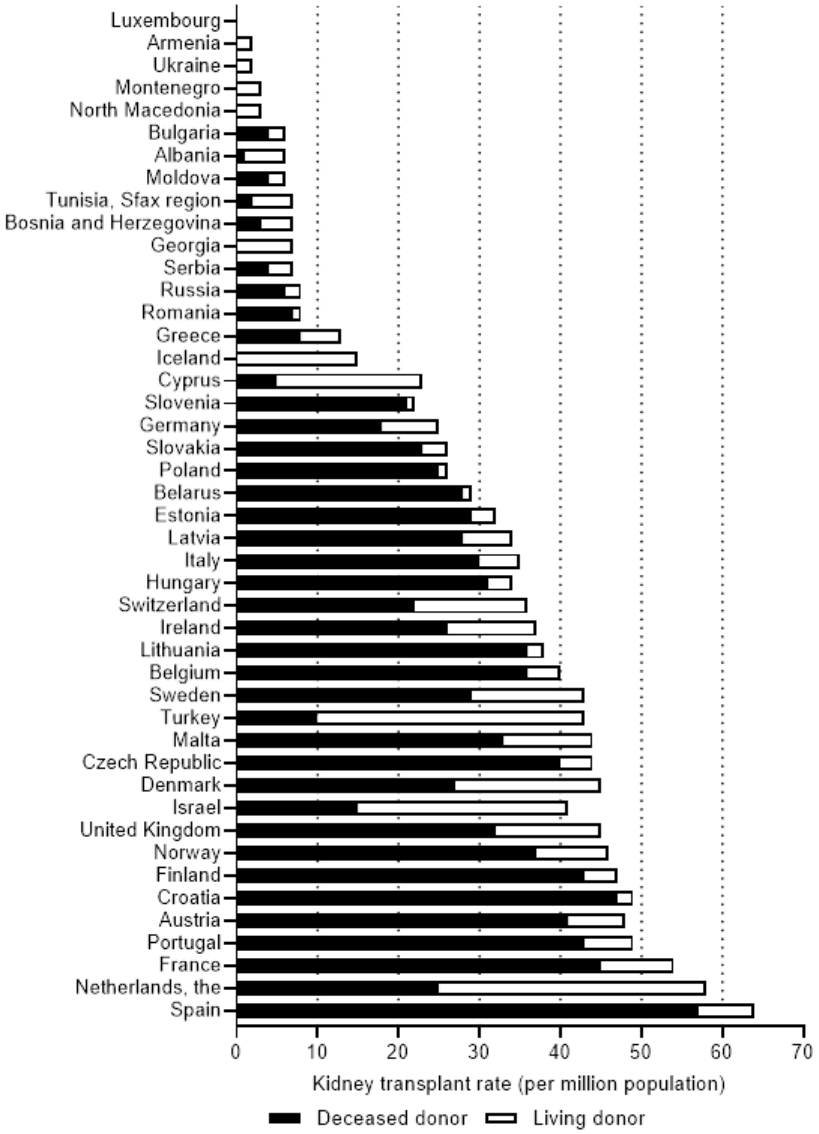

Figure 12: Kidney transplantations performed per million population in 2016, by donor source

I.3.4 Comprehensive conservative management

Under the umbrella of the EDITH nephrologist survey, 581 nephrologists estimated the percentage of patients in their clinic who were offered CCM instead of RRT, whereas 587 nephrologists estimated the prevalence of CCM in their clinic.

Figures 13 and 14 provide the estimated median percentage of patients who were offered CCM and the prevalence of CCM in 2018 for countries with at least five respondents on the survey. In the remaining 28 countries, the estimated percentage of ESKD patients who were offered CCM varied between 0.0% (Slovakia and Slovenia) to 20.0% (Finland). The estimated prevalence of CCM varied between 0.0% (Slovenia) and 15.0% (Hungary).

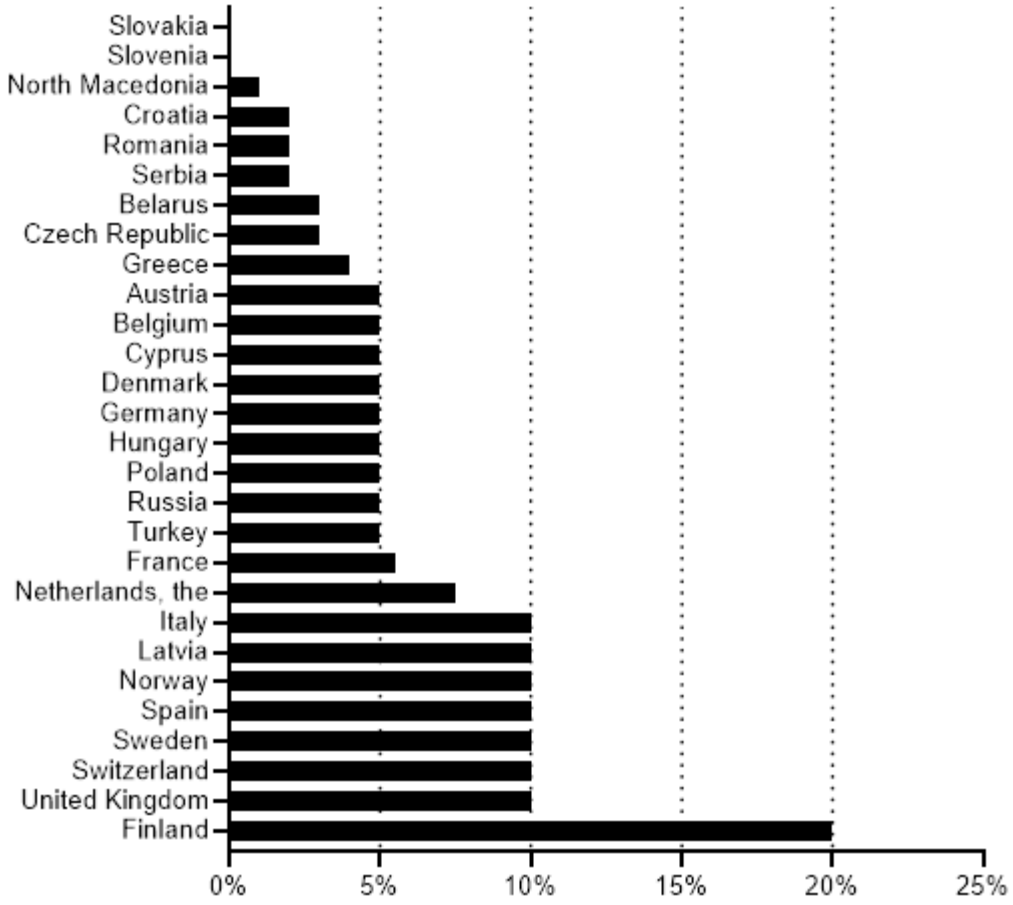

Figure 13: Proportion of patients with end-stage kidney disease in the clinic who got offered comprehensive conservative management in 2018

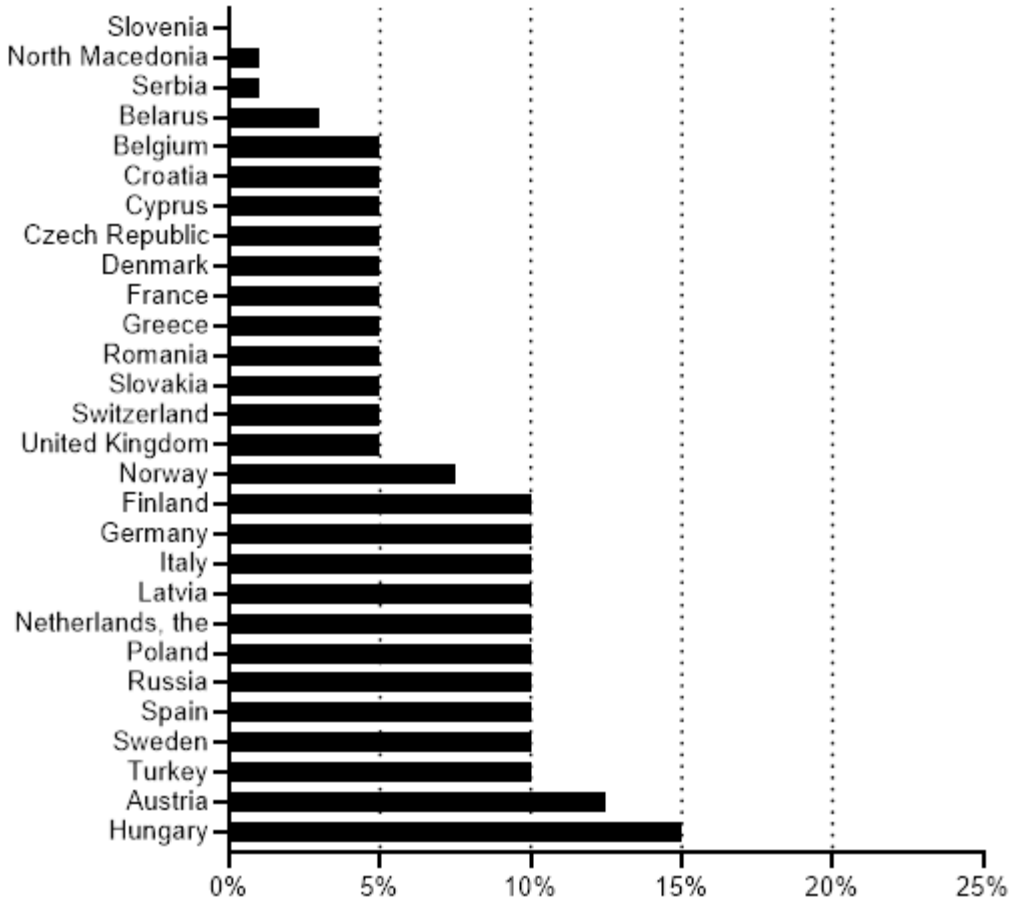

Figure 14: Proportion of patients with end-stage kidney disease in the clinic who received comprehensive conservative management in 2018

The data are presented as medians. Only countries with at least 5 survey respondents are included.

I.3.5 Summary statistics

In 2016, the overall incidence of RRT was 132 pmp, meaning that in this year 1 in 7584 Europeans (0.013%) started RRT (Table 3). The overall prevalence of RRT was 985 pmp, meaning that 1 in 1016 Europeans (0.098%) were treated with RRT. The overall number of kidney transplants performed was 38 pmp.

Table 3: Summary statistics of European countries on incidence and prevalence by treatment modality and the number of performed transplants by donor source, per million population, in 2016

	RRT	HD	PD	TX	LTX	DTX
Incidence pmp on day 1	132	109	17	5		
Incidence pmp on day 91	122	99	17	5		
Prevalence pmp on 31 December 2016	985	502	52	430		
Number of performed kidney transplants pmp				38	8	30

Categories may not add up because of missing values or rounding off.
Abbreviations used; RRT: renal replacement therapy, HD: hemodialysis, PD: peritoneal dialysis, TX: kidney transplantation, LTX: living kidney donor transplantation, DTX: deceased kidney donor transplantation, pmp: per million population
The summary statistics are based on the following countries: Albania, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Denmark, Estonia, Finland, France, Georgia, Greece, Iceland, Italy, Latvia, Lithuania, Netherlands, North Macedonia, Norway, Portugal, Romania, Serbia, Spain, Sweden, Switzerland, Ukraine, United Kingdom

I.4. Impact

The results from this deliverable comprise the most extensive overview of the frequency of RRT for ESKD in Europe to date and include data from 46 European countries and countries bordering the Mediterranean Sea. In addition to ERA-EDTA Registry data, data on 10 new countries (Armenia, Germany, Hungary, Ireland, Kosovo, Luxembourg, Malta, Moldovia, Montenegro and Slovenia) are included. This means that, with the exception of some very small countries (Andorra, Liechtenstein, Monaco, San Marino, and Vatican City), all countries in Europe are represented. Moreover, this study provides estimates for the frequency of CCM for ESKD in 33 European countries.

These results may prove useful as a first important step in identifying the European differences in allocation of ESKD patients to RRT modalities and comprehensive conservative management which may facilitate initiatives to increase the optimal treatment modalities for patients with ESKD or the development of successful preventive measures to reduce chronic kidney disease.

Kidney transplantation is associated with a better survival and quality of life and lower costs compared to dialysis [Haller 2011; Tonelli 2011; Wolfe 1999; Wyld 2012]. However, not all patients with ESKD who are suitable to receive a kidney transplantation do receive this treatment. This line of thought is supported by the large variation in the number of kidney transplants performed across EU and non-EU countries. Even in those countries with high kidney transplantation rates suitable persons may not receive the desired kidney transplant. On the other hand, several patients with ESKD may be unsuitable for a kidney transplant, due to for example medical contra-indications. In this case, dialysis (in a center or at home) or comprehensive conservative management could be the most appropriate treatment. This means that the optimal treatment of patients with ESKD may differ from individual to individual, but clearly, currently not all of these patients may receive the most appropriate treatment. This may be due to important barriers. Therefore, in deliverable 4.2 of the EDITH project we further report on the factors influencing the modality choice (different RRT treatment modalities and for comprehensive conservative management) in Europe..

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I.6. Annex

Annex 1: Sources used to obtain information on the frequency of RRT, kidney transplantation and comprehensive conservative management for patients with ESKD in different European countries

Country	Population data	Incidence of RRT on day 1	Incidence of RRT on day 91	Prevalence of RRT	Kidney transplantation rate	Comprehensive conservative management
Albania	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	
Armenia	Eurostat			Transplant Newsletter (dialysis) Prevalence of kidney transplantation estimated[1]	GODT website	
Austria	Austrian statistics	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Belarus	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Belgium	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Bosnia and Herzegovina	Bosnian statistics (2013)	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	
Bulgaria	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	
Croatia	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Cyprus	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	Personal communication	ERA-EDTA Registry	EDITH Nephrologist survey
Czech Republic	Provided by renal registry	ERA-EDTA Registry (dialysis)		ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Denmark	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Estonia	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey

Country	Population data	Incidence of RRT on day 1	Incidence of RRT on day 91	Prevalence of RRT	Kidney transplantation rate	Comprehensive conservative management
Finland	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
France	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Georgia	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	
Germany	Eurostat	GBA report (personal communication with Wolfgang Weber van MNC - Medical Netcare GmbH) (dialysis) Eurotransplant Annual report (kidney transplantation)		GBA report (dialysis) Prevalence of kidney transplantation estimated[1]	GODT website	EDITH Nephrologist survey
Greece	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Hungary	Eurostat	USRDS[2]		USRDS	GODT website	EDITH Nephrologist survey
Iceland	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	
Ireland	Eurostat			National Renal Office, Dublin	GODT website	EDITH Nephrologist survey
Israel	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry (dialysis) USRDS (kidney transplantation)	ERA-EDTA Registry	
Italy	Provided by renal registry	ERA-EDTA Registry[3]	ERA-EDTA Registry[3]	ERA-EDTA Registry[3]	GODT website	EDITH Nephrologist survey
Kosovo*	Eurostat			Dialysis Services Reimbursement survey (personal communication with professor Raymond Vanholder) (dialysis)	not available	
Latvia	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Lithuania	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	

Country	Population data	Incidence of RRT on day 1	Incidence of RRT on day 91	Prevalence of RRT	Kidney transplantation rate	Comprehensive conservative management
Luxembourg	Eurostat				Eurotransplant Annual Report	
Malta	Eurostat			Transplant Newsletter (dialysis) Prevalence of kidney transplantation estimated[1]	GODT website	EDITH Nephrologist survey
Moldova	Eurostat			Transplant Newsletter (dialysis) Prevalence of kidney transplantation estimated[1]	GODT website	EDITH Nephrologist survey
Montenegro	Eurostat			Dialysis Services Reimbursement survey (personal communication with professor Raymond Vanholder) (dialysis) Spasovski et al., Kidney Int (2019) (kidney transplantation)	GODT website	
Netherlands, the	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
North Macedonia	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Norway	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Poland	Provided by renal registry	ERA-EDTA Registry (dialysis)		ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Portugal	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	
Romania	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Russia	Provided by renal registry	ERA-EDTA Registry (dialysis)		ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Serbia	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Slovakia	Provided by renal registry	ERA-EDTA Registry (dialysis)	ERA-EDTA Registry (dialysis)	USRDS	ERA-EDTA Registry	EDITH Nephrologist survey

Country	Population data	Incidence of RRT on day 1	Incidence of RRT on day 91	Prevalence of RRT	Kidney transplantation rate	Comprehensive conservative management
Slovenia	Eurostat	Eurotransplant Annual Report (kidney transplantation)		Dialysis Services Reimbursement survey (personal communication with professor Raymond Vanholder) (dialysis) Prevalence of kidney transplantation estimated[1]	GODT website	EDITH Nephrologist survey
Spain	Spanish government statistics	ERA-EDTA Registry[4]	ERA-EDTA Registry[4]	ERA-EDTA Registry[4]	ERA-EDTA Registry	EDITH Nephrologist survey
Sweden	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Switzerland	Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Tunisia, Sfax region	Provided by renal registry	ERA-EDTA Registry (dialysis)	ERA-EDTA Registry (dialysis)	ERA-EDTA Registry	ERA-EDTA Registry	
Turkey	Provided by renal registry	ERA-EDTA Registry		ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
Ukraine	Provided by renal registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey
United Kingdom	UK government statistics	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	ERA-EDTA Registry	EDITH Nephrologist survey

No data were available for the following countries in Europe: Andorra, Liechtenstein, Monaco, San Marino, Vatican City

* This designation is without prejudice to positions on status, and is in line with UNSCR 1244/99 and the ICJ Opinion on the Kosovo declaration of independence.

When cells are left empty, the data were unavailable.

1 Prevalence of kidney transplantation estimated with kidney transplantation rate (formula based on data from countries with known kidney transplantation prevalence and kidney transplantation rate)

2 Only RRT incidence available

3 Incidence and prevalence based on data from 6 of 20 Italian regions

4 Incidence and prevalence based on data from 14 of 19 Spanish regions

Annex 2: How to increase kidney transplant activity throughout Europe—an advocacy review by the European Kidney Health Alliance

The review is published in a scientific paper:

Vanholder R, Stel VS, Jager KJ, Lameire N, Loud F, Oberbauer R, de Jong RW, Zoccali C. How to increase kidney transplant activity throughout Europe-an advocacy review by the European Kidney Health Alliance. Nephrol Dial Transplant. 2019 Aug 1;34(8):1254-1261. doi: 10.1093/ndt/gfy390. PMID: 30629203.

Abstract

Kidney transplantation offers better outcomes and quality of life at lower societal costs compared with other options of renal replacement therapy. In this review of the European Kidney Health Alliance, the current status of kidney transplantation throughout Europe and suggestions for improvement of transplantation rates are reported. Although the European Union (EU) has made considerable efforts in the previous decade to stimulate transplantation activity, the discrepancies among European countries suggest that there is still room for improvement. The EU efforts have partially been neutralized by external factors such as economic crises or legal issues, especially the illicit manipulation of waiting lists. Hence, growth in the application of transplantation throughout Europe virtually remained unchanged over the last few years. Continued efforts are warranted to further stimulate transplantation rates, along with the current registration and data analysis efforts supported by the EU in the Effect of Differing Kidney Disease Treatment Modalities and Organ Donation and Transplantation Practices on Health Expenditure and Patient Outcomes project. Future actions should concentrate on organization, harmonization and improvement of the legal consent framework, population education and financial stimuli.

Keywords: European policy; chronic renal failure; kidney transplantation; quality of life; renal replacement therapy.

Impact of treatment modality choice on health outcomes like quality of life and patient survival

II. Report on impact of treatment modality choice on health outcomes (D4.2)

Responsible partner: AMC
Document. Deliverable D4.2 18112020_DEF of 18.11.2020

II.1. Patient survival and graft survival of patients with end stage kidney disease (ESKD) treated by renal replacement therapy (RRT) in European countries

Despite continuous improvement [Pippias 2015] patients with end-stage kidney disease (ESKD) treated by renal replacement therapy (RRT) have a high mortality risk. This EDITH deliverable provides an overview on the current status of the patient and graft survival in patients with ESKD treated by RRT in European countries using data from the ERA-EDTA Registry. We will supplement the discussion of our results with a discussion of the current literature.

II.1.1 Methods

The ERA-EDTA Registry collects data on renal replacement therapy (RRT) via national and regional renal registries in Europe and countries bordering the Mediterranean Sea (ERA-EDTA Registry Annual report 2018). Details of the methods used for data collection and data processing in the ERA-EDTA Registry database are described in the ERA-EDTA Registry annual report [ERA-EDTA Registry Annual Report 2018].

Data from the following national or regional renal registries, providing individual patient data on patients receiving chronic RRT for ESKD to the ERA-EDTA Registry between 2007 and 2016, were included in this deliverable: Austria, Belgium (Dutch-speaking), Belgium (French-speaking), Denmark, Finland, France, Greece, Iceland, Norway, Spain (Andalusia), Spain (Aragon), Spain (Asturias), Spain (Basque country), Spain (Cantabria), Spain (Castile and León), Spain (Castile-La Mancha), Spain (Catalonia), Spain (Extremadura), Spain (Galicia), Spain (Community of Madrid), Spain (Valencian region), Sweden, the Netherlands, United Kingdom (England/Wales/Northern Ireland) and United Kingdom (Scotland). In addition, the Annex provides results of the survival analyses including only EU Member States (thus excluding Iceland and Norway).

The survival analyses include patients commencing RRT, dialysis or receiving a first kidney transplant between 2007-2011 or 2010-2014. For those who started between 2007-2011, we present the 90 day, one-, two- and five-year survival probabilities. For those who started between 2010-2014, we present the 90 day, one- and two- year survival probabilities.

The Cox regression model was used to calculate the survival probabilities. The survival time was taken from day 1 of commencing dialysis and from the first day of receiving a kidney transplant. The survival time was taken at day 91 (i.e. 90 days after the start of dialysis) when comparing the survival between hemodialysis and peritoneal dialysis as some patients receive hemodialysis for a short period while preparations are made for peritoneal dialysis. The survival time ended with either the event of interest, a censored observation or the end of the follow-up time, which was set at 31 December 2016. Table 4 shows an overview of the events, and censoring defined for the different survival analyses. We report unadjusted survival probabilities. Adjusted survival analysis was used when comparing different forms of RRT (i.e. hemodialysis versus peritoneal dialysis; kidneys from living versus deceased donors) and when comparing the RRT survival by primary renal disease. Table

5 shows an overview of the variables used to adjust the survival probabilities. The survival probabilities were adjusted for fixed values of age, sex and primary renal disease.

Table 4: Overview of the events and censoring defined for the survival analysis

Survival type	Event	Censoring
Patients on renal replacement therapy	Death of patient	Recovery of renal function Loss to follow-up End of follow-up time
Patients on dialysis	Death of patient	Transplantation Recovery of renal function Loss to follow-up End of follow-up time
Patients on hemodialysis	Death of patient	Transplantation Switch to peritoneal dialysis Recovery of renal function Loss to follow-up End of follow-up time
Patients on peritoneal dialysis	Death of patient	Transplantation Switch to hemodialysis Recovery of renal function Loss to follow-up End of follow-up time
First transplant recipients	Death of patient	Loss to follow-up End of follow-up time
First graft	Death of patient Graft failure Re-transplantation	Loss to follow-up End of follow-up time

Table 5: Overview of the variables used to adjust the survival probabilities

Survival type	Age	Sex	Primary renal disease
Patients on renal replacement therapy	67 years	63% men	24% diabetes 19% hypertension/renal vascular disease 11% glomerulonephritis 46% other causes
Patients on hemodialysis	67 years	63% men	24% diabetes 19% hypertension/renal vascular disease 11% glomerulonephritis 46% other causes
Patients on peritoneal dialysis	67 years	63% men	24% diabetes 19% hypertension/renal vascular disease 11% glomerulonephritis 46% other causes
First transplant recipients (deceased donor)	50 years	63% men	14% diabetes 10% hypertension/renal vascular disease 23% glomerulonephritis 53% other causes
First transplant recipients (living donor)	50 years	63% men	14% diabetes 10% hypertension/renal vascular disease 23% glomerulonephritis 53% other causes

II.1.2 Results

Tables 6-11 show the unadjusted 90 day-, one-, two- and five- year survival probabilities from day 1 of RRT and dialysis and from the day of kidney transplant for the two five year cohorts (cohort 2007-2011 and cohort 2010-2014) for both EU Member States and non-EU countries together. The Annex shows these tables for EU Member States only (by excluding Iceland and Norway).

Renal replacement therapy RRT

The five-year unadjusted survival of RRT was 50.5% (95% confidence interval (CI): 50.4-50.6%) (Table 6). The two-year unadjusted survival of RRT was higher in the most recent cohort (cohort 2007-2011: 73.2% (95% CI: 73.1-73.4%); cohort 2010-2014: 74.6% (95% CI: 74.5-74.8%)). As expected the RRT survival decreases with age: for adult patients starting RRT between 20-44 years of age the five-year unadjusted RRT survival was 89.1% (95% CI: 88.7-89.5%) whereas this was 23.7% (95% CI: 23.6-23.8%) for patients starting RRT after the age of 75 years.

Table 6: Patient survival on renal replacement therapy from day 1, unadjusted, EU Member States plus Iceland and Norway

	Cohort 2007-2011				Cohort 2010-2014		
	90 day	**1 year**	**2 year**	**5 year**	**90 day**	**1 year**	**2 year**
0-19 years	99.3 (98.7-99.6)	97.2 (96.3-97.9)	96.2 (95.2-97.0)	94.6 (93.4-95.5)	99.2 (98.6-99.5)	97.9 (97.1-98.5)	96.5 (95.4-97.3)
20-44 years	99.1 (99.0-99.3)	97.0 (96.8-97.2)	94.6 (94.2-94.9)	89.1 (88.7-89.5)	99.1 (99.0-99.3)	97.2 (97.0-97.4)	95.0 (94.7-95.3)
45-64 years	97.1 (97.0-97.3)	90.8 (90.5-91.0)	84.1 (83.8-84.4)	67.7 (67.4-68.0)	97.4 (97.3-97.5)	91.5 (91.3-91.7)	85.5 (85.2-85.8)
65-74 years	94.0 (93.8-94.2)	82.0 (81.7-82.3)	70.3 (69.9-70.6)	43.3 (43.1-43.5)	94.6 (94.3-94.8)	83.8 (83.5-84.1)	72.8 (72.5-73.1)
75+ years	89.9 (89.7-90.1)	72.4 (72.1-72.7)	56.4 (56.2-56.7)	23.7 (23.6-23.8)	90.7 (90.4-90.9)	74.1 (73.8-74.3)	58.3 (58.0-58.5)
Men	94.4 (94.2-94.5)	83.5 (83.3-83.7)	73.0 (72.8-73.2)	49.8 (49.6-49.9)	94.7 (94.6-94.8)	84.5 (84.3-84.7)	74.3 (74.1-74.5)
Women	94.2 (94.1-94.4)	83.7 (83.4-83.9)	73.6 (73.3-73.9)	51.8 (51.5-52.0)	94.7 (94.5-94.8)	84.7 (84.5-85.0)	75.2 (75.0-75.5)
Diabetes	95.1 (94.9-95.3)	84.1 (83.7-84.4)	71.7 (71.4-72.0)	43.5 (43.2-43.7)	95.6 (95.4-95.8)	85.7 (85.4-86.0)	74.0 (73.7-74.4)
Hypertension/renal vascular disease	94.1 (93.8-94.3)	81.8 (81.5-82.2)	68.9 (68.5-69.3)	40.9 (40.7-41.1)	94.3 (94.1-94.5)	82.9 (82.5-83.2)	70.6 (70.2-70.9)
Glomerulonephritis	97.5 (97.2-97.7)	92.3 (91.9-92.6)	86.7 (86.3-87.2)	72.5 (72.1-73.0)	97.5 (97.2-97.7)	92.3 (91.9-92.6)	86.9 (86.5-87.3)
Other causes	93.5 (93.4-93.7)	82.5 (82.2-82.7)	73.1 (72.8-73.3)	53.0 (52.8-53.2)	94.0 (93.8-94.2)	83.2 (83.0-83.5)	73.9 (73.6-74.1)
All	94.3 (94.2-94.4)	83.6 (83.4-83.7)	73.2 (73.1-73.4)	50.5 (50.4-50.6)	94.7 (94.6-94.8)	84.6 (84.4-84.7)	74.6 (74.5-74.8)
Survival probabilities as % (95% confidence interval)							

Figure 15 shows the adjusted patient survival by primary renal disease for incident RRT patients from day 1, adjusted for age and sex. Patients on RRT for ESKD due to glomerulonephritis had a higher five-year adjusted survival probability (64.1%; 95% CI: 63.2-64.9%) compared to those with hypertension/renal vascular disease (52.9%; 95% CI: 52.4%-53.5%) and those with diabetes mellitus (43.4%; 95% CI: 42.8-43.9%) as primary renal disease.

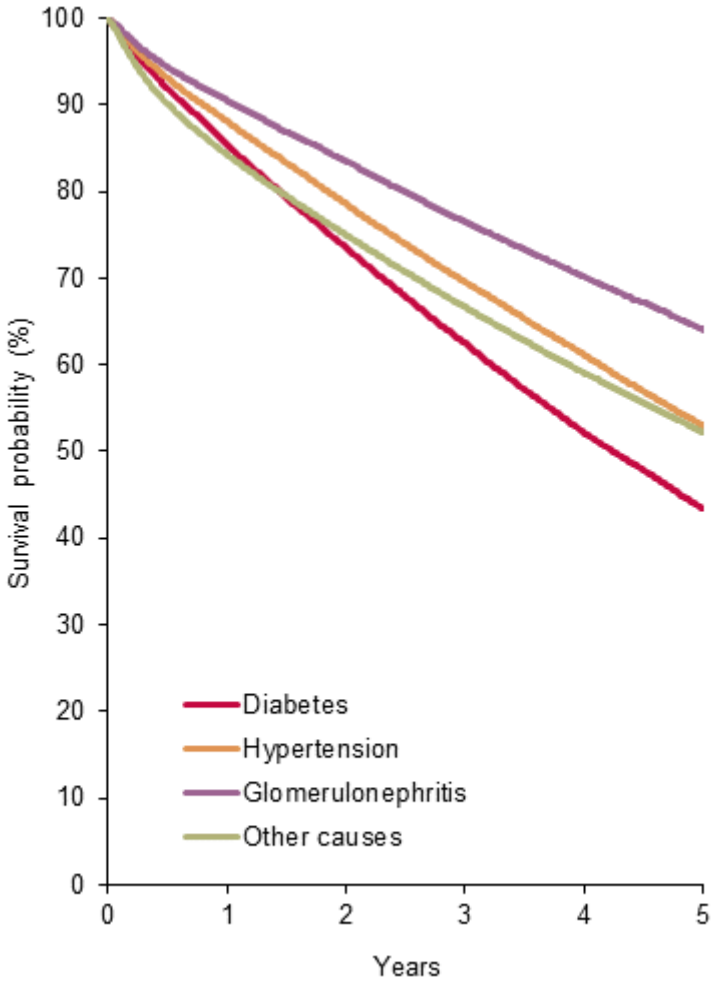

Figure 15: Adjusted patient survival by primary renal disease for incident renal replacement therapy patients from day 1, adjusted for age and sex

The unadjusted five-year survival of patients on dialysis from day 1 was 42.1% (95% CI: 42.0-42.3%) (Table 7).

Table 7: Patient survival on dialysis day 1, unadjusted, EU Member States plus Iceland and Norway

	Cohort 2007-2011				Cohort 2010-2014		
	90 day	**1 year**	**2 year**	**5 year**	**90 day**	**1 year**	**2 year**
0-19 years	99.0 (98.3-99.5)	96.3 (95.0-97.3)	94.1 (92.2-95.5)	89.5 (86.5-91.9)	99.0 (98.2-99.5)	97.6 (96.4-98.4)	94.2 (92.1-95.7)
20-44 years	99.1 (98.9-99.2)	96.4 (96.1-96.7)	92.9 (92.5-93.3)	82.1 (81.4-82.8)	99.0 (98.9-99.2)	96.7 (96.4-96.9)	93.4 (92.9-93.8)
45-64 years	97.0 (96.8-97.1)	90.0 (89.7-90.3)	82.0 (81.7-82.4)	59.3 (59.0-59.6)	97.2 (97.1-97.4)	90.6 (90.4-90.9)	83.4 (83.1-83.7)
65-74 years	93.9 (93.7-94.1)	81.6 (81.3-81.9)	69.4 (69.0-69.7)	40.3 (40.1-40.5)	94.4 (94.2-94.6)	83.2 (82.9-83.6)	71.6 (71.2-71.9)
75+ years	89.8 (89.6-90.1)	72.3 (72.0-72.6)	56.3 (56.0-56.5)	23.4 (23.4-23.5)	90.6 (90.4-90.8)	74.0 (73.7-74.2)	58.1 (57.8-58.3)
Men	94.1 (94.0-94.3)	82.5 (82.3-82.7)	70.6 (70.4-70.8)	41.3 (41.1-41.4)	94.4 (94.3-94.6)	83.4 (83.2-83.6)	71.7 (71.5-71.9)
Women	94.0 (93.8-94.1)	82.6 (82.3-82.8)	71.2 (70.9-71.4)	43.6 (43.4-43.8)	94.4 (94.2-94.6)	83.6 (83.3-83.8)	72.6 (72.3-72.9)
Diabetes	95.0 (94.8-95.2)	83.5 (83.2-83.9)	70.4 (70.0-70.7)	38.3 (38.1-38.5)	95.5 (95.3-95.7)	85.2 (84.9-85.6)	72.8 (72.4-73.1)
Hypertension/renal vascular disease	94.0 (93.7-94.2)	81.3 (81.0-81.7)	67.7 (67.3-68.1)	36.3 (36.1-36.5)	94.2 (93.9-94.4)	82.4 (82.0-82.7)	69.3 (68.9-69.7)
Glomerulonephritis	97.3 (97.0-97.5)	91.3 (90.9-91.7)	84.2 (83.7-84.7)	62.0 (61.4-62.6)	97.2 (97.0-97.5)	91.2 (90.8-91.6)	84.3 (83.8-84.8)
Other causes	93.2 (93.0-93.3)	81.1 (80.8-81.3)	70.2 (69.9-70.4)	43.7 (43.5-43.9)	93.6 (93.4-93.8)	81.7 (81.5-82.0)	70.7 (70.4-70.9)
All	94.1 (93.9-94.2)	82.5 (82.4-82.7)	70.8 (70.6-71.0)	42.1 (42.0-42.3)	94.4 (94.3-94.5)	83.5 (83.3-83.6)	72.1 (71.9-72.2)
Survival probabilities as % (95% confidence interval)							

Figure 16 shows the adjusted patient survival for patients starting haemodialysis and peritoneal dialysis from day 91. The one-year adjusted survival was higher for peritoneal dialysis (90.2%; 95% CI: 89.8-90.6%) than for haemodialysis patients (86.5%; 95% CI: 86.3-86.7%), whereas such difference is no longer present in the five -year adjusted survival (haemodialysis (46.7%; 95% CI: 46.4-47.1%) and peritoneal dialysis (47.4%; 95% CI: 46.3-48.6%)).

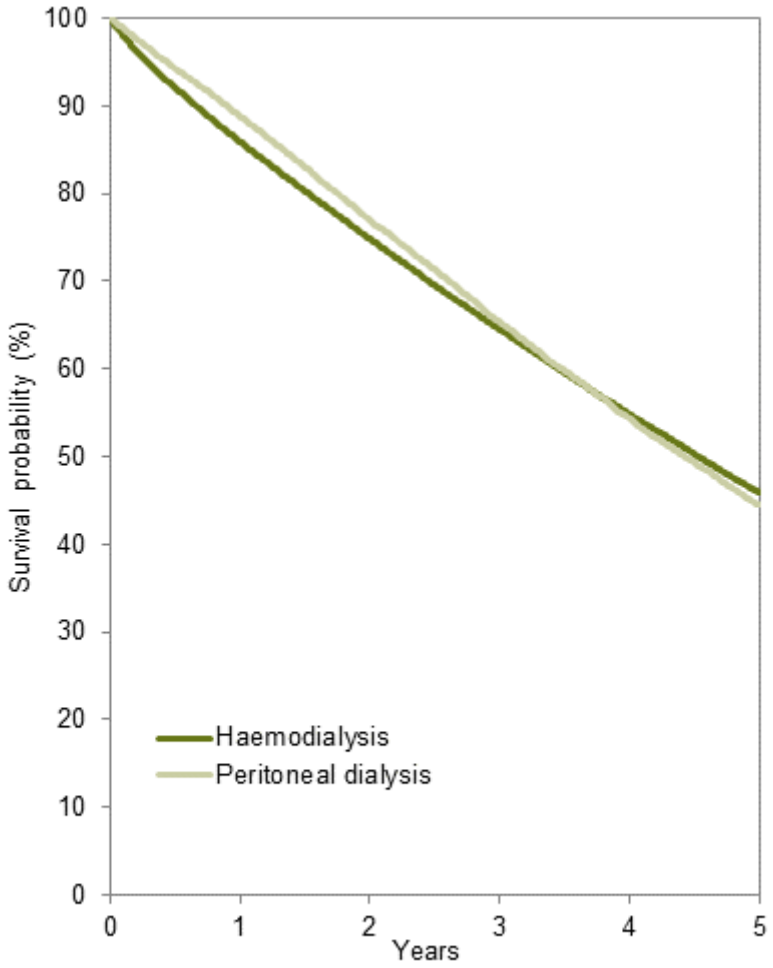

Figure 16: Adjusted patient survival by modality for incident dialysis patients from day 91, adjusted for age, sex and primary renal disease

Kidney transplantation

Tables 8 and 9 show the unadjusted patient survival by donor type from the day of kidney transplantation (in this analysis the death of the patient is the event). After 5 years, the unadjusted patient survival was 87.7% (95% CI: 87.3-88.0%) for patients who received a kidney transplant from a deceased donor and 94.1% (95% CI: 93.6-94.5%) for patients who received a kidney transplant from a living donor.

Table 8: Patient survival after first kidney transplant (deceased donor), unadjusted, EU Member States plus Iceland and Norway

	Cohort 2007-2011			Cohort 2010-2014	
	1 year	**2 year**	**5 year**	**1 year**	**2 year**
0-19 years	99.1 (98.1-99.6)	99.0 (98.0-99.5)	97.8 (96.5-98.6)	98.3 (97.0-99.0)	97.8 (96.5-98.7)
20-44 years	98.5 (98.2-98.8)	97.8 (97.5-98.1)	95.7 (95.2-96.1)	98.8 (98.5-99.0)	98.1 (97.8-98.4)
45-64 years	96.8 (96.5-97.0)	94.7 (94.4-95.1)	88.2 (87.8-88.7)	96.9 (96.6-97.1)	95.1 (94.7-95.4)
65+ years	91.5 (90.8-92.2)	87.9 (87.1-88.7)	73.4 (72.5-74.3)	92.5 (91.9-93.0)	88.3 (87.7-88.9)
Men	96.0 (95.7-96.3)	93.8 (93.5-94.2)	86.6 (86.1-87.0)	96.2 (96.0-96.5)	93.9 (93.6-94.2)
Women	96.8 (96.4-97.1)	95.3 (94.9-95.7)	89.6 (89.1-90.1)	96.6 (96.2-96.9)	94.9 (94.5-95.2)
Diabetes	95.1 (94.4-95.6)	92.3 (91.5-93.0)	83.0 (82.1-83.9)	94.7 (94.1-95.2)	91.7 (91.0-92.3)
Hypertension/renal vascular disease	94.1 (93.2-94.8)	91.4 (90.4-92.2)	82.0 (80.8-83.1)	94.9 (94.2-95.5)	91.8 (91.0-92.5)
Glomerulonephritis	97.5 (97.1-97.8)	96.2 (95.7-96.7)	90.9 (90.2-91.5)	97.6 (97.2-97.9)	96.2 (95.7-96.6)
Other causes	96.7 (96.4-97.0)	94.9 (94.6-95.3)	89.0 (88.6-89.5)	96.8 (96.5-97.0)	95.0 (94.6-95.3)
All	96.3 (96.1-96.5)	94.4 (94.1-94.6)	87.7 (87.3-88.0)	96.3 (96.1-96.5)	94.3 (94.0-94.5)
Survival probabilities as % (95% confidence interval)					

Table 9: Patient survival after first kidney transplant (living donor), unadjusted, EU Member States plus Iceland and Norway

	Cohort 2007-2011			Cohort 2010-2014	
	1 year	**2 year**	**5 year**	**1 year**	**2 year**
0-19 years	99.4 (98.0-99.8)	99.4 (98.0-99.8)	99.1 (97.7-99.7)	99.6 (98.4-99.9)	99.6 (98.4-99.9)
20-44 years	99.5 (99.3-99.7)	99.3 (99.0-99.5)	97.8 (97.3-98.2)	99.8 (99.6-99.9)	99.5 (99.2-99.6)
45-64 years	98.3 (97.9-98.7)	97.1 (96.6-97.6)	92.7 (91.9-93.4)	98.9 (98.5-99.1)	97.8 (97.4-98.2)
65+ years	95.8 (94.3-96.9)	92.6 (90.7-94.1)	80.5 (78.1-82.5)	96.9 (95.8-97.7)	94.0 (92.6-95.2)
Men	98.6 (98.3-98.9)	97.8 (97.4-98.1)	94.0 (93.4-94.5)	99.0 (98.7-99.2)	98.0 (97.7-98.3)
Women	98.7 (98.3-99.1)	97.7 (97.1-98.1)	94.3 (93.6-95.0)	99.2 (98.9-99.4)	98.3 (97.9-98.6)
Diabetes	96.9 (95.5-97.9)	94.8 (93.1-96.1)	85.0 (82.7-87.0)	97.6 (96.4-98.4)	95.8 (94.3-96.9)
Hypertension/renal vascular disease	97.4 (96.0-98.3)	95.8 (94.2-96.9)	89.9 (87.8-91.7)	98.3 (97.2-98.9)	96.8 (95.5-97.7)
Glomerulonephritis	99.3 (98.9-99.6)	98.7 (98.2-99.1)	96.6 (95.8-97.2)	99.3 (98.9-99.5)	98.6 (98.1-99.0)
Other causes	98.9 (98.6-99.2)	98.1 (97.7-98.5)	95.0 (94.4-95.6)	99.3 (99.1-99.5)	98.5 (98.2-98.8)
All	98.7 (98.4-98.9)	97.8 (97.4-98.0)	94.1 (93.6-94.5)	99.1 (98.9-99.2)	98.1 (97.9-98.4)
Survival probabilities as % (95% confidence interval)					

Tables 10 and 11 show the unadjusted graft survival by donor type from the day of kidney transplant (in this analysis death of the patient, graft failure and re-transplantation are events). After 5 years, the graft survival of kidneys from deceased donors was 78.7% (95% CI 78.3-79.1) whereas the graft survival of kidneys from living donors was 87.5% (95% CI: 86.9-88.0%).

Table 10: Graft survival after first kidney transplant (deceased donor), unadjusted, EU Member States plus Iceland and Norway

	Cohort 2007-2011			Cohort 2010-2014	
	1 year	**2 year**	**5 year**	**1 year**	**2 year**
0-19 years	92.5 (90.6-94.0)	90.1 (88.1-91.9)	83.7 (81.3-85.7)	92.8 (90.8-94.4)	90.3 (88.2-92.1)
20-44 years	94.0 (93.5-94.5)	92.0 (91.4-92.6)	85.4 (84.7-86.0)	94.2 (93.7-94.7)	92.3 (91.8-92.9)
45-64 years	91.6 (91.1-92.0)	88.7 (88.2-89.1)	79.9 (79.4-80.4)	91.8 (91.5-92.2)	89.1 (88.7-89.5)
65+ years	85.2 (84.4-86.0)	81.1 (80.2-81.9)	65.3 (64.4-66.1)	85.9 (85.3-86.6)	81.1 (80.4-81.8)
Men	90.9 (90.5-91.3)	87.9 (87.4-88.3)	78.0 (77.5-78.5)	90.9 (90.5-91.2)	87.6 (87.2-88.0)
Women	91.3 (90.8-91.8)	88.7 (88.2-89.3)	79.9 (79.2-80.5)	91.3 (90.8-91.7)	88.7 (88.2-89.2)
Diabetes	90.5 (89.7-91.2)	86.9 (86.0-87.8)	75.3 (74.3-76.2)	89.8 (89.1-90.5)	86.1 (85.3-86.9)
Hypertension/renal vascular disease	88.4 (87.3-89.4)	85.3 (84.2-86.3)	71.9 (70.8-73.1)	88.7 (87.8-89.6)	84.8 (83.8-85.7)
Glomerulonephritis	91.8 (91.2-92.4)	89.1 (88.4-89.8)	80.7 (79.9-81.5)	91.8 (91.2-92.4)	89.0 (88.3-89.6)
Other causes	91.5 (91.0-91.9)	88.8 (88.4-89.3)	80.4 (79.9-80.9)	91.7 (91.3-92.1)	89.0 (88.6-89.4)
All	91.1 (90.7-91.4)	88.2 (87.9-88.5)	78.7 (78.3-79.1)	91.0 (90.8-91.3)	88.0 (87.7-88.3)
Survival probabilities as % (95% confidence interval)					

Table 11: Graft survival after first kidney transplant (living donor), unadjusted, EU Member States plus Iceland and Norway

	Cohort 2007-2011			Cohort 2010-2014	
	1 year	**2 year**	**5 year**	**1 year**	**2 year**
0-19 years	96.8 (94.8-98.0)	95.9 (93.8-97.3)	90.9 (88.1-93)	97.0 (95.2-98.2)	96.0 (94.0-97.4)
20-44 years	96.5 (95.9-97.0)	94.8 (94.1-95.4)	89.2 (88.3-90.1)	97.5 (97.0-97.9)	96.1 (95.5-96.6)
45-64 years	95.8 (95.2-96.3)	94.0 (93.2-94.6)	87.6 (86.6-88.4)	96.6 (96.0-97.0)	94.8 (94.2-95.3)
65+ years	93.2 (91.4-94.7)	89.8 (87.7-91.5)	76.2 (73.9-78.4)	95.4 (94.2-96.4)	92.0 (90.5-93.3)
Men	95.9 (95.4-96.3)	94.4 (93.8-94.9)	87.7 (86.9-88.4)	96.8 (96.4-97.2)	95.2 (94.7-95.7)
Women	96.0 (95.3-96.5)	93.6 (92.7-94.3)	87.0 (86.0-88.0)	96.8 (96.3-97.3)	94.8 (94.1-95.4)
Diabetes	94.4 (92.7-95.8)	91.7 (89.8-93.3)	79.5 (77.1-81.7)	94.9 (93.4-96.1)	92.4 (90.6-93.8)
Hypertension/renal vascular disease	94.7 (93.0-96.0)	91.9 (89.9-93.5)	83.0 (80.6-85.1)	96.3 (94.9-97.3)	93.8 (92.2-95.1)
Glomerulonephritis	95.7 (94.9-96.4)	94.0 (93-94.8)	87.5 (86.3-88.6)	96.8 (96.1-97.4)	95.2 (94.4-95.9)
Other causes	96.4 (95.8-96.8)	94.8 (94.2-95.3)	89.3 (88.5-90.0)	97.1 (96.7-97.5)	95.5 (95.0-96.0)
All	95.9 (95.5-96.3)	94.1 (93.6-94.5)	87.5 (86.9-88.0)	96.8 (96.5-97.1)	95.1 (94.7-95.4)
Survival probabilities as % (95% confidence interval)					

Figure 17 shows the adjusted patient survival by donor type from the day of kidney transplantation, adjusted for age, sex and primary renal disease. The five-year adjusted patient survival was higher for patients who received a kidney from a living donor (94.6%; 95% CI: 94.1-95.1%) than for those who received a kidney from a deceased donor (91.9%; 95% CI: 91.6-92.3%).

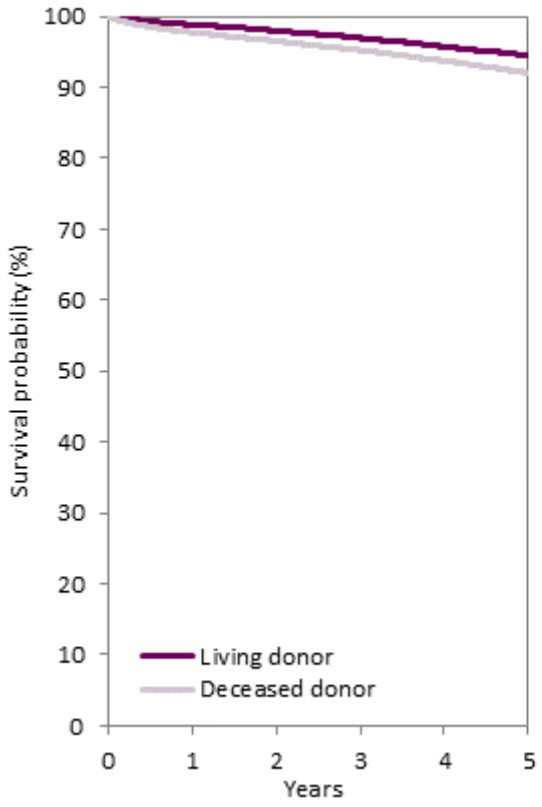

Figure 17: Adjusted patient survival by donor type for patients receiving a first kidney transplant from day 91, adjusted for age, sex and primary renal disease

II.1.3 Impact

The ERA-EDTA Registry provides the unique opportunity to report on the current status of patient and graft survival of RRT modalities for a large part of Europe with (almost) 100% coverage of the patients.

Dialysis versus kidney transplantation

So far, the results of published papers have indicated that kidney transplantation is associated with better survival than dialysis (at least for the age below 75 years) [Tonelli 2011; Wolfe 1999]. There are, however, no randomized controlled trials comparing outcomes in dialysis versus kidney transplant patients because it is perceived unethical to withhold beneficial (transplantation) treatment from patients with ESKD. Current evidence is therefore based on observational data, despite their drawbacks. Indeed, within observational studies, a fair comparison between the two groups is difficult to make as patients receiving a kidney transplant are usually younger and healthier compared to those on dialysis. Suitability for kidney transplantation is assessed before a patient is waitlisted and patients on dialysis who are not waitlisted are older and have more comorbidities then their counterparts on the waitlist [McDonald 2002]. At this moment, it is not possible to compare the survival of dialysis and transplant patients using the ERA-EDTA Registry database as waiting list data are unavailable at the individual patient level. Waiting list data are needed as for a fair comparison between dialysis and transplantation one needs to calculate the mortality risk during waiting time for patients suitable for kidney transplantation but remaining on dialysis. A few years ago, such analyses have been done in for example Scotland and Canada [Oniscu 2005, Rabbat 1999] showing superior survival for transplanted patients compared to waitlisted patients remaining on dialysis.

Please note that some of our analyses were adjusted for the age of 67 years for survival on dialysis and for the age of 50 years for survival on a kidney transplant. This means that a good comparison between the survival on dialysis and kidney transplantation is not possible, not only because of unmeasured co-morbidities in these treatment groups but also due to the different age distributions of the patient populations.

Haemodialysis versus peritoneal dialysis

Again, evidence on treatment comparisons between haemodialysis and peritoneal dialysis is based on observational studies. Korevaar et al. (2003) did an attempt to compare the outcomes of haemodialysis as initial chronic dialysis treatment with those of peritoneal dialysis in a randomized controlled trial. This RCT was however prematurely stopped due to the low inclusion rate [Korevaar 2003]. A new trial has started in China (trial registration NCT01413074 at clinicaltrials.gov) but the results of this trial have not been published yet. Up to now, the results of published observational studies suggest that overall survival on haemodialysis and peritoneal dialysis is similar, that peritoneal dialysis is associated with better survival for some specific patient subgroups but with worse survival in other subgroups [Mehrotra 2011; van de Luijtgaarden 2011; Yeates 2012; McDonald 2009; Noordzij 2012; Wong 2017].

The results of the ERA-EDTA Registry presented in this deliverable show that the 1 year adjusted survival was higher for those who started peritoneal dialysis than for those who started haemodialysis, whereas this difference was no longer present after 5 years. Of note, in a previous published study using ERA-EDTA Registry data, we have shown that results on dialysis modality choice and related patient survival from the propensity score matched analysis (an advanced statistical method to create more comparable treatment groups) were similar to the results from the conventional Cox regression analysis [van de Luijtgaarden 2016]. In this study by van de Luijtgaarden et al. the investigators also used competing risk analyses to account for the differences in transplant rates between the two treatment groups. The results show that 5 year after the start of haemodialysis, 53% of the patients died, 3% was on peritoneal dialysis, 18% received a kidney transplant and 26% was still on haemodialysis whereas 5 year after the start of peritoneal dialysis, 28% of the patients died, 34% was on haemodialysis, 30% received a kidney transplant and 9% was still on peritoneal dialysis.

Living donor versus deceased donor kidney transplantation

In line with the results presented in this deliverable, recipients of living donor kidney transplants generally have better graft survival rates than recipients of deceased donor kidney transplants [Terasaki 1995; US Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients 2009; Fuggle 2010]. This may be due to shorter time on dialysis for recipients of a living donor kidney, shorter ischemia time and better preparation and planning of, for example, pre-operative immunosuppression. Of note, pre-emptive (mainly living) donor kidney transplantation provides patients with ESKD the option of avoiding dialysis, which improves survival [Kasiske BL 2002].

II.1.4 References

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II.2. Literature study on patient survival of patients with ESKD treated by comprehensive conservative management

Where in developed countries the use of renal replacement therapy (RRT) has increased over the previous decades, in the recent past comprehensive conservative management (CCM) as a treatment alternative for end-stage kidney disease (ESKD) in elderly patients with multi-morbidity and poor prognosis has gained acceptance [Kurella Tamura 2016]. This EDITH deliverable reports on the survival of ESKD patients treated by this comprehensive conservative management. To put their survival into perspective it was compared with survival of similar patients treated by dialysis.

II.2.1 Methods

We non-systematically searched Pubmed for systematic reviews published since 2010, which compared the survival of patients with ESKD who received dialysis or comprehensive conservative management. We used the following key words: 'systematic review', 'survival', 'end stage kidney disease', 'end stage renal disease', 'kidney failure', 'conservative care' and 'palliative care'. In addition, we searched for original articles published in 2016 and later.

II.2.2 Results

Current evidence comes from systematic reviews of observational studies (Table 12), as RCTs comparing the outcomes of comprehensive conservative management and dialysis have not been published. As expected the patient populations primarily include elderly patients. One systematic review reported that the one-year survival of elderly patients on dialysis was 84.2% and that in comprehensive conservative management was 72.7% [Foote 2016]. The difference between survival on dialysis and that on comprehensive conservative management increased with follow-up time [Foote 2016]. A meta-analysis including three out of twelve studies analyzed [Shum 2014, Chandna 2011, Brown 2015] showed that patients choosing dialysis had half the risk of death compared to those opting for conservative management (pooled adjusted hazard ratio 0.53 (95%CI 0.30 to 0.91)) [Wongrakpanich 2017]. Three other systematic reviews performed on partly the same original studies confirmed these findings [O'Connor 2012, Pacilio 2015, Vega-Aleva 2016]. In all systematic reviews at least half of the included studies reported a loss of survival benefit with dialysis in the presence of high comorbidity and in the very elderly [Foote 2016, Wongrakpanich 2017, O'Connor 2012, Pacilio 2016, Vega-Alava 2016].

More recently published original articles not included in the systematic reviews pointed into exactly the same direction: in most studies dialysis conferred a survival advantage [Teruel 2015, Martinez Echevers 2016, Morton 2016, Kwok 2016, Tam-Tham 2018, Raman 2018], which was lost at high age [Martinez Echevers 2016] and high comorbidity [Kwok 2016], whereas one study showed similar survival [Rouveure 2015].

Table 12: Systematic reviews and meta-analyses on the survival of elderly ESKD patients on dialysis versus comprehensive conservative management (CCM)

First author	Title	Journal	Year	Time frame	Number of studies	Patient age	Study quality & reported bias	Result / Conclusion
Foote	Survival outcomes of supportive care versus dialysis therapies for elderly patients with end stage kidney disease: a systematic review and meta-analysis	Nephrology	2016	start - 2014	6	Mean age Undifferentiated dialysis: 77.4 years HD: 73.5 years PD: 76.3 years CCM: 79.2 years	Median quality score: 5 out of 8; Lead time bias; Publication bias.	1 year survival: dialysis 84.2% and supportive care: 72.7%. Three studies demonstrated loss of survival benefit in dialysis in the presence of high comorbidity and one study showed a marked decrease in survival gain.
O'Connor	Conservative management of end-stage renal disease without dialysis: a systematic review	Journal of Palliative Medicine	2012	start - 2011	5	Median age dialysis: 58.5-83.2 years (range) Median age CCM: 77.5-84.1 years (range)	3 good quality and 2 limited quality. Bias not discussed.	Three studies found a survival benefit with dialysis, but the other two found no difference. Patients with multiple comorbid conditions, especially ischemic heart disease, were the least likely to experience a survival benefit.
Pacilio	Stage 5-CKD under nephrology care: to dialyze or not to dialyze, that is the question	Journal of Nephrology	2015	2005-2015	10	Mean age dialysis: 56.0-79.6 years (range) Mean age CCM: 60.5-83.0 years (range)	Quality not assessed. Bias not discussed.	Five studies showed similar survival; three studies showed a survival advantage on dialysis which was lost with high comorbidity and in the very elderly. One study showed higher survival on CCM.

First author	Title	Journal	Year	Time frame	Number of studies	Patient age	Study quality & reported bias	Result / Conclusion
Vega-Alava	A comparison between dialysis versus conservative management as modes of treatment in the management of elderly patients with end stage renal disease: a systematic review	Philippine Journal of Internal Medicine	2016	2004-2014	7	Mean/median age dialysis: 58.5-83.2 years (range) Mean/median age CCM: 77.5-84.1 years (range)	Quality not assessed. Bias not discussed.	Median survival: dialysis 39.5 months and CCM 18.9 months. No significant difference in patients with multiple comorbid conditions.
Wongrakpanich	Dialysis therapy and conservative management of advanced chronic kidney disease in the elderly: a systematic review	Nephron Clinical Practice	2017	start - 2016	12 of which 3 were included in a meta-analysis	> 65 and >75 years	2 good quality and 1 fair quality. Lead time bias. Confounding by indication.	Median survival: dialysis 8-67 months and CCM 6-30 months. In patients ≥ 65 years of age and eGFR < 15 ml/min/1.73m^2 inclusion of age and comorbidities in the multivariable analysis provided a pooled adjusted hazard ratio of 0.53 (95% CI 0.30-0.91) for dialysis in the meta-analysis.
Abbreviations used; HD: hemodialysis, PD: peritoneal dialysis, CCM: comprehensive conservative management, eGFR: estimated glomerular filtration rate, CI: confidence interval								

Limitations

The original articles included in the five systematic reviews were overlapping. It therefore comes as no surprise that their conclusions were roughly similar. More importantly, it is likely that in all included studies the choice for comprehensive conservative management or dialysis suffered from confounding by indication, which hampers the interpretation of study findings. Furthermore, many of these comparisons may have suffered from lead-time bias. Finally, publication bias may hamper valid conclusions.

II.2.3 Impact

Systematic reviews and more recently published original articles with observational study designs have shown a survival advantage for patients starting dialysis compared to those treated with comprehensive conservative management. These comparisons were however likely flawed by confounding by indication and different types of bias. It can therefore be concluded that the literature does not allow a confident estimate of the relative survival benefits of these treatments [Foote 2016]. Only RCTs will be able to provide us with valid answers to this question and hopefully an ongoing RCT in the UK will help to shed some light on this [https://doi.org/10.1186/ISRCTN17133653].

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II.3. Quality of life of patients on different treatment modalities for ESKD

Treatments for patients with end-stage kidney disease (ESKD) include kidney transplantation, dialysis and comprehensive conservative management. In many countries in and outside Europe, the use of renal replacement therapy (kidney transplantation and dialysis) has increased over the previous decades [ERA-EDTA Registry 2018; USRDS 2018]. Also, in particular in high-income countries, comprehensive conservative management as a treatment alternative for ESKD in elderly patients with multi-morbidity and poor prognosis has gained acceptance [Kurella Tamura 2016]. This treatment includes planned patient-centered holistic care (but no dialysis) for patients with ESKD to delay the progression of kidney disease and decrease the risk of adverse events by for example active symptom management, advance care planning and psychological support [Davison 2015].

The mortality in patients with ESKD is high, especially for those on dialysis and comprehensive conservative management [ERA-EDTA Registry 2018; USRDS 2018; Foote 2016]. Remaining life expectancies of renal replacement therapy patients are therefore substantially lower than those of the age- and sex matched general population: in dialysis patients life expectancy is reduced to almost 30% and in transplant recipients to 60-70% compared to the life expectancy of the general population [ERA-EDTA Registry 2018; USRDS 2018].

In addition, patients with ESKD face an enormous impact from their treatment on for example their physical and mental condition. Hence, it is not only important to assess the mortality in patients with ESKD but also their quality of life (QOL). As a consequence, a large number of studies have assessed the QOL in patients with ESKD using a variety of QOL surveys [Edgell 1996].

In this EDITH deliverable, we therefore aimed at describing the QOL for patients with ESKD on different treatment modalities, i.e. kidney transplantation, dialysis (both hemodialysis (HD) and peritoneal dialysis (PD)) and comprehensive conservative management (CCM).

II.3.1 Methods

Literature search

We non-systematically searched Medline, Embase and Google Scholar for systematic reviews published since 2000 which described the QOL of patients with ESKD who received renal replacement therapy (kidney transplantation and dialysis) or comprehensive conservative management. We used the following key words: ‘systematic review’, ‘end stage kidney disease’, ‘end stage renal disease’, and ‘quality of life’, and also checked the references of the systematic reviews. As many studies on QOL have been published, we may have missed original studies through our

approach. However, the systematic reviews in our study themselves systemically searched for studies, which limits the chance of missing individual original articles. The systematic reviews and meta-analyses focused on the QOL of kidney patients versus the general population or between different treatment modalities (e.g. dialysis versus kidney transplant patients). Some but not all meta- analyses adjusted their analyses for at least age and gender. It should be noted that in the study of Tonelli et al. (2011) the results were broadly similar for unadjusted and adjusted analyses comparing QOL between transplant and dialysis patients.

Methods to assess QOL

Different surveys exist to assess the QOL some of which are generic, such as the Short Form Health Survey (SF)-36, CHOICE Health Experience Questionnaire (CHEQ), World Health Organization Quality of Life (WHOQOL), and the General Health Questionnaire (GHQ), or ESKD targeted, such as the Kidney Disease Quality of Life (KDQOL) survey. The QOL surveys may assess different dimensions of QOL, like physical, mental, social and disease domains.

II.3.2 Results

Table 13 provides an extensive overview of the results of 16 systematic reviews and meta-analyses on the QOL of patients on renal replacement therapy and comprehensive conservative management that have been published since 2000. Original studies can be included in one or in more systematic reviews or meta-analyses.

Table 13:Systematic reviews and meta-analyses on the quality of life of patients on different treatment modalities for patients with ESKD

First author	Title	Journal	Year	Age	Time frame	Number of studies	Modalities	Aim	Result
Boateng	The impact of dialysis modality on quality of life: a systematic review	Journal of Renal Care	2011	adult	start - 2010	26	HD PD	QOL in HD and PD	Overall, PD higher QOL than HD, but HD better QOL in physical dimension over time than PD. Mental health is similar for HD and PD.
Cameron	Differences in quality of life across renal replacement therapies: A meta-analytic comparison	American Journal of Kidney Diseases	2000	> 18 years	start - 1998	61	HD PD HHD TX	QOL (emotional distress and psychological well-being) in HD, PD and TX	TX better: lower emotional distress, and greater psychological well-being than HD and CAPD.
Ho	The influence of different dialysis modalities on the quality of life of patients with end-stage renal disease: A systematic literature review	Psychology & Health	2016		1990 - 2016	34	HD PD	Health related (HR) QOL in HD and PD	Overall, no difference in HR-QOL between HD and PD. However, higher % of patients that received PD had a better HR-QOL in terms of physical, mental, social and disease symptoms than HD.
Homaie, Rad	Health-related Quality of Life in Patients on Hemodialysis and Peritoneal Dialysis: a Meta-Analysis of Iranian Studies.	Iranian Journal of Kidney Disease	2015		-2014	26	HD PD	QOL in HD and PD	No difference in QOL between HD and PD
Landreneau	Quality of life in patients undergoing hemodialysis and renal transplantation--a meta-analytic review	Nephrology Nursing Journal	2010		start - 2007	16	HD PD Tx	QOL in HD, PD and TX	TX better QOL than HD, in particular overall QOL and physical functioning

First author	Title	Journal	Year	Age	Time frame	Number of studies	Modalities	Aim	Result
Liem	Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis	Value in Health	2008		start - 2006	27	HD PD TX	QOL in HD, PD and TX	TX better QOL than HD and PD. No difference in QOL between HD ad PD.
O'Connor	Conservative management of end-stage renal disease without dialysis: a systematic review	Journal of Palliative Medicine	2012		start - 2011	13	CCM dialysis?	QOL in CCM and dialysis	QOL generally similar in DL and CCM
Pacillio	Stage 5-CKD under nephrology care: to dialyze or not to dialyze, that is the question	Journal of Nephrology	2016		2005 - 2015	11	CCM dialysis?	QOL in CCM and dialysis	No difference in QOL between CCM and dialysis (neither in survival). Studies were mostly performed in elderly patients.
Segall	Dialysis modality choice in elderly patients with end-stage renal disease: a narrative review of the available evidence	Nephrology Dialysis Transplantation	2017	elderly			HD PD	QOL in PD and home HD	No difference in QOL between home HD and PD
Spiegel	Biomarkers and health-related quality of life in end-stage renal disease: a systematic review.	Clinical Journal of the American Society of Nephrology	2008		1990 - 2007	47	DL	HR QOL domains between DL and general population	HR QOL in DL is most affected by physical domain (in comparison with general population)
Tonelli	Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes.	American Journal of Transplantation	2011		-2010	110	DL Tx	QOL in DL and TX	TX better QOL than DL
Tsai	Conservative management and health-related quality of life in end-stage renal disease: a systematic review.	Clinical Investigative Medicine	2017		-2016	4	DL CCM	QOL in CCM and DL	Only 4 papers with different results. Mental HR QOL in CCM better than in DL.

First author	Title	Journal	Year	Age	Time frame	Number of studies	Modalities	Aim	Result
Vega-Alava	A comparison between dialysis versus conservative management as modes of treatment in the management of elderly patients with end stage renal disease: A systematic review	Phillippine Journal of Internal Medicine	2016	> 70 years	2004-2014	7	HD PD? CCM	QOL in CCM and DL	QOL equal in CCM and DL
Wyld	A Systematic Review and Meta-Analysis of Utility-Based Quality of Life in Chronic Kidney Disease Treatments	Plos Medicine	2012	> 18 years		190	HD PD CAPD APD Tx CCM	QOL in CCM, HD, PD and TX	QOL lower in pre CKD (CCM) and DL than TX, QOL lowest in CM QOL higher in APD than CAPD
Zazzeroni	Comparison of Quality of Life in Patients Undergoing Hemodialysis and Peritoneal Dialysis: a Systematic Review and Meta-Analysis.	Kidney & Blood Pressure Research	2017		2011 - 2016	7	HD PD	QOL in HD and PD	QOL equal in HD and PD, with some study exceptions

Dialysis versus general population

A systematic review including 47 studies has found that the QOL was lower for patients on dialysis than in the general population [Spiegel 2008]. In patients on dialysis, the health related QOL was most affected with respect to physical functioning (e.g. vitality) and least affected with respect to mental functioning (e.g. mental health, emotion).

Transplantation versus dialysis

All systematic reviews and meta-analyses have consistently shown that QOL was higher for patients with a kidney transplant than for those on dialysis [Cameron 2000; Landreneau 2010; Liem 2008; Tonelli 2011; Wyld 2012].

Hemodialysis versus peritoneal dialysis

The vast majority of systematic reviews and meta-analyses have reported similar QOL for those on HD and PD [Ho 2016; Homai Rad 2015; Liem 2008; Segall 2017; Wyld 2012; Zazzeroni 2017]. In contrast, the systematic review of Boateng et al. (2011) found that PD patients mostly rate their QOL higher than HD patients with some exceptions in the physical and mental domains [Boateng 2011]. Furthermore, a publication by Segall et al. (2017) has shown similar QOL in home HD and PD in the elderly, whereas Wyld et al. (2012) found that the QOL was higher for those on automated peritoneal dialysis (APD) compared to continuous ambulatory peritoneal dialysis (CAPD).

Dialysis versus comprehensive conservative management

Three systematic reviews and meta-analyses have shown no difference in QOL between conservative management and dialysis [O'Connor 2012; Pacillio 2016; Vega-Alva 2016], whereas the systematic review and meta-analysis by Wyld et al. (2012) has found that the QOL was lower in patients treated by comprehensive conservative management compared to dialysis. Almost all included studies comparing QOL in patients treated by comprehensive conservative management versus dialysis were performed in the elderly. Studies on this topic are however rather scarce (e.g. the systematic reviews and meta-analysis included 3 to 13 studies). Moreover, the definition of comprehensive conservative management was sometimes not clear and may have differed across the studies.

Limitations

The results should be interpreted with caution for different reasons, the most important of which are described below. First, most of the included studies had a cross sectional study design and treatment was never allocated using a randomized controlled trial. As a consequence, the case-mix of patients (measured and unmeasured) was likely different across the different treatment modalities and may have confounded the comparison. Second, the heterogeneity of studies was very substantial, including for example differences in QOL surveys, sample sizes, and population characteristics, making it difficult to make a comparison between studies. Third, QOL will not only depend on the treatment modality but also on other factors, such as physical and mental co-morbidities (e.g. depression), psychosocial variables (e.g. marital status, employment status) [Lowney 2015; Rebollo 2001] and socio-economic status. Fourth, in the comparison of QOL between dialysis and comprehensive conservative management, only few studies were performed and those performed were done in elderly patients. Only few studies focused on the QOL of home HD, CAPD and APD. Also, elderly patients who were unable to participate because of cognitive, functional or vision or hearing impairments may have been excluded from many studies, making the results less generalizable to the respective overall treatment modality populations.

II.3.3 Impact

A large number of systematic reviews and meta-analyses have consistently found that the QOL was higher for kidney transplant patients than for dialysis patients. All systematic reviews and meta-analyses have failed to show a difference in the QOL for HD and PD patients, with one exception in

favour of PD. In addition, the results of a small number of studies indicate that there may be no difference in the QOL between comprehensive conservative management and dialysis in elderly patients with ESKD. The results of this report should be interpreted with caution due to case-mix differences of patients on the different treatment modalities, the heterogeneity of studies and the sometimes low number of studies included in particular those aiming to compare QOL between dialysis and comprehensive conservative management.

The results confirm that for those patients with ESKD who are suitable to receive a kidney transplant, this treatment is the preferred treatment modality both in terms of survival and QOL. Currently PD use is declining in most countries in Europe, although no (large) differences exist in the five year survival for PD compared to HD (see activity goal 1 of this EDITH deliverable) and PD has usually lower costs [Haller 2011; Mohnen 2019]. Moreover, this report shows that the vast majority of studies found no difference in QOL between PD and HD patients. Because of its lower costs PD may be the preferred first dialysis modality more often, depending on patient preference. In addition, with respect to QOL comprehensive conservative management seems to be a valid treatment option for selected, in particular older, patients. Another part of this deliverable focuses on the survival of patients on comprehensive conservative management.

II.3.4 References

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II.4. Annex: Patient and graft survival, EU Member States only

Patient survival on renal replacement therapy from day 1, unadjusted, EU Member States only							
	Cohort 2007-2011				**Cohort 2010-2014**		
	90 day	**1 year**	**2 year**	**5 year**	**90 day**	**1 year**	**2 year**
0-19 years	99.2 (98.6-99.6)	97.2 (96.3-97.9)	96.1 (95.1-97.0)	94.5 (93.3-95.5)	99.2 (98.5-99.5)	97.9 (97.0-98.5)	96.6 (95.5-97.4)
20-44 years	99.1 (99.0-99.3)	97.0 (96.8-97.2)	94.6 (94.3-94.9)	89.1 (88.6-89.5)	99.1 (99.0-99.3)	97.2 (97.0-97.5)	95.0 (94.7-95.3)
45-64 years	97.1 (97.0-97.3)	90.8 (90.5-91.0)	84.1 (83.8-84.3)	67.6 (67.3-67.9)	97.4 (97.2-97.5)	91.5 (91.3-91.7)	85.5 (85.2-85.7)
65-74 years	94.0 (93.8-94.2)	82.0 (81.7-82.3)	70.2 (69.9-70.6)	43.2 (43.0-43.4)	94.5 (94.3-94.7)	83.8 (83.5-84.1)	72.8 (72.5-73.1)
75+ years	89.9 (89.6-90.1)	72.4 (72.2-72.7)	56.5 (56.2-56.7)	23.8 (23.7-23.9)	90.6 (90.4-90.8)	74.1 (73.8-74.4)	58.3 (58.1-58.6)
Men	94.3 (94.2-94.5)	83.5 (83.3-83.7)	73.0 (72.8-73.2)	49.7 (49.5-49.8)	94.7 (94.5-94.8)	84.5 (84.3-84.7)	74.2 (74.0-74.4)
Women	94.2 (94.0-94.4)	83.6 (83.4-83.9)	73.6 (73.3-73.8)	51.7 (51.5-51.9)	94.6 (94.5-94.8)	84.7 (84.5-85.0)	75.2 (75.0-75.5)
Diabetes	95.1 (94.9-95.3)	84.1 (83.7-84.4)	71.7 (71.3-72.0)	43.3 (43.1-43.6)	95.5 (95.3-95.7)	85.7 (85.4-86.0)	74.0 (73.7-74.4)
Hypertension/renal vascular disease	94.1 (93.8-94.3)	81.8 (81.5-82.2)	69.0 (68.6-69.4)	40.9 (40.7-41.2)	94.3 (94.0-94.5)	82.9 (82.5-83.2)	70.6 (70.2-71.0)
Glomerulonephritis	97.4 (97.2-97.7)	92.2 (91.9-92.6)	86.7 (86.2-87.1)	72.4 (71.9-72.9)	97.4 (97.2-97.6)	92.2 (91.8-92.5)	86.8 (86.4-87.2)
Other causes	93.5 (93.3-93.7)	82.4 (82.2-82.7)	73.0 (72.8-73.3)	52.9 (52.7-53.1)	94.0 (93.8-94.1)	83.2 (83.0-83.4)	73.8 (73.6-74.1)
All	94.3 (94.2-94.4)	83.6 (83.4-83.7)	73.2 (73.0-73.4)	50.4 (50.3-50.5)	94.7 (94.6-94.8)	84.6 (84.4-84.7)	74.6 (74.4-74.7)
Survival probabilities as % (95% confidence interval)							

Patient survival on dialysis from day 1, unadjusted, EU Member States only							
	Cohort 2007-2011				**Cohort 2010-2014**		
	90 day	**1 year**	**2 year**	**5 year**	**90 day**	**1 year**	**2 year**
0-19 years	99.0 (98.2-99.4)	96.3 (94.9-97.3)	94.0 (92.2-95.5)	89.3 (86.2-91.8)	99.0 (98.2-99.5)	97.6 (96.4-98.4)	94.6 (92.6-96.0)
20-44 years	99.1 (98.9-99.2)	96.4 (96.1-96.7)	93.0 (92.5-93.4)	82.2 (81.5-82.9)	99.0 (98.9-99.2)	96.7 (96.4-97.0)	93.4 (92.9-93.8)
45-64 years	97.0 (96.8-97.1)	90.0 (89.7-90.3)	82.1 (81.8-82.4)	59.4 (59.1-59.7)	97.2 (97.1-97.4)	90.6 (90.4-90.9)	83.4 (83.1-83.7)
65-74 years	93.9 (93.7-94.1)	81.6 (81.3-81.9)	69.4 (69.0-69.7)	40.3 (40.1-40.5)	94.4 (94.2-94.6)	83.3 (82.9-83.6)	71.6 (71.3-72.0)
75+ years	89.8 (89.6-90.1)	72.3 (72.0-72.6)	56.3 (56.1-56.6)	23.6 (23.5-23.7)	90.6 (90.3-90.8)	74.0 (73.7-74.3)	58.1 (57.9-58.4)
Men	94.1 (93.9-94.2)	82.5 (82.3-82.7)	70.7 (70.5-70.9)	41.4 (41.2-41.5)	94.4 (94.3-94.6)	83.4 (83.2-83.6)	71. 71.6-72.0)
Women	94.0 (93.8-94.1)	82.6 (82.3-82.8)	71.2 (70.9-71.5)	43.7 (43.5-43.9)	94.4 (94.2-94.5)	83.6 (83.3-83.9)	72.7 (72.4-72.9)
Diabetes	95.0 (94.8-95.2)	83.5 (83.2-83.9)	70.4 (70.0-70.7)	38.3 (38.1-38.5)	95.5 (95.2-95.7)	85.2 (84.9-85.6)	72.8 (72.5-73.1)
Hypertension/renal vascular disease	94.0 (93.7-94.2)	81.4 (81.0-81.8)	67.9 (67.5-68.3)	36.5 (36.3-36.7)	94.1 (93.9-94.4)	82.4 (82.0-82.8)	69.4 (69.0-69.8)
Glomerulonephritis	97.3 (97.0-97.5)	91.4 (91.0-91.8)	84.3 (83.8-84.8)	62.2 (61.6-62.8)	97.2 (96.9-97.4)	91.2 (90.8-91.6)	84.3 (83.8-84.8)
Other causes	93.1 (93.0-93.3)	81.1 (80.9-81.4)	70.2 (69.9-70.4)	43.7 (43.5-43.9)	93.6 (93.4-93.7)	81.7 (81.5-82.0)	70.7 (70.5-71.0)
All	94.0 (93.9-94.2)	82.5 (82.4-82.7)	70.9 (70.7-71.0)	42.2 (42.1-42.4)	94.4 (94.3-94.5)	83.5 (83.3-83.7)	72.1 (71.9-72.3)
Survival probabilities as % (95% confidence interval)							

Patient survival after first kidney transplant (deceased donor), unadjusted, EU Member States only					
	Cohort 2007-2011			**Cohort 2010-2014**	
	1 year	**2 year**	**5 year**	**1 year**	**2 year**
0-19 years	99.3 (98.4-99.7)	99.2 (98.3-99.6)	98.0 (96.8-98.8)	98.4 (97.1-99.1)	98.0 (96.6-98.8)
20-44 years	98.5 (98.2-98.8)	97.8 (97.5-98.1)	95.7 (95.2-96.1)	98.8 (98.5-99.0)	98.1 (97.8-98.4)
45-64 years	96.8 (96.5-97.0)	94.8 (94.4-95.1)	88.3 (87.8-88.7)	96.9 (96.6-97.1)	95.1 (94.7-95.4)
65+ years	91.5 (90.7-92.2)	87.8 (87.0-88.6)	73.6 (72.6-74.4)	92.5 (91.9-93.0)	88.3 (87.7-88.9)
Men	96.1 (95.8-96.3)	93.9 (93.5-94.2)	86.7 (86.3-87.2)	96.2 (96.0-96.5)	93.9 (93.6-94.2)
Women	96.8 (96.4-97.1)	95.3 (94.9-95.7)	89.6 (89.1-90.1)	96.5 (96.2-96.8)	94.9 (94.5-95.2)
Diabetes	95.1 (94.4-95.7)	92.4 (91.6-93.1)	83.1 (82.1-84.0)	94.7 (94.1-95.2)	91.7 (91.0-92.3)
Hypertension/renal vascular disease	94.0 (93.1-94.8)	91.3 (90.3-92.2)	82.3 (81.1-83.4)	94.9 (94.2-95.6)	91.9 (91.1-92.7)
Glomerulonephritis	97.5 (97.1-97.9)	96.3 (95.8-96.7)	90.9 (90.2-91.5)	97.6 (97.2-97.9)	96.2 (95.7-96.6)
Other causes	96.7 (96.4-97.0)	95.0 (94.6-95.3)	89.2 (88.7-89.6)	96.8 (96.5-97.0)	95.0 (94.7-95.3)
All	96.3 (96.1-96.5)	94.4 (94.2-94.7)	87.8 (87.5-88.2)	96.3 (96.1-96.5)	94.3 (94.0-94.5)
Survival probabilities as % (95% confidence interval)					

Patient survival after first kidney transplant (living donor), unadjusted, EU Member States only					
	Cohort 2007-2011			**Cohort 2010-2014**	
	1 year	**2 year**	**5 year**	**1 year**	**2 year**
0-19 years	99.3 (97.9-99.8)	99.3 (97.9-99.8)	99.1 (97.5-99.6)	99.6 (98.3-99.9)	99.6 (98.3-99.9)
20-44 years	99.5 (99.3-99.7)	99.2 (98.9-99.5)	97.7 (97.2-98.1)	99.8 (99.6-99.9)	99.4 (99.2-99.6)
45-64 years	98.3 (97.8-98.6)	97.0 (96.5-97.5)	92.6 (91.8-93.4)	98.9 (98.5-99.1)	97.8 (97.4-98.2)
65+ years	96.1 (94.5-97.2)	93.0 (91.2-94.5)	81.1 (78.7-83.2)	96.9 (95.7-97.7)	94.1 (92.7-95.2)
Men	98.7 (98.3-98.9)	97.8 (97.4-98.2)	94.0 (93.4-94.5)	98.9 (98.7-99.1)	98.0 (97.7-98.3)
Women	98.7 (98.3-99.0)	97.6 (97.1-98.1)	94.4 (93.6-95.1)	99.2 (98.9-99.5)	98.3 (97.9-98.7)
Diabetes	96.9 (95.4-97.9)	94.7 (93.0-96.1)	85.0 (82.7-87.0)	97.5 (96.2-98.3)	95.7 (94.2-96.8)
Hypertension/renal vascular disease	97.4 (96.0-98.4)	96.2 (94.5-97.3)	89.8 (87.6-91.7)	98.3 (97.2-99.0)	96.8 (95.5-97.8)
Glomerulonephritis	99.2 (98.8-99.5)	98.7 (98.1-99.1)	96.6 (95.8-97.3)	99.2 (98.8-99.5)	98.5 (98.0-98.9)
Other causes	98.9 (98.6-99.2)	98.1 (97.7-98.4)	95.0 (94.4-95.6)	99.3 (99.1-99.5)	98.6 (98.2-98.8)
All	98.7 (98.4-98.9)	97.7 (97.4-98.0)	94.1 (93.6-94.6)	99.0 (98.8-99.2)	98.1 (97.9-98.4)
Survival probabilities as % (95% confidence interval)					

Graft survival after first kidney transplant (deceased donor), unadjusted, EU Member States only					
	Cohort 2007-2011			**Cohort 2010-2014**	
	1 year	**2 year**	**5 year**	**1 year**	**2 year**
0-19 years	92.7 (90.8-94.2)	90.3 (88.2-92.0)	83.8 (81.4-85.8)	92.8 (90.8-94.4)	90.3 (88.1-92.2)
20-44 years	93.9 (93.4-94.4)	92.0 (91.4-92.5)	85.3 (84.6-86.0)	94.2 (93.6-94.6)	92.3 (91.7-92.8)
45-64 years	91.5 (91.1-91.9)	88.6 (88.1-89.1)	79.8 (79.3-80.4)	91.7 (91.3-92.1)	89.0 (88.5-89.4)
65+ years	85.0 (84.2-85.8)	80.8 (79.9-81.7)	65.1 (64.3-66.0)	85.8 (85.1-86.5)	81.0 (80.3-81.7)
Men	90.8 (90.4-91.2)	87.8 (87.3-88.2)	78.1 (77.6-78.5)	90.8 (90.4-91.2)	87.5 (87.1-87.9)
Women	91.2 (90.7-91.7)	88.7 (88.1-89.2)	79.8 (79.1-80.4)	91.2 (90.8-91.7)	88.7 (88.2-89.2)
Diabetes	90.4 (89.6-91.2)	86.9 (86.0-87.7)	75.2 (74.2-76.2)	89.7 (88.9-90.4)	86.0 (85.1-86.7)
Hypertension/ renal vascular disease	88.1 (87.0-89.1)	84.9 (83.8-86.0)	71.9 (70.7-73.0)	88.6 (87.6-89.4)	84.6 (83.6-85.5)
Glomerulonephritis	91.7 (91.0-92.3)	89.0 (88.3-89.7)	80.5 (79.7-81.3)	91.7 (91.1-92.3)	88.9 (88.2-89.5)
Other causes	91.4 (91.0-91.8)	88.8 (88.3-89.3)	80.4 (79.9-81.0)	91.7 (91.3-92.0)	89.0 (88.6-89.4)
All	91.0 (90.7-91.3)	88.1 (87.8-88.5)	78.7 (78.3-79.1)	91.0 (90.7-91.2)	87.9 (87.6-88.2)
Survival probabilities as % (95% confidence interval)					

Graft survival after first kidney transplant (living donor), unadjusted, EU Member States only					
	Cohort 2007-2011			**Cohort 2010-2014**	
	1 year	**2 year**	**5 year**	**1 year**	**2 year**
0-19 years	96.5 (94.3-97.8)	95.5 (93.2-97.1)	90.8 (87.9-93.0)	96.8 (94.8-98.0)	95.7 (93.5-97.1)
20-44 years	96.4 (95.7-96.9)	94.7 (93.9-95.3)	89.1 (88.2-90.0)	97.4 (96.9-97.9)	96.0 (95.4-96.6)
45-64 years	95.7 (95.0-96.2)	93.8 (93.1-94.5)	87.5 (86.5-88.3)	96.6 (96.0-97.0)	94.8 (94.1-95.3)
65+ years	93.3 (91.4-94.8)	90.0 (87.9-91.8)	76.6 (74.2-78.8)	95.4 (94.1-96.4)	92.0 (90.4-93.3)
Men	95.8 (95.2-96.2)	94.3 (93.7-94.8)	87.7 (86.9-88.4)	96.8 (96.3-97.1)	95.1 (94.6-95.6)
Women	95.9 (95.2-96.5)	93.4 (92.5-94.1)	86.9 (85.9-87.9)	96.9 (96.3-97.3)	94.8 (94.1-95.4)
Diabetes	94.3 (92.5-95.7)	91.5 (89.5-93.2)	79.3 (76.9-81.5)	94.7 (93.2-96.0)	92.2 (90.4-93.7)
Hypertension/renal vascular disease	94.6 (92.8-96.0)	92.0 (90.0-93.7)	82.5 (80.1-84.7)	96.2 (94.8-97.3)	93.7 (92.0-95.1)
Glomerulonephritis	95.5 (94.6-96.3)	93.8 (92.8-94.7)	87.7 (86.4-88.8)	96.8 (96.0-97.4)	95.1 (94.3-95.9)
Other causes	96.3 (95.7-96.8)	94.6 (94.0-95.2)	89.2 (88.4-89.9)	97.1 (96.7-97.5)	95.5 (94.9-96.0)
All	95.8 (95.4-96.2)	93.9 (93.4-94.4)	87.4 (86.8-88.0)	96.8 (96.5-97.1)	95.0 (94.6-95.4)
Survival probabilities as % (95% confidence interval)					

Factors influencing the choice of treatment modalities by patients and doctors

III. Report on factors influencing the choice of treatment modalities by patients and doctors (D4.3)

Responsible partner: AMC
Document. Deliverable D4.3 18112020_DEF of 18.11.2020

III.1. Systematic review on non-medical barriers reported by nephrologists when providing the most appropriate form of RRT or CCM

The systematic review is published in a scientific paper:

de Jong RW, Stel VS, Heaf JG, Murphy M, Massy ZA, Jager KJ. Non-medical barriers reported by nephrologists when providing renal replacement therapy or comprehensive conservative management to end-stage kidney disease patients: a systematic review. Nephrol Dial Transplant. 2020 Jan 3. pii: gfz271. doi: 10.1093/ndt/gfz271. [Epub ahead of print]

Following chapter gives a summary of this scientific paper.

III.1.1 A systematic review on non-medical barriers reported by nephrologists when providing the most appropriate form of RRT or CCM

Large international differences exist in access to renal replacement therapy (RRT) modalities and comprehensive conservative management (CCM) for patients with end-stage kidney disease (ESKD), suggesting that some patients are not receiving the most appropriate treatment [Robinson, 2016]. Previous studies mainly focused on barriers reported by patients [Lockwood 2016; Navaneethan 2006; Sauvé 2016] or medical barriers (e.g. comorbidities) reported by nephrologists [Jager 2004; Jassal 2002; Mendelssohn 2001; Jung 2001]. This systematic review will add to the literature by providing an overview of the non-medical barriers reported by nephrologists when providing the most appropriate form of RRT (other than conventional in-center hemodialysis) or CCM.

Methods

We searched in EMBASE and PubMed for original articles with a cross-sectional design (surveys, interviews or focus groups) published between January 2010 and September 2018. We included studies in which nephrologists reported barriers when providing RRT or CCM to adult patients with ESKD. We used the barriers and facilitators survey by Peters et al. [Ruimte Voor Verandering? Knelpunten en Mogelijkheden Voor Verbeteringen in de Patiëntenzorg. Nijmegen: Afdeling Kwaliteit van zorg (WOK), 2003] as preliminary framework to create our own model and performed meta-ethnographic analysis of non-medical barriers in text, tables and figures. More details about the methods are described in the scientific paper.

Results

The tables of this deliverable are shown in the scientific paper attached to this deliverable (de Jong et al., NDT 2020, complete reference see above). Due to the large size of these tables, they were not published in this deliverable.

Of the 5973 articles screened, 16 articles were included using surveys (n = 10), interviews (n = 5) and focus groups (n = 1) (Figure 18, Table 14).

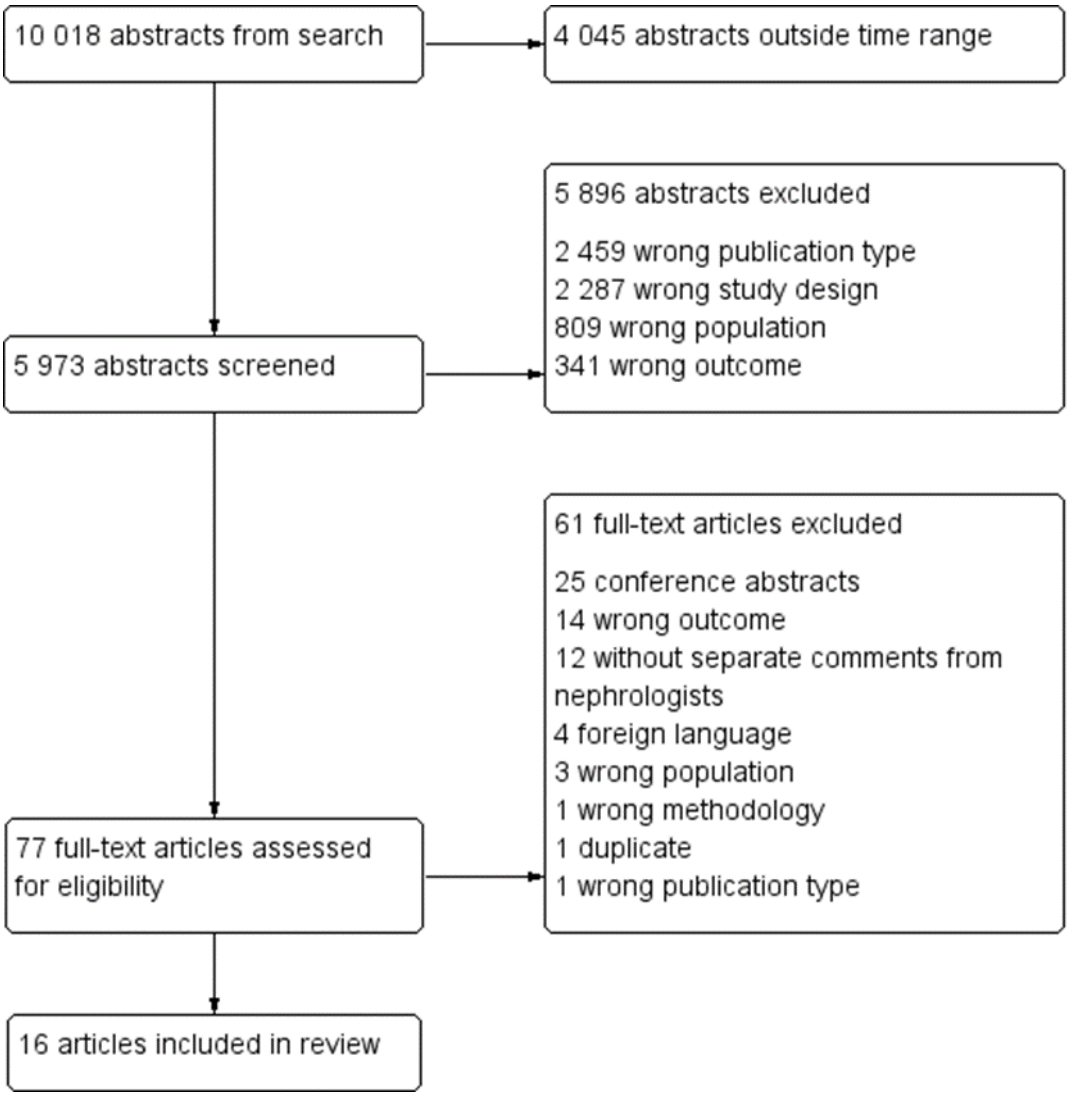

Figure 18: PRISMA flow diagram

Table 14: Characteristics of included articles

First author	Country	Methodology	Modalities discussed	N of adult nephrologists
Qualitative studies				
Combes	UK	Interview	HHD, PD	29
Ghahramani	USA	Focus group	kidney transplantation	16
Grubbs	UK, USA	Interview	CCM	59
Hanson	Australia, New Zealand	Interview	living kidney donor transplantation	41
Ladin	USA	Interview	CCM	35
Tong	Italy, Portugal, France, Germany, Sweden, Argentina	Interview	HHD	28
Quantitative studies				
Allen	International	Survey	NCHD	259
Dahlan	Saudi Arabia	Survey	PD	124
Desmet	Belgium	Survey	PD	97
Jayanti	International	Survey	HHD	272
Ludlow	Australia	Survey	HHD, PD	44

First author	Country	Methodology	Modalities discussed	N of adult nephrologists
Parvez	USA	Survey	CCM	265
Savla	Bangladesh	Survey	PD	43
Thumfart	Germany	Survey	NCHD	286
Walker (2014)	New Zealand	Survey	PD	30
Walker (2017)	New Zealand	Survey	HHD PD	49
Abbreviations used; HHD: home hemodialysis, PD: peritoneal dialysis, CCM: comprehensive conservative management, NCHD: non-conventional hemodialysis				

Barriers for CCM and different RRT modalities

We categorized the barriers into three levels: patient level (e.g. attitude, role perception, motivation, knowledge and socio-cultural background), level of the healthcare professional (e.g. fears and concerns, working style, communication skills) and level of the healthcare system (e.g. financial barriers, supportive staff and practice organization).

An overview of all non-medical barriers as experienced by nephrologists is presented in Table 2 (see scientific paper) separated for non-conventional hemodialysis (NCHD), home hemodialysis (HHD), peritoneal dialysis (PD), kidney transplantation and CCM. Barriers for HHD, PD and CCM were described both in quantitative and qualitative studies, barriers for NCHD were only described in quantitative studies and barriers for kidney transplantation were only described in qualitative studies.

Table 3 (see scientific paper) contains all themes, description and illustrative quotations (indicated by Q1 until Q26 in the text below).

Barriers on the patient level

Patient's attitude, role perception and motivation could limit the care provision by attachment to professionals and concurrent lack of motivation to take responsibility for one's own treatment (Q1). This attitude could result from a lack of knowledge and limited health literacy or from concerns about particular aspects of the treatment (for example surgery, immunosuppressive medication, alarms of the dialysis machine) (Q2).

Characteristics of the sociocultural background (e.g. distrust, religious or language barriers) often challenged nephrologists when informing patients about different treatment options for ESKD (Q3-4). The provision of home dialysis modalities was limited by unsuitable living circumstances and distant locality (Q5-6). Patients often had to invest time and financial resources to apply for home dialysis or kidney transplantation. They did not always have caregivers or social support to pursue home dialysis or kidney transplantation (Q7). Finally, nephrologists reported patient adherence and poor hygiene as barriers for home dialysis and kidney transplantation (Q8).

Barriers on the level of the healthcare professional

Nephrologists recognized that their own attitude, role perception and motivation influenced the uptake of NCHD, PD, kidney transplantation and CCM (Q9-10). Nephrologists also reported lack of knowledge and fears and concerns in particular about home dialysis and CCM (Q11-12). Selection of patients for CCM was hampered by nephrologist's uncertainty about eligibility. In addition, nephrologists reported lack of skills and confidence to communicate with patients about RRT and CCM. Lastly, nephrologists were sometimes frustrated by a lack of uniformity in working style (e.g. following guidelines and dealing with risks (Q13-14)).

Barriers on the level of the healthcare system

Financial barriers were reported for all RRT modalities and CCM. Additional costs for water and electricity, home adaptation and assistance with home dialysis were often not reimbursed (Q16) and some nephrologists suggested that private doctors may not promote pre-emptive kidney transplantation as they would lose income when a patient was not treated with dialysis first (Q15). Lack of skilled staff (nephrologists, nurses, surgeons, transplant coordinators) was reported as a barrier for all dialysis modalities and kidney transplantation. Several nephrologists reported competition between treatment modalities as conventional hemodialysis was widely available and different forms of non-conventional dialysis had to share financial measure and patient interest (Q17-18). In addition, nephrologists experienced various external pressures: other nephrologists and other specialists were not in favor of certain treatments, there was pressure from the patient's family and several transplant nephrologists mentioned the need to protect their centers reputation (Q23-24).

Three aspects of the organization of healthcare - organizational culture (1), facilities (2) and practice organization (3) - also limited the provision of RRT modalities. Strict division between dialysis and transplantation centers prevented efficient communication, knowledge transfer and involvement in each other's specialization (Q19). Lack of space, supplies and training facilities limited the uptake of non-conventional dialysis forms (Q20). Problems with the coordination of care and cooperation with other healthcare professionals limited the provision of kidney transplantation and CCM (Q21-22).

Moreover, a perceived lack of scientific evidence, and lack of prognostic tools limited the uptake of NCHD, HHD, PD and CCM (Q25). Finally, insufficient pre-dialysis education, caused by complexity of information, limited time and lack of staff, were reported as a barrier for home dialysis and kidney transplantation (Q26).

Impact

Within this systematic review, we found a large number of non-medical barriers experienced by nephrologists for the provision of different RRT modalities (other than conventional in-center hemodialysis) and CCM to patients with ESKD. Modalities could have similar barriers, and a successful approach of a barrier for one modality may also work if the barrier is experienced for another modality. The nature and importance of these barriers may vary by country, which needs to be investigated in further research. This overview of non-medical barriers may support the development of interventions to target modifiable barriers. Guided by nephrologists' experiences, interventions could focus on improving education and optimizing the financing structure of healthcare systems. Education could increase knowledge, which may influence attitude and motivation and could reduce fears and concerns of both patients and nephrologists. Financial stimuli could increase the uptake of home dialysis, CCM or transplantation, by, for instance, reimbursing home modification, employing extra nursing staff and financial compensation for living donors. These kinds of interventions may improve the access to RRT and CCM so that more patients receive the treatment that is most appropriate for them..

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III.2. Results of the EDITH Nephrologist survey and the EDITH kidney patient survey on factors influencing treatment modality choice for end-stage kidney disease

The optimal treatment for patients with end-stage kidney disease (ESKD) differs from individual to individual. Although kidney transplantation offers superior quality of life and survival compared to dialysis for patients with ESKD [Tonelli 2011; Wolfe 1999, Cameron 2000], a substantial number of patients with ESKD are medically unsuitable to receive a kidney transplant. For those patients a form of dialysis (in-center hemodialysis [ICHD], out-center hemodialysis [OCHD], home hemodialysis [HHD] or peritoneal dialysis [PD]) may be the optimal treatment. Additionally, comprehensive conservative management (CCM) may be an appropriate treatment for elderly patients with severe comorbidities [Verberne 2016]. Unfortunately, not all patients with ESKD in Europe have access to the optimal treatment, which may influence patient survival and quality of life [ERA-EDTA Registry annual report 2019; Bello 2019].

To improve access to the optimal treatment for patients with ESKD in Europe, information on factors influencing modality choice (e.g. barriers, information provision and decision-making) experienced by both nephrologists and patients with ESKD is needed.

So far, several studies have examined the opinion of nephrologists [Jung 1999; Mendelssohn 2001; Bouvier 2009; Desmet 2013; Fluck 2014] as well as the opinion of patients [van Biesen 2014; CEAPIR 2006; Urquhart-Secord 2016, Dahlerus 2016; Fadem 2011, Morton 2010] about these factors. However, most of these studies have been conducted in high-income countries. Information of these factors from Eastern European countries is scarce, whereas their kidney healthcare systems may be different from those in Western Europe [Bello 2019; Spasovski 2019].

The first aim of this part of the EDITH deliverable is to report the results of the EDITH Nephrologist survey about information provision to patients, decision-making and external pressure, nephrologists' attitudes towards and satisfaction with uptake of different treatments and barriers when providing treatments as experienced by nephrologists and kidney transplant surgeons treating adult patients with ESKD.

The second aim of this part of the EDITH deliverable is to report on the results the EDITH kidney patient survey in which we surveyed adult patients who were on dialysis or were living with a

functioning kidney transplant in Europe about information provision, decision-making, reasons for (not) having a modality and experience with their treatment.

We compared the answers from respondents (both professionals and kidney patients) from European countries with low, middle and high Gross Domestic Product Purchasing Power Parity (GDP PPP).

III.2.1 EDITH nephrologist survey

Methods

Development of the survey

We designed the EDITH nephrologist survey in English using Lime survey [Limesurvey], based on results from a previously performed systematic review on barriers for nephrologists to provide RRT or CCM [de Jong 2020] and on input from nephrologists. Respondents received questions that were adapted based on prior answers. They were able to review and change their answers but resuming was not possible. Six nephrologists from different countries tested the survey and we modified the survey based on their feedback.

Participants and data collection

The survey was promoted and distributed by national societies of nephrology, the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA) and the European Society of Organ Transplantation (ESOT). All European nephrologists and kidney transplant surgeons (including those in training) who treated adult patients with ESKD were eligible to participate. The EDITH nephrologist survey was publicly accessible from March 14, 2019 until May 19, 2019.

Ethical aspects

The Medical Ethics Review Committee of the Academic Medical Center in Amsterdam, the Netherlands, waived the need for ethical approval (W18_279#18.323). In addition, representatives or national societies were consulted about the need for additional ethical approval in their country. All individual respondents provided online written informed consent.

Data analysis

Results from participants from countries for which additional ethical approval was not needed, or from countries where additional approval was received before the start of the survey, were included in the final analysis. In addition, respondents needed complete answers on mandatory questions. Analyses were performed for all respondents together and per tertile of GDP PPP (further indicated as GDP). For the GDP tertiles, we used 2016 data from the World Bank [World Bank]. We used Fisher's exact tests and Kruskall Wallis tests to compare categorical and continuous outcomes between the GDP tertiles. A p-value below 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 25.0 [IBM Corporation, 2017] and SAS software [SAS Institute].

Results

General and professional characteristics

We included 681 respondents (54.9% male) from 33 countries in Europe (Figure 19). Of these, 31.0% were under 40 years, 52.6% were between 41-60 years of age and 16.4% were 61 years or older. Most respondents were practicing nephrologists (86.5%). Of all respondents, 56.8% practiced in an academic clinic, 91.9% practiced in an urban area and 78.2% practiced in a public center (Table 15). ICHD was available in 95.4% of the centers whereas HHD was the least-available treatment (36.6%).

Respondents from low-GDP countries were more often women, were younger and were more often working in private clinics (Table 15, $p<0.05$). In centers in low-GDP countries, other treatments than ICHD were less often available compared to centers in middle- or high-GDP countries ($p<0.01$).

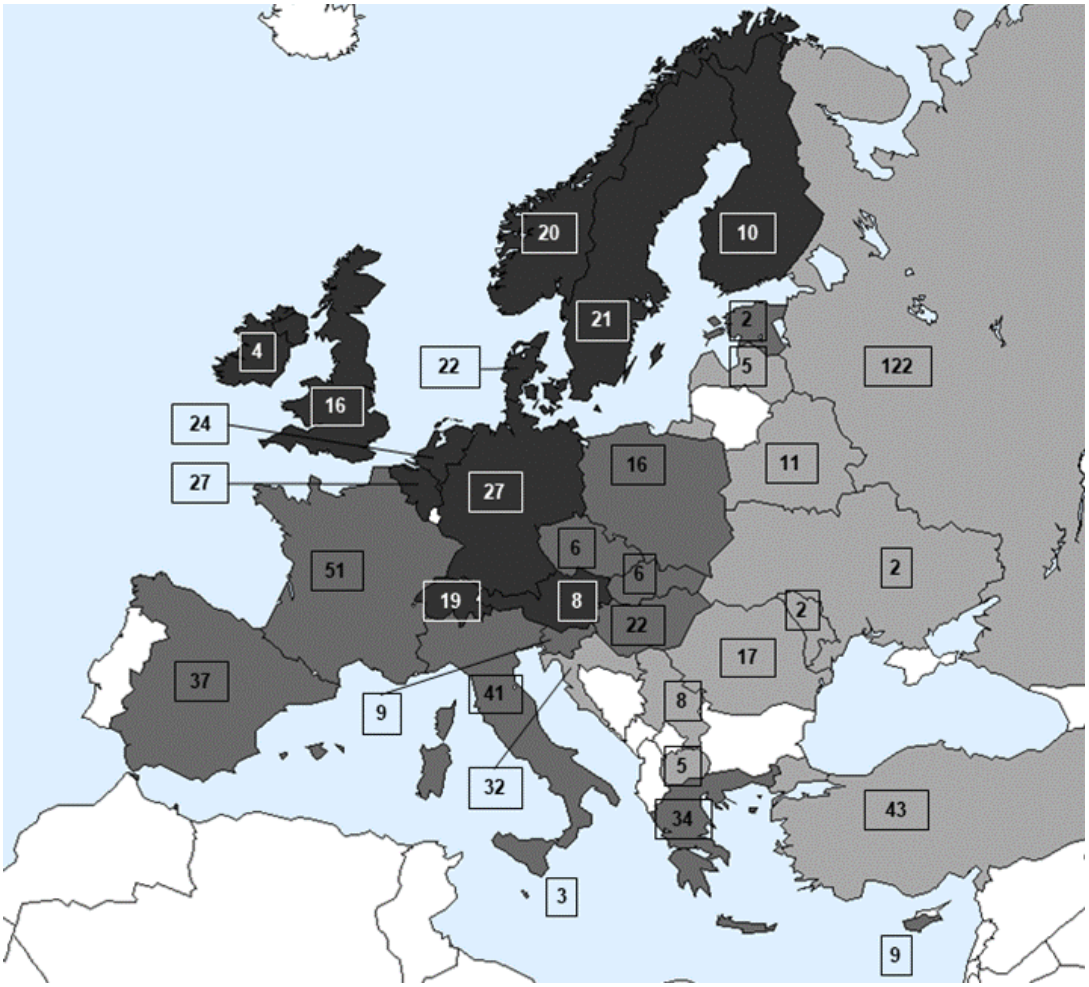

Figure 19: Country of origin of respondents

Light grey countries (GDP < 26618 US$): Belarus, Croatia, Latvia, Moldova, North Macedonia, Romania, Russia, Serbia, Turkey, Ukraine

Middle grey countries (GDP 26618 - 42357 US$): Cyprus, Czech Republic, Estonia, France, Greece, Hungary, Italy, Malta, Poland, Slovak Republic, Slovenia, Spain

Dark grey countries (GDP > 42357 US$): Austria, Belgium, Denmark, Finland, Germany, Ireland, Netherlands, Norway, Sweden, Switzerland, United Kingdom

White countries (no ethical approval obtained or no decisive answer): Albania, Bulgaria, Iceland, Kosovo*, Latvia, Montenegro, Portugal. No responses: Bosnia and Herzegovina. N is number of respondents per country.

* This designation is without prejudice to positions on status, and is in line with UNSCR 1244/99 and the ICJ Opinion on the Kosovo declaration of independence.

Table 15: General and professional characteristics of respondents

	All respondents N=681	GDP lowest tertile[1] N=247	GDP middle tertile[1] N=252	GDP highest tertile[1] N=182	P- value*
Sex, % male	54.9	48.2	57.6	60.1	0.024
Age in categories, %					<0.001
< 40 years	31.0	41.3	29.2	20.2	
41-60 years	52.6	48.2	52.5	58.1	
>= 61 years	16.4	10.5	18.2	21.7	
Professional background, %					0.078
Nephrologist	86.5	86.6	89.4	82.8	
nephrologist in training	4.4	2.4	3.4	8.1	
internal medicine specialist	5.4	7.3	3.8	5.1	
kidney transplant surgeon	3.7	3.6	3.4	4.0	
Working in academic clinic, %	56.8	53.3	53.0	65.7	0.010
Working in urban clinic, %	91.9	92.7	95.3	86.9	0.006
Working in public clinic, %	78.2	71.3	76.5	88.8	<0.001
Clinic size, %					<0.001
< 50 patients	6.3	10.0	5.5	2.8	
50-100 patients	18.3	26.5	17.4	9.4	
101-200 patients	22.9	24.7	24.2	19.3	
> 200 patients	52.5	38.8	53.0	68.5	
Treatment available in clinic, %					
ICHD	95.4	92.3	95.3	99.5	<0.001
OCHD	45.5	23.6	43.4	74.7	0.001
HHD	36.6	10.4	31.5	74.7	<0.001
PD	79.6	62.8	83.1	96.0	<0.001
LTX	53.8	32.0	57.6	75.8	<0.001
DTX	56.7	36.5	61.4	75.8	<0.001
CCM	75.6	61.3	77.1	91.4	<0.001

*P-value calculated with Fisher's Exact test to compare GDP tertiles.
Abbreviation used; GDP: gross domestic product
1 For the categorization of countries per GDP category, see Figure 19

Information provision to patients

72.1% of the respondents reported to provide information on all available modalities and not only on those suitable for a specific patient (Table 16). Our respondents provided information about ICHD (97.4%), PD (86.9%), living kidney donor transplantation (LTX) and deceased kidney donor transplantation (DTX) (82.8% respectively 85.7%) but less often about CCM (65.5%), OCHD (47.3%) or HHD (40.4%). According to respondents, patients commonly received information from the nephrologist (98.3%), nurse (72.1%) and from brochures or booklets (63.6%). 31.2% of the patients received information more than one year before start of RRT and 10.3% of the patients received no information before start of RRT.

Table 16: Information provision, decision-making and external pressure

	All respondents N=681	GDP lowest tertile[1] N=247	GDP middle tertile[1] N=252	GDP highest tertile[1] N=182	P- value*
Information provision about all treatments available in the centre, %	72.1	81.7	71.2	62.3	<0.001
Patients receive information about,					
ICHD	97.4	96.5	97.6	98.3	0.544
OCHD	47.3	23.3	48.6	73.3	<0.001
HHD	40.4	14.4	37.5	73.9	<0.001
PD	86.9	73.8	89.9	98.3	<0.001
LTX	82.8	69.3	83.2	97.7	<0.001
DTX	85.7	72.8	88.0	97.7	<0.001
CCM	65.5	51.0	67.8	79.5	<0.001
Source of information, %					
Nephrologist	98.3	99.5	97.6	97.7	0.249
Kidney transplant surgeon	19.0	19.3	16.4	21.6	0.422
Other doctor (e.g. general practitioner, other medical specialist)	19.7	29.7	17.4	10.8	<0.001
Nurse	72.1	46.0	79.2	93.8	<0.001
Other kidney patients	48.5	52.0	44.9	48.9	0.363
Brochure/booklet	63.6	56.4	53.1	84.1	<0.001
Website/internet	45.1	49.0	36.7	50.6	0.009
Timing of information provision, mean % per category	31.2	23.1	34.8	37.0	<0.001
More than 12 months before start of RRT	28.4	23.5	30.7	31.7	<0.001
4-12 months before start of RRT	17.7	21.2	15.9	15.3	<0.001
1-3 months before start of RRT	12.5	18.0	10.0	8.4	<0.001
Less than 1 month before start of RRT	10.3	14.2	8.6	7.6	0.106
No information before of start of RRT					
Style of modality decision making, %					<0.001
Patient alone	7.8	8.1	9.4	5.7	
Patient with input from doctor	32.5	25.8	40.9	30.5	
Together	48.5	47.0	42.4	57.5	
Doctor with input from patient	9.4	14.6	6.9	6.3	
Doctor alone	0.0	0.0	0.0	0.0	
Decision left to doctor	1.7	4.5	0.5	0.0	
Experiencing external pressure, %	36.9	40.7	34.5	35.5	0.435
Source of pressure, %					
Family of the patient	88.1	85.1	91.3	88.1	0.524
Opinion of colleagues	45.0	55.4	42.0	35.6	0.060
Opinion of supervisor	19.3	29.7	18.8	6.8	0.003
Opinion of other medical specialists	42.6	47.3	47.8	30.5	0.084
Hospital management	21.8	32.4	15.9	15.3	0.024
Insurers	10.9	16.2	8.7	6.8	0.178

*P-value calculated with Fisher's Exact test and Kruskall Wallis test to compare GDP tertiles on categorical and continuous outcomes.
Abbreviations used; GDP: gross domestic product; RRT: renal replacement therapy
1 For the categorization of countries per GDP category, see Figure 19

Respondents from low- and middle-GDP countries more often provided information only about all available modalities in their center than respondents from high GDP countries (respectively 81.7%, 70.3%, 62.7%, p<0.01, Table 2). In general, respondents from low-GDP countries less often provided information about OCHD, HHD, PD, LTX, DTX and CCM than respondents from middle- or high-GDP

countries (p<0.01). Next to nephrologists, nurses more often provided information in middle- and high-GDP countries, while other doctors more frequently provided information in low-GDP countries p<0.01). In low-GDP countries, patients tended to receive information closer to the start of RRT (p<0.01), but the percentage of patients starting RRT without having received any information did not differ between the GDP categories (low 14.2%, middle 8.6%, high 7.6%, p>0.05).

Decision making

According to the respondents, in 48.5% of the cases the decision on modality choice was shared between doctor and patient, whereas in 32.5% the patient decided with input from the doctor and in 9.4% the doctor decided with input from the patient. 7.8% of the patients made the decision alone and 1.7% left the decision to their doctor (Table 16). None of the respondents reported to make decisions without influence from the patient. Respondents from low-GDP countries tended to report more influence of the doctor in decision-making (p<0.01).

External pressure

36.9% of all respondents experienced external pressure when providing RRT or CCM (Table 16). The sources of that external pressure included family of the patient (88.1%), colleagues (45.0%), other medical specialists (42.6%), hospital management (21.8%), supervisors (19.3%) and insurers (10.9%). The prevalence of external pressure was similar across the GDP categories (p=0.435), but respondents from low-GDP countries experienced more pressure from supervisors and hospital management (p<0.05).

Attitude towards different RRT modalities and CCM

Figure 20 shows the attitude of respondents towards the different treatment modalities, overall and per GDP category. 97.8% of the respondents were positive or very positive about DTX and 94.3% about LTX. With respect to dialysis modalities, respondents were positive or very positive about PD (89.8%) followed by ICHD (79.6%), HHD (69.6%) and OCHD (64.1%). 68.3% of the respondents were positive or very positive about CCM. Few respondents reported a negative or very negative attitude towards treatment modalities.

Respondents from low-GDP countries tended to be more positive about ICHD and less positive about OCHD, HHD, LTX and CCM than those from middle- and high-GDP countries (p<0.01). Attitudes towards PD and DTX did not differ between the GDP categories (p>0.05).

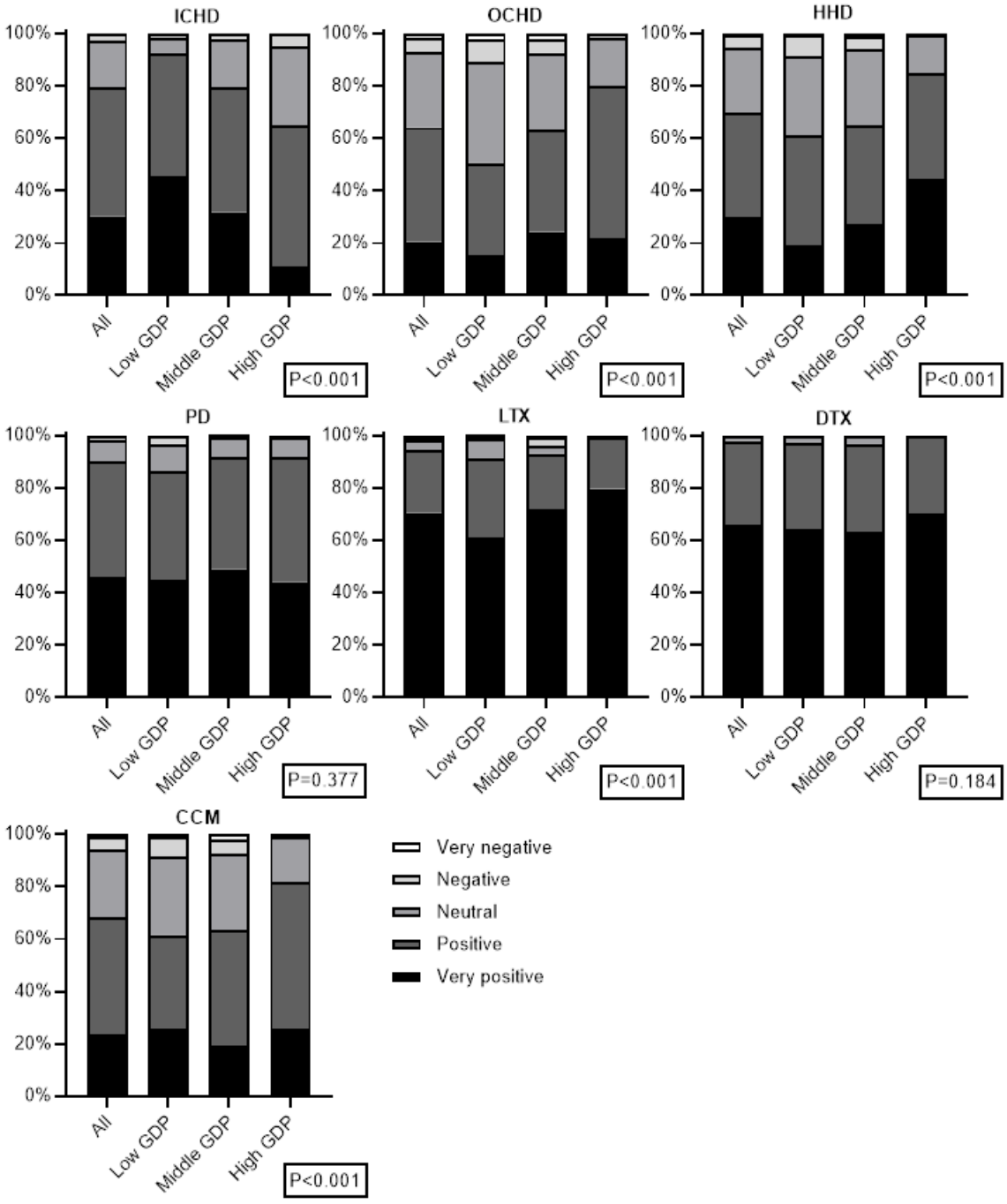

Figure 20: Attitude towards different RRT modalities and CCM

P-value calculated with Fisher's Exact test to compare GDP tertiles.
Abbreviations used; RRT: renal replacement therapy, GDP: gross domestic product; ICHD: in-center hemodialysis, OCHD: out-center hemodialysis, HHD: home hemodialysis, PD: peritoneal dialysis, LTX: living kidney donor transplantation, DTX: deceased kidney donor transplantation, CCM: comprehensive conservative management
For the categorization of countries per GDP category, see Figure 19

Uptake of different RRT modalities and CCM

A majority of respondents thought that the uptake of HHD (78.8%), LTX (70.7%), DTX (67.0%), PD (62.2%) and CCM (58.0%) should be increased. 47.1% of the respondents wanted to increase uptake of OCHD. A majority (72.9%) thought that the current uptake of ICHD was sufficient and more than a

quarter were satisfied with the current uptake of LTX and DTX (Figure 21). Respondents from middle- and high-GDP countries were more likely to report sufficient uptake of ICHD and OCHD. The proportion of respondents eager to increase uptake of HHD, PD and CCM decreased somewhat with increasing GDP.

Barriers to provide unavailable treatments

We studied the occurrence of barriers when a treatment was not available in the center of the respondent. Barriers for ICHD are not reported because of only 22 responses to these questions. If HHD or PD were unavailable, the most reported barriers for provision were lack of supportive staff (71.9% and 57.9% respectively) and practical aspects (79.9% and 67.0% respectively). If kidney transplantation was unavailable, lack of donors was the most reported barrier for both LTX (64.1%) and DTX (56.4%), whereas lack of supportive staff was the most reported barrier for CCM (59.2%). Knowledge or attitude of the nephrologist was the least reported barrier for HHD (27.7%), PD (21.3%), LTX (12.4%) and DTX (10.7%) (Figure 22).

Respondents from low-GDP countries reported more financial barriers for HHD and both forms of TX ($p<0.05$). They were also more limited by the nephrologists' knowledge or attitude about LTX ($p<0.05$) and by a lack of donors and legal barriers for TX ($p<0.01$). In addition, they more often reported a financial incentive to offer dialysis as barrier to CCM ($p<0.01$).

Barriers to provide available treatments

We studied the frequency of barriers when a treatment was available in the center. When HHD or PD were available, the most frequently experienced barriers to offer these treatments for our respondents were on the patient level (knowledge or attitude of the patient, medical or psychological comorbidity and living circumstances) (Figure 23). The most frequently experienced barrier to offer TX for our respondents was the lack of donors, but also patients' medical or psychological comorbidity and patients' knowledge or attitude made it more difficult to offer them a transplant. Costs for patients or insufficient hospital reimbursement were the least frequently experienced barriers when HHD, PD or kidney transplantation were available. When offering CCM, patients' knowledge or attitude was the most frequently experienced barrier, followed by nephrologists' knowledge or attitude and lack of skilled staff whereas a financial incentive to offer dialysis was least frequently reported.

Generally, the frequency of barriers was highest in low-GDP countries. However, medical or psychological comorbidities for HHD, PD and LTX were experienced with similar frequency in low-, middle- and high-GDP countries ($p>0.05$)..

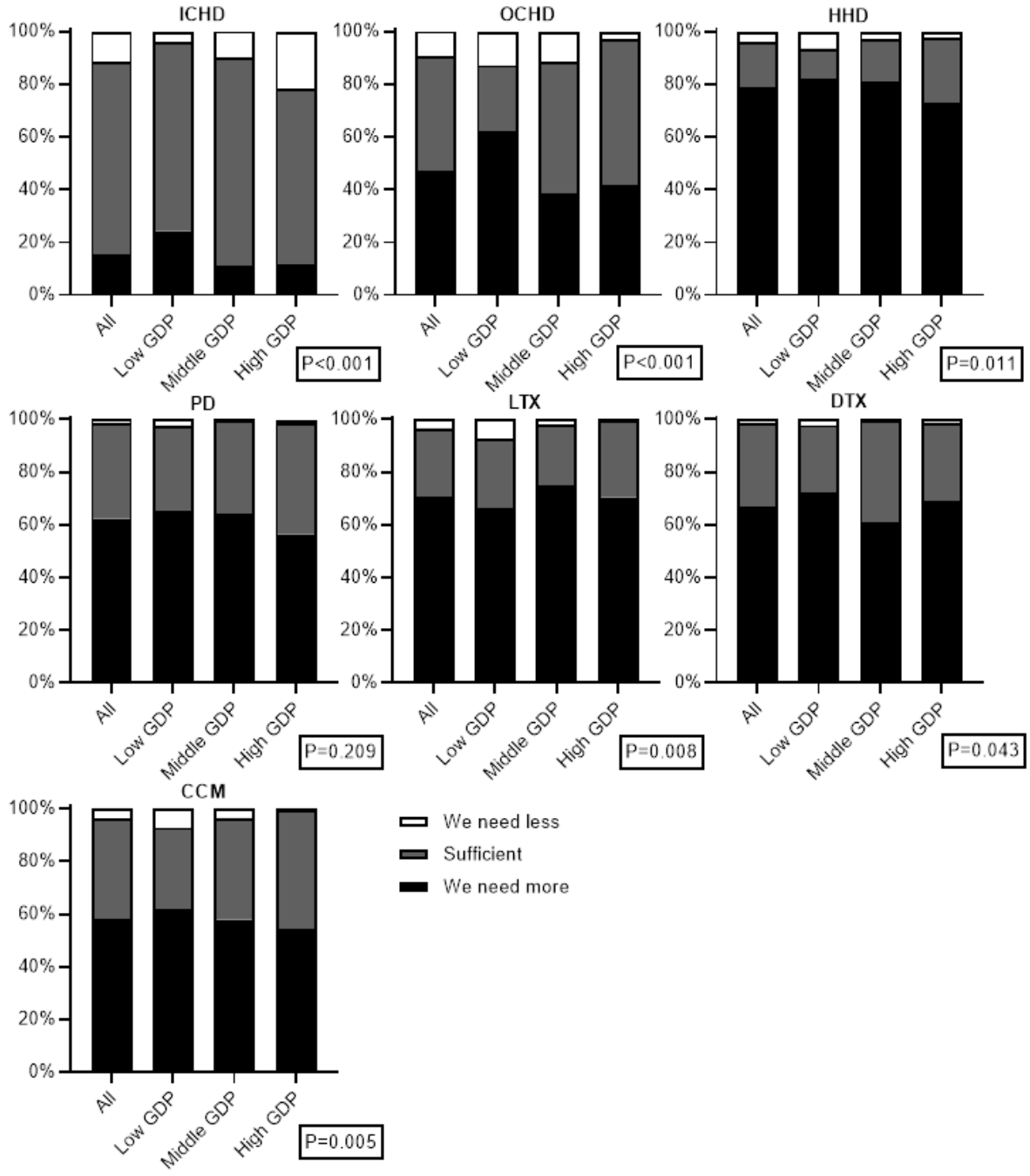

Figure 21: Uptake of different RRT modalities and CCM

P-value calculated with Fisher's Exact test to compare GDP tertiles.
Abbreviations used; RRT: renal replacement therapy, GDP: gross domestic product; ICHD: in-center hemodialysis, OCHD: out-center hemodialysis, HHD: home hemodialysis, PD: peritoneal dialysis, LTX: living kidney donor transplantation, DTX: deceased kidney donor transplantation, CCM: comprehensive conservative management
For the categorisation of countries per GDP category, see Figure 19

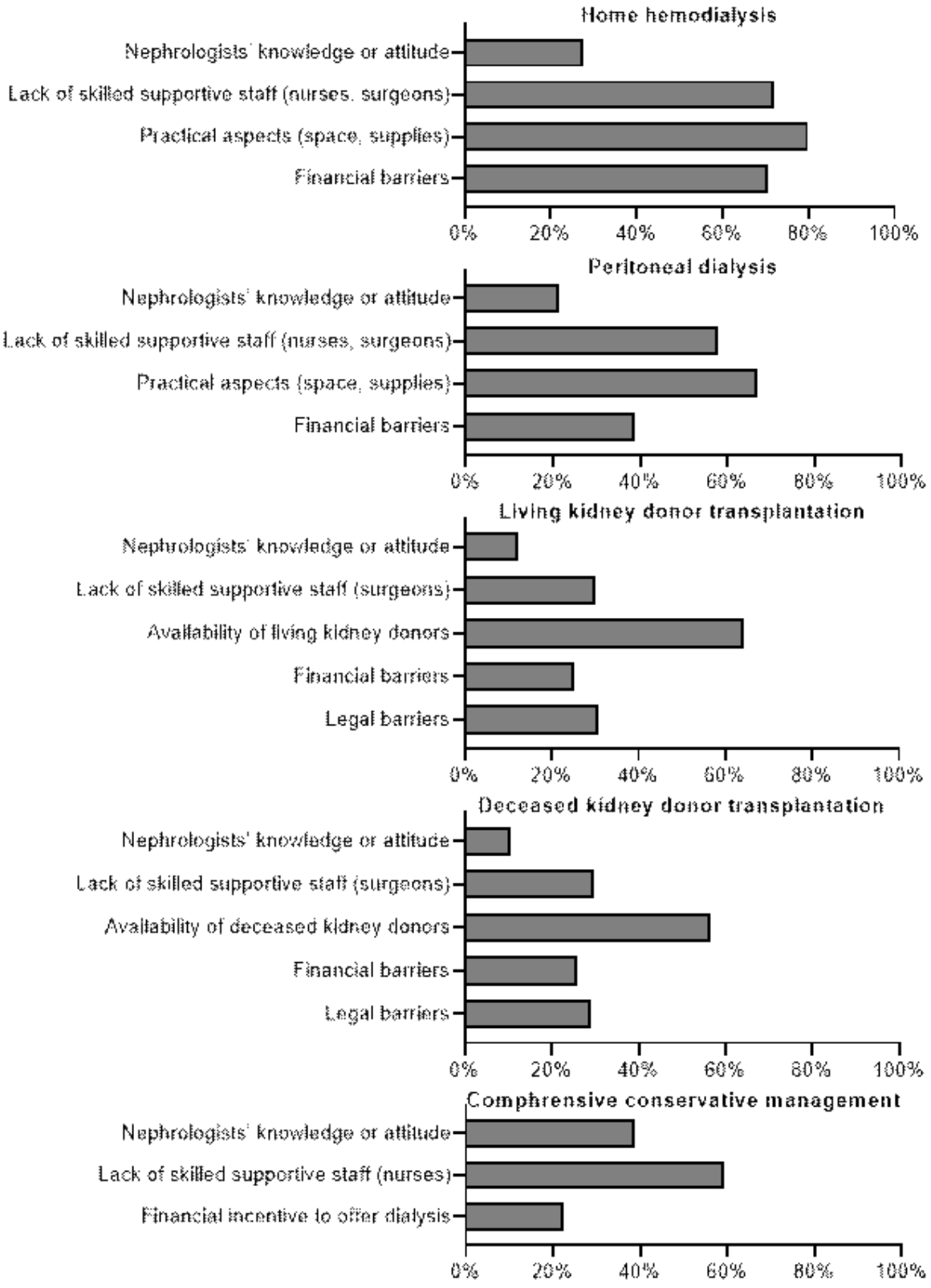

Figure 22: Barriers to provide unavailable treatments – all respondents

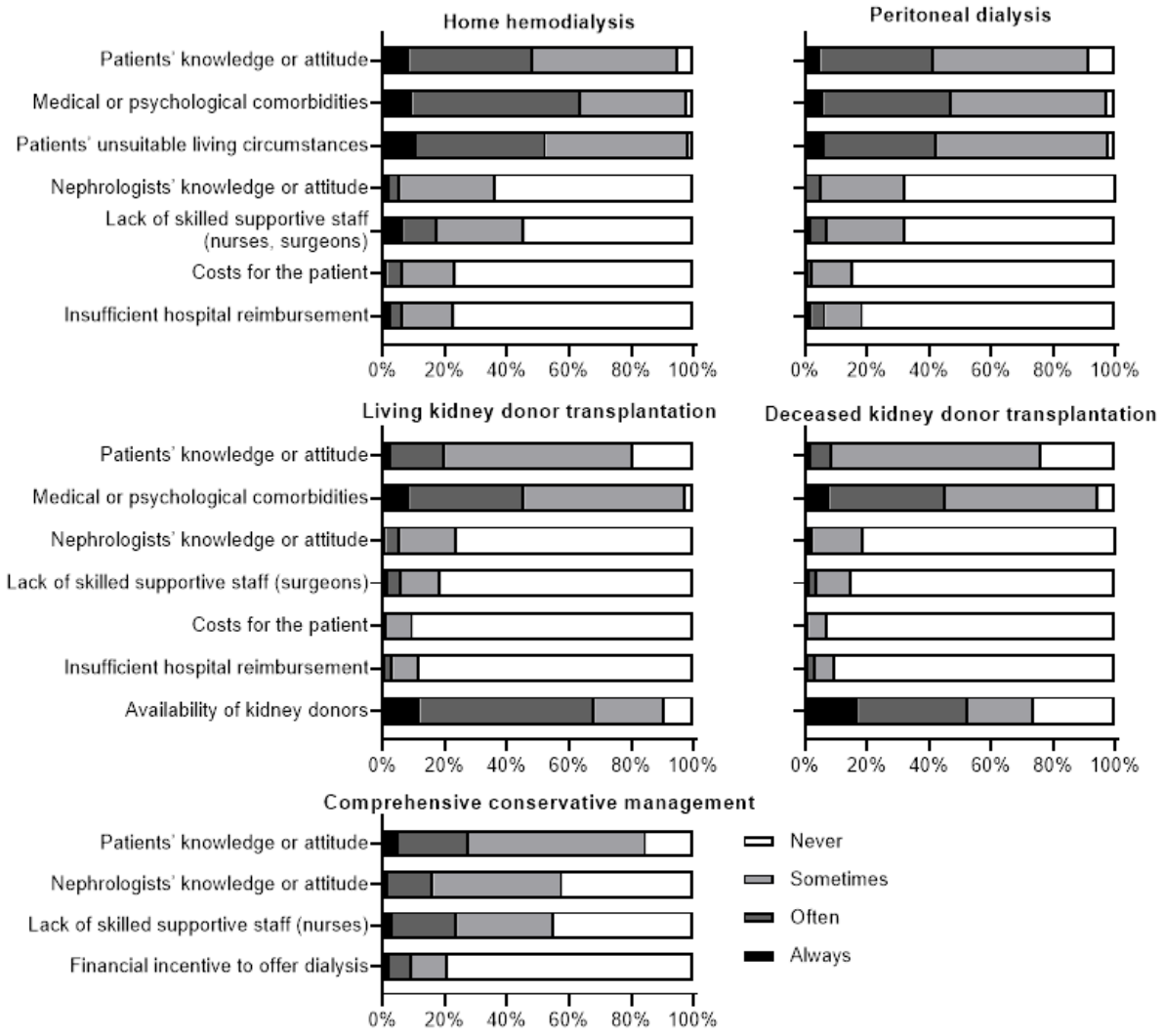

Figure 23: Barriers to provide available treatments – all respondents

III.2.2 EDITH kidney patient survey

Methods

Development of the survey

We designed the EDITH kidney patient survey using literature and input from patients treated with dialysis or with a kidney transplant. We first developed an English online survey in Lime Survey [Lime survey]. Five dialysis patients and two kidney transplant recipients (from Belgium, the Netherlands and Spain) and two nephrologists provided feedback on draft versions of this online English version and we modified the survey accordingly.

Thereafter, the English survey was voluntarily translated into 31 local and national languages by two native speakers with a medical background (e.g. medical doctor, nurse or medical student). One person translated the survey and the other provided feedback. Translators were asked to translate as literally as possible, but were encouraged to use language specific and patient friendly terms to clarify questions to patients. At the request of several countries, we have made paper versions of the survey.

Participants and data collection

The survey was distributed and promoted by local and national kidney patients' associations, the European Kidney Patients' Federation (EKPF), the European Renal Association – European Dialysis

and Transplantation Association (ERA-EDTA), national societies of nephrology and individual nephrologists known to the authors. All European adult patients with ESKD treated by any form of dialysis or kidney transplantation were eligible to participate in this survey. The survey was publicly accessible from November 2017 to January 2019.

Ethical aspects

The Medical Ethics Review Committee of the Academic Medical Center in Amsterdam, the Netherlands, reviewed the protocol and draft version of the survey and waived the need for ethical approval (W17_291#17.343). Several nephrologists obtained local approval from their ethics committee. Ethical approval was not obtained in the United Kingdom due to time constraints, therefore responses from British respondents were removed. Participation in this survey was voluntary.

Data analysis

Data from paper versions of the survey were entered manually into Lime Survey and were subject to the same value limits (e.g. start date between 1950 and 2018) and logic (e.g. if the patient received peritoneal dialysis, questions about this treatment needed to be answered) as responses from online surveys. Duplicate responses were detected using a statistics program and were removed. In the final analysis, we included participants from which we knew the country origin, who reported to receive at least one form of RRT and started RRT above the age of 18 years.

Analyses were performed for all respondents together and per tertile of GDP PPP (further indicated as GDP). For the GDP tertiles, we used 2016 data from the World Bank [World Bank]. We used Chi square test and Kruskall Wallis tests to compare categorical and continuous outcomes between the GDP tertiles. A p-value below 0.05 was considered statistically significant. Statistical analysis were performed using IBM SPSS Statistics 25.0 [IBM corporation 2019] and SAS software [SAS Institute]..

Results

Of the 12014 received responses, 7820 responses from 38 European countries were included in the final analysis (Figure 24, Table 17).

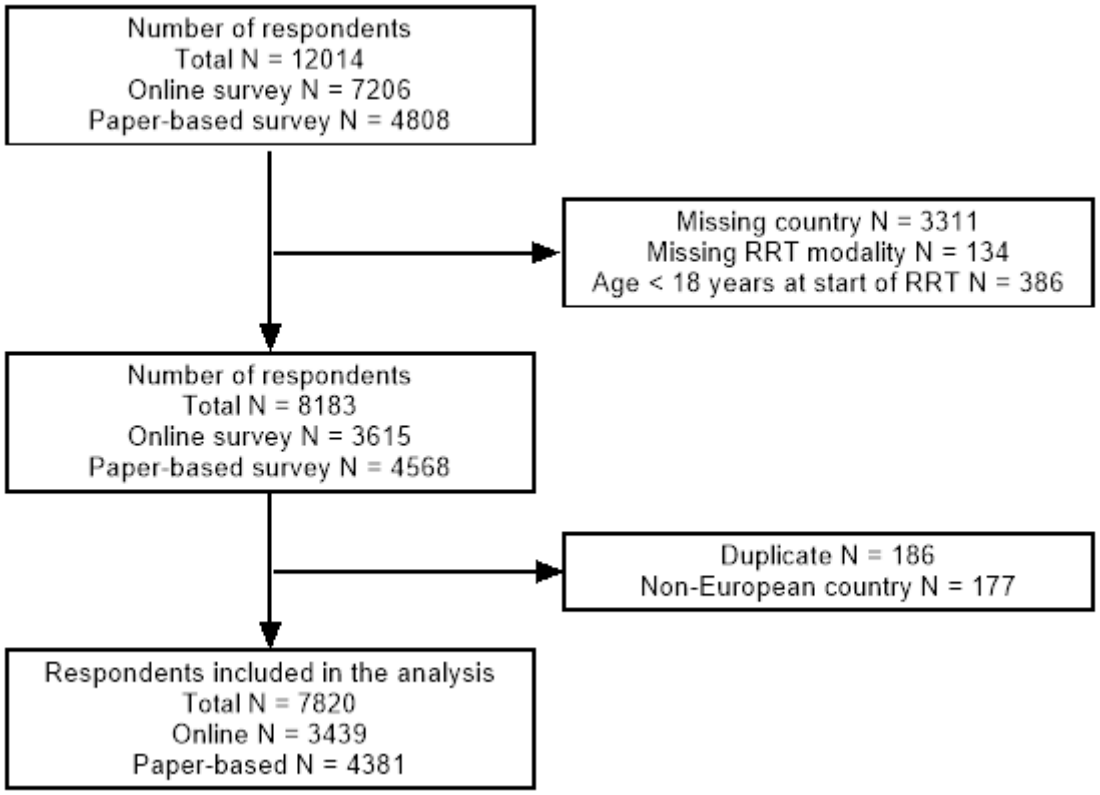

Figure 24: Flowchart

Table 17: Number of respondents per country

First tertile < 26618 US$	**N of respondents**	**Second tertile 26618 - 42357 US$**	**N of respondents**	**Third tertile > 42357 US$**	**N of respondents**
Albania	12	Cyprus	37	Austria	295
Belarus	41	Czech Republic	2	Belgium	142
Bosnia and Herzegovina	329	Estonia	7	Denmark	577
Bulgaria	10	France	434	Finland	284
Croatia	887	Greece	344	Germany	70
Latvia	130	Hungary	287	Iceland	22
Moldova	95	Italy	338	Ireland	159
North Macedonia	183	Lithuania	65	Luxembourg	88
Romania	96	Malta*		Netherlands	227
Russia	1495	Poland	120	Norway	38
Serbia	38	Portugal	137	Sweden	404
Turkey	69	Slovak Republic	1	Switzerland	55
Ukraine	14	Slovenia	82	United Kingdom*	
		Spain	206		

Abbreviation used; GDP PPP: Gross Domestic Product Purchasing Power Parity
All countries participating either the EDITH nephrologist survey or the EDITH kidney patients survey were clustered. Countries marked with an asterisk (*) did not participate in the EDITH kidney patient survey

Characteristics of the respondents

The mean age of the 7820 respondents (55.7% male) was 59.2 years (standard deviation [SD] 14.0 years) (Table 18). The majority of respondents (60.7%) were married and higher educated (vocational or higher education; 59.2%) and 36.5% of respondents below 65 years were employed and working.

Two thirds of the respondents were currently on center haemodialysis (CHD), 2.2% on home haemodialysis (HHD), 6.0% on peritoneal dialysis (PD) and 29.3% lived with a functioning kidney transplant (Table 18).CHD (77.6%) and PD (16.1%) were the most common first treatments and 5.3% of the respondents received a pre-emptive kidney transplantation. The mean duration of RRT was 8.9 years (SD 8.2 years). 22.0% of the current dialysis patients were on the waiting list for a kidney transplantation. The most reported reason for not being on the waiting list were medical reasons (32.0%). Of all respondents, 27.8% and 5.9% reported to have diabetes mellitus and malignancy, respectively.

Of the participating respondents, 43.5% lived in a low GDP country, 26.3% in a middle GDP country and 30.2% in a high GDP country (Table 18). The mean age of the respondents was 58.7 years in low GDP countries, 58.0 years in middle GDP countries and 60.9 years in high GDP countries ($p<0.001$). The percentage of males, higher educated respondents and respondents who were employed and working (for those ≤65 years) were higher in high GDP countries compared to middle and low GDP countries ($p<0.05$) (Table 18).

A larger proportion of respondents were treated with CHD in low GDP countries (82.9%) compared to middle (55.3%) and high (39.5%) GDP countries. In contrast, the percentage of respondents treated with PD and living with a functioning kidney transplant was higher in middle and high GDP countries ($p<0.001$). HHD was more often practiced by respondents in high GDP countries (5.9% in high GDP countries versus <1% in middle and low GDP countries).

Information provision

23.4% of the respondents reported to have received information more than 12 months before start of RRT (Figure 25). On the other hand, 25.2% of the respondents answered that they did not receive any information about the treatment modalities before the start of RRT. Respondents were not always informed about all treatment modalities (i.e. all forms of RRT and comprehensive conservative management (CCM)); this was most common for HHD (42.1%) and CCM (33.0%) (Figure 26). Respondents who were on home dialysis or received a kidney transplant as first treatment received the information earlier (data not shown). The most common sources of information were the nephrologist (92.1%), nurse (38.1%) and brochures/booklets (26.7%) (Figure 27). Most respondents reported that they were (very) satisfied with the information provided about all modalities, but the satisfaction was highest for the information about CHD and deceased kidney donor transplantation (DTx) whereas this was lowest for HHD (Figure 28).

In general, information provision was earlier (i.e. longer before the start of RRT) in high GDP than in low and middle GDP countries ($p<0.001$) (Figure 25). In low GDP countries, a higher percentage of respondents reported to receive no information about HHD, PD and kidney transplantation ($p<0.001$) (Figure 26). Respondents from low, middle and high GDP countries got their information most often from the nephrologist. However, in high GDP countries, respondents got their information more often from nurses and brochures/booklets compared to middle and high GDP countries ($p<0.001$) (Figure 27). Satisfaction with the information provision was slightly higher in middle and high GDP countries ($p<0.001$) (Figure 28).

Table 18: Characteristics of respondents per GDP tertile

	All respondents N=7820	**Lowest tertile[1] N=3399**	**Middle tertile[1] N=2060**	**Highest tertile[1] N=2361**	**P-value***
Male sex, **%**	55.7	53.8	56.7	57.7	0.009
Mean age (SD), years	59.2 (14.0)	58.7 (14.3)	58.0 (13.6)	60.9 (13.8)	<0.001
Marital status, % married	60.7	62.1	58.2	60.8	0.018
Educational level, % higher educated	59.2	52.7	57.2	70.0	<0.001
Employed and working, % of patients ≤ 65 years	36.5	24.3	41.5	46.6	<0.001
Current treatment, %					<0.001
CHD	62.5	82.9	55.3	39.5	
HHD	2.2	0.5	0.9	5.9	
PD	6.0	2.2	7.9	9.8	
LTx	8.7	4.6	6.5	16.4	
DTx	20.6	9.8	29.5	28.3	
First treatment, %					<0.001
CHD	77.6	90.5	75.0	61.7	
HHD	1.0	0.3	1.2	1.7	
PD	16.1	6.7	18.5	27.5	
LTx	3.4	1.6	2.6	6.5	
DTx	1.9	0.9	2.7	2.7	
Mean duration of RRT (SD), years	8.9 (8.2)	7.4 (6.4)	10.1 (9.2)	9.9 (9.2)	<0.001
On transplant waitlist, %					<0.001
Yes					
No	22.0	13.7	34.9	27.4	
I do not know	72.7	81.1	60.0	66.5	
	5.4	5.2	5.1	6.0	
Reason not on transplant waitlist, %					<0.001
Medical reasons	32.0	30.0	35.3	34.7	
Will receive kidney from living donor	2.9	2.2	4.0	3.9	
Will be on the waiting list later on	17.6	13.5	23.0	24.1	
Don't want a kidney transplant	21.4	21.6	19.5	22.5	
Cannot afford a kidney transplant	4.9	6.8	4.0	0.5	
My hospital does not offer kidney Transplantation	5.9	7.3	2.4	5.4	
Reason unknown	15.2	18.7	11.7	8.8	
Self-reported comorbidity, %					
Diabetes mellitus	27.8	32.7	23.2	25.7	<0.001
Polycystic kidney disease	26.8	29.7	26.9	23.2	<0.001
Glomerulonephritis	25.0	37.9	21.1	11.8	<0.001
Malignancy	5.9	4.8	6.7	6.5	0.033

*P-value calculated with Chi square test and Kruskall Wallis test to compare GDP tertiles on categorical and continuous outcomes

Abbreviations used; GDP: Gross Domestic Product, SD: standard deviation, IQR: interquartile range, ESKD: end-stage kidney disease, RRT: renal replacement therapy

[1] For the categorization of countries per GDP category, see Table 15

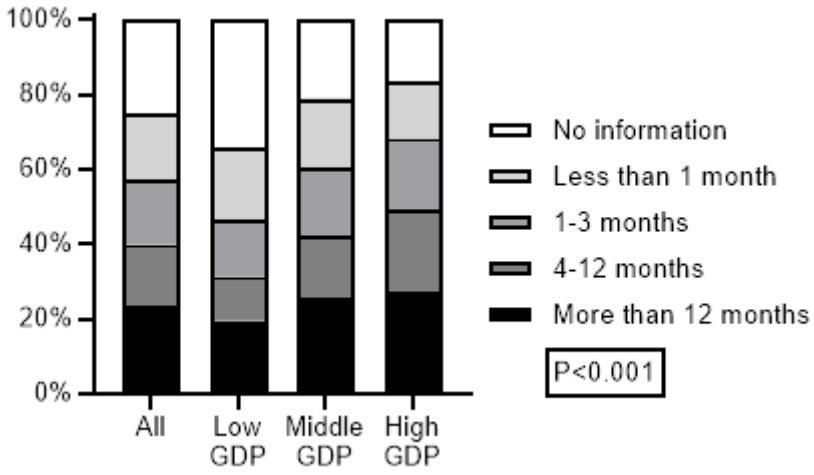

Figure 25: Timing of information before start of renal replacement therapy

P-value calculated with Chi square test to compare GDP tertiles

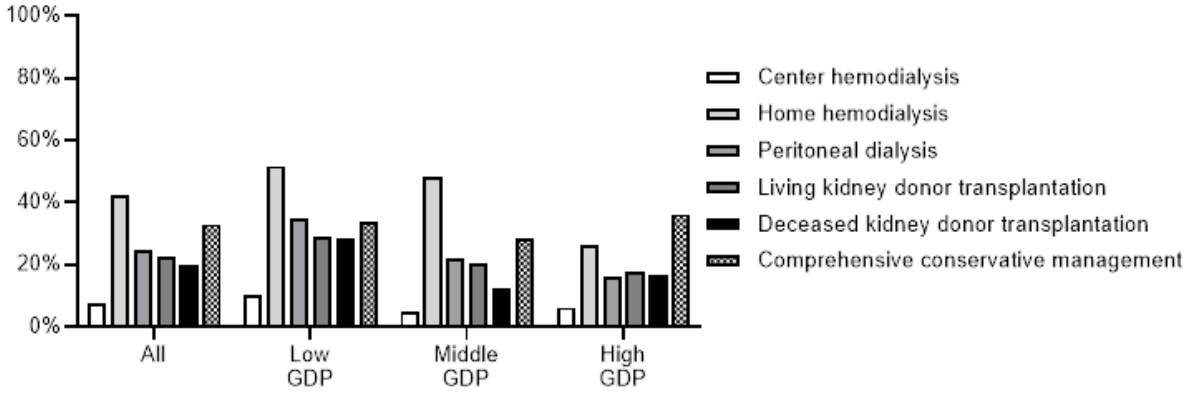

Figure 26: No information received

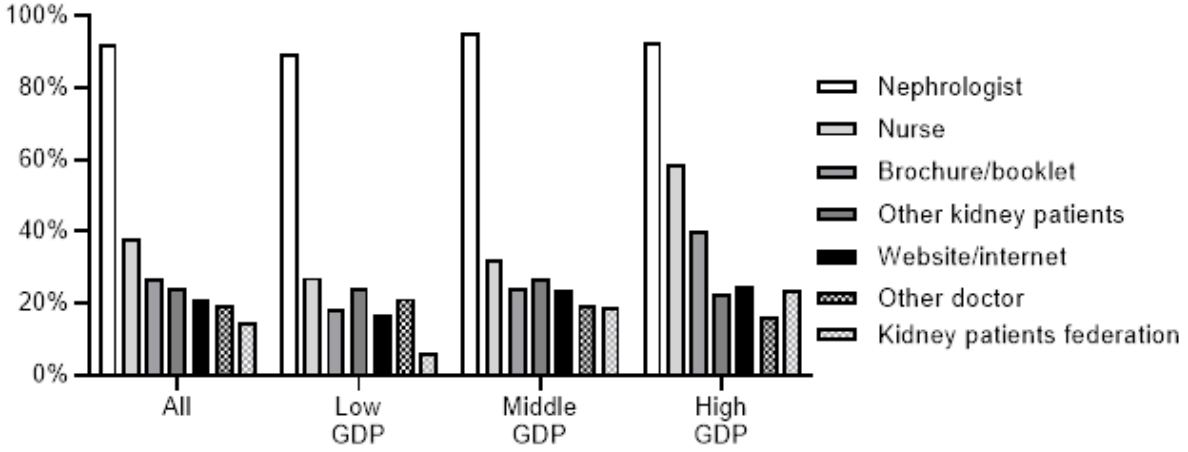

Figure 27: Sources of information

Abbreviation used; GDP: gross domestic product.
For the categorization of countries per GDP category, see Table 15

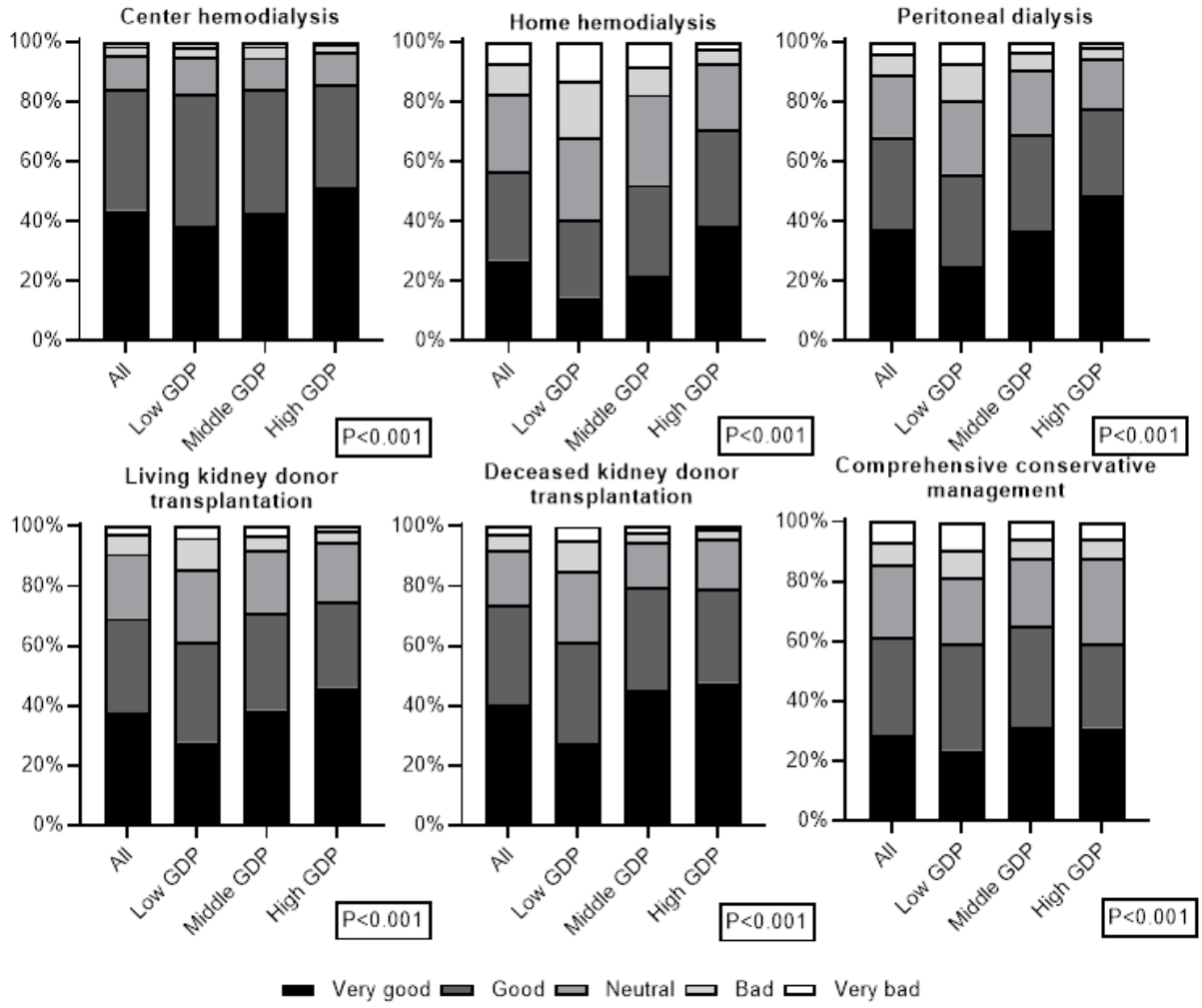

Figure 28: Satisfaction with information provision about treatments

P-value calculated with Chi square test to compare GDP tertiles. Abbreviation used; GDP: gross domestic product
For the categorization of countries per GDP category, see Table 15

Decision making

Figure 29 and 30 show the results about style of decision-making and satisfaction with decision-making for the different treatment modalities. In these analyses, we included respondents who had only 1 treatment modality for ESKD (CHD; home dialysis including both HHD and PD; or kidney transplantation) so far in their lives. For each treatment, the decision was most often made together by the patient and the doctor (CHD 29.7%, home dialysis 35.8%, Tx 43.6%). A smaller group reported that they left the decision to their doctor (CHD 17.9%, home dialysis 6.0%, Tx 5.7%) or the doctor decided alone (CHD 9.1%, home dialysis 1.5%, Tx 0.9%). Satisfaction with decision-making was (very) good among all respondents, regardless their treatment, but transplant recipients tended to be most satisfied (CHD; 81.2% reported 'good' or 'very good'; home dialysis 87.2%; Tx; 91.1%) (Figure 29). Almost all respondents (99.7%) indicated that other people influenced the decision about the choice of the treatment (Figure 31) such as their doctor (81.3%), partner (39.9%), other family members (30.2%) or their nurse (17.2%).

With regard to the style of decision-making, similar trends were seen across the GDP tertiles (data not shown). In high GDP countries, a higher percentage of respondents reported that their choice

was influenced by their partner (low GDP 29.5%, middle GDP 39.3%, high GDP 55.2%) and their nurse (low GDP 7.0%, middle GDP 14.7%, high GDP 33.9%) ($p<0.001$).

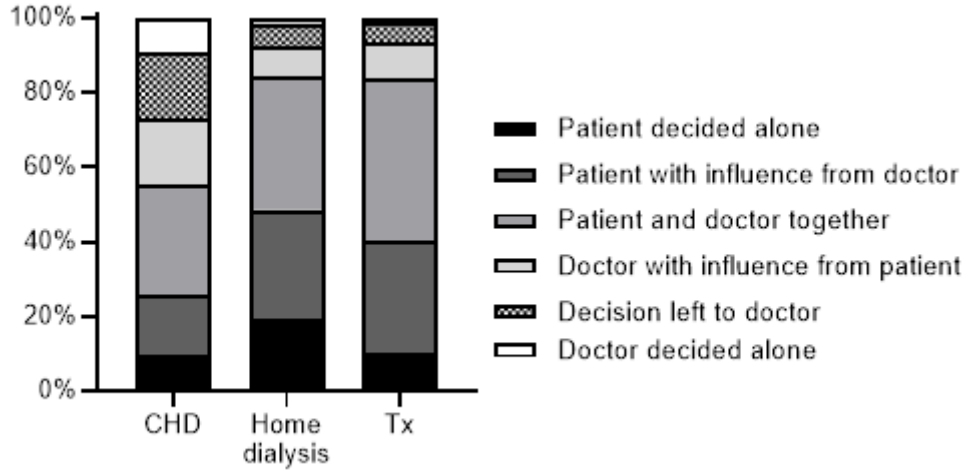

Figure 29: Style of decision-making for respondents undergoing only one treatment

'Home' includes respondents on home hemodialysis and peritoneal dialysis

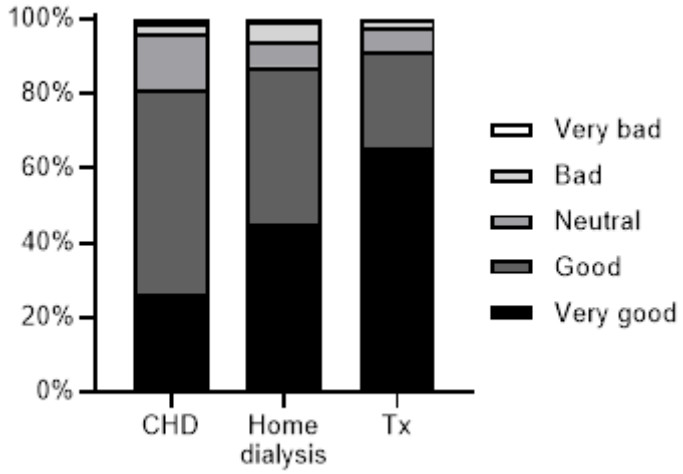

Figure 30: Satisfaction with decision-making for respondents undergoing only one treatment

'Home' includes respondents on home hemodialysis and peritoneal dialysis.
Abbreviations used; CHD: center hemodialysis, Tx: kidney transplantation

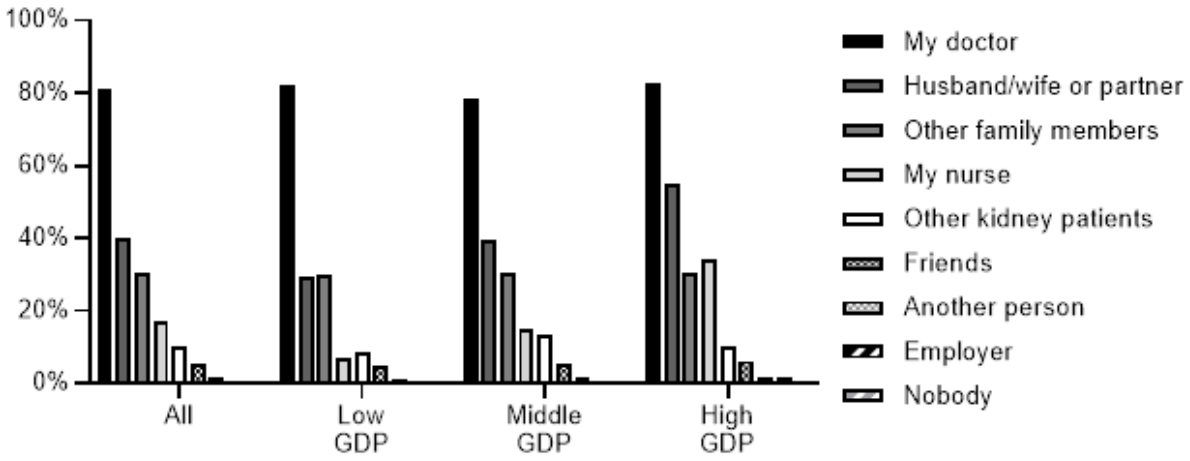

Figure 31: Persons influencing decision-making

Abbreviation used; GDP: gross domestic product.
For the categorization of countries per GDP category, see Table 15

Importance of factors when choosing an RRT modality

According to the respondents, the three most important factors playing a role in making a treatment modality choice were quality of life (97.3% reported 'important' or 'very important'), survival (96.6%) and safety (92.1%%) (Figure 32). The three least important factors were company of other patients (41.8% reported 'important' or 'very important), costs (41.9%) and body appearance (50.7%). The top three most important factors were similar across the GDP tertiles. The factors social life and work/study were more often reported by respondents from high GDP countries whereas the factor costs was more often mentioned by respondents living in low GDP countries (results not shown).

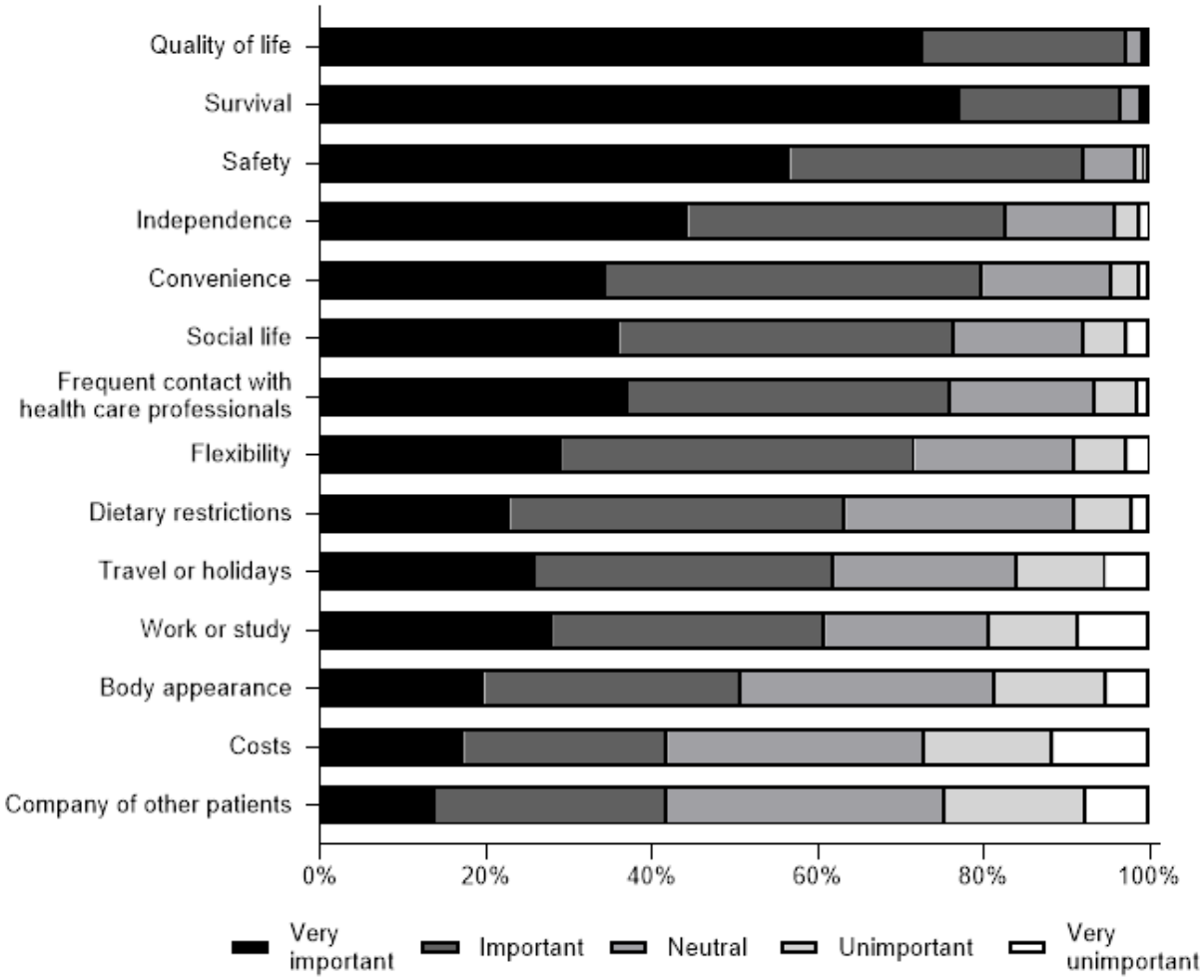

Figure 32: Importance of factors when choosing a RRT modality

Abbreviation used; RRT: renal replacement therapy

Treatment specific reasons

In addition to the more general factors as described above, respondents were asked about the five main reasons why they did or did not receive a particular form of RRT (Figure 33).

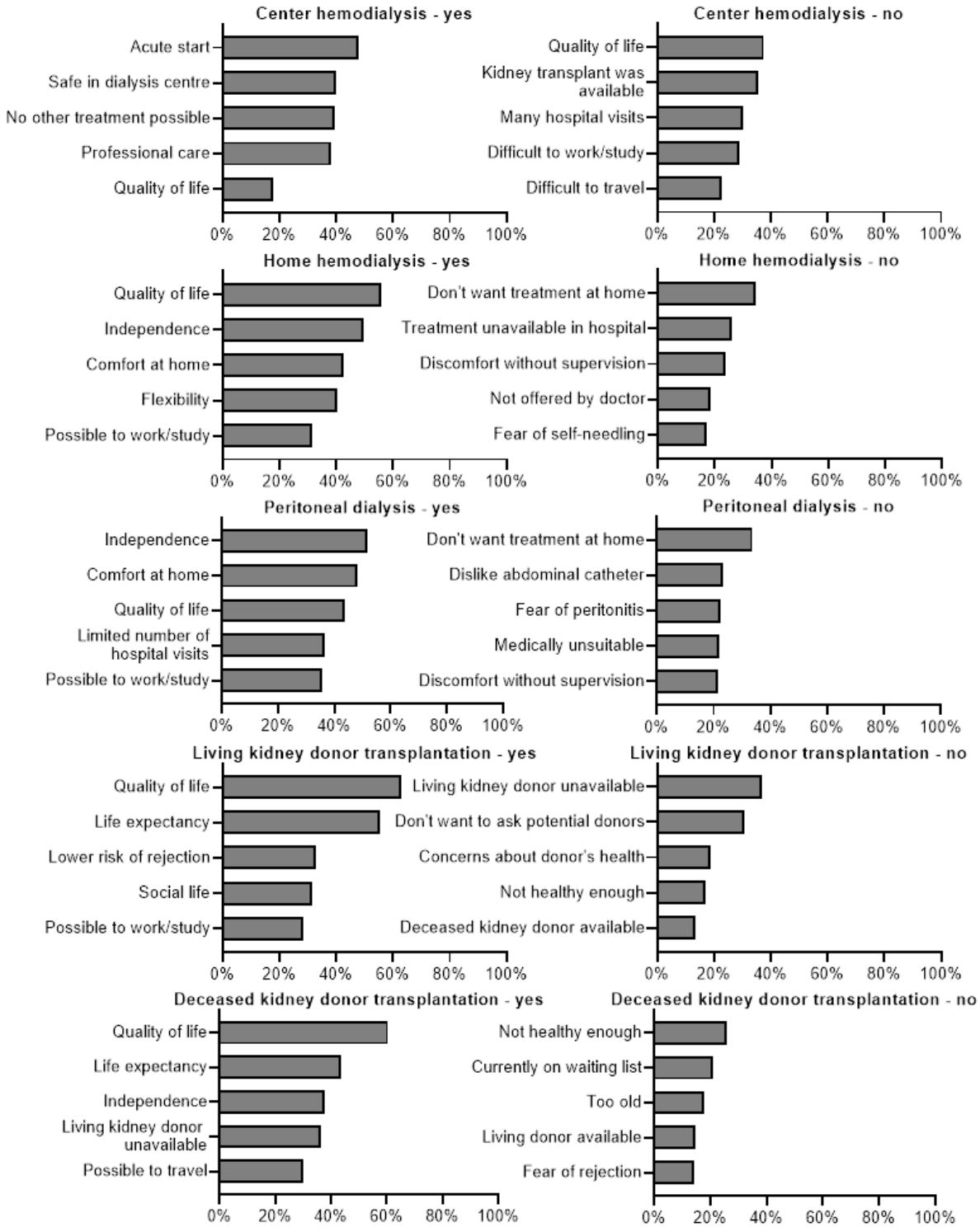

Figure 33: 5 treatment specific reasons to receive (+) or not receive (-) the treatment

Experience with treatments

Most respondents indicated to have a 'good' or 'very good' experience with the treatment they were on (LTX (92.8%), DTX (91.1%), HHD (89.9%), CHD (85.4%) and PD (81.4%)) (Figure 34). Respondents from middle and high GDP countries tended to have a better experience with their treatment modality than those from low GDP countries especially for HHD (low GDP; 73.9% reported 'good' or 'very good', middle GDP; 85.3%, high GDP; 92.6%).

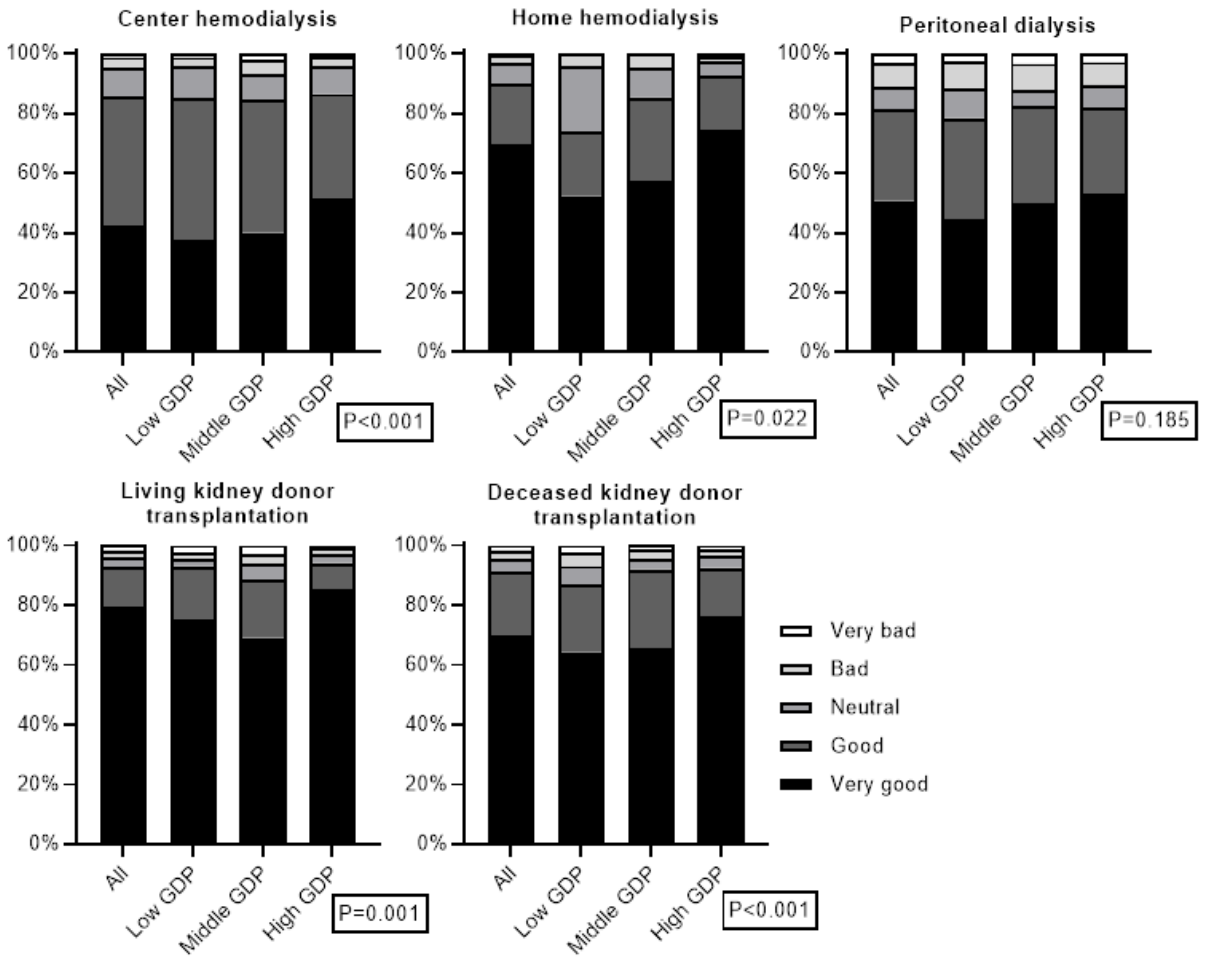

Figure 34: Experiences with a treatment

P-value calculated with Chi square test to compare GDP tertiles
Abbreviation used; GDP: gross domestic product
For the categorization of countries per GDP category, see Table 15

Impact

The results of the EDITH Nephrologist survey among European nephrologists and few kidney transplant surgeons and EDITH kidney patient survey among European adult dialysis and kidney transplant patients show that many factors influencing treatment modality choice for adults with ESKD differed between low, middle and high GDP countries. One should keep in mind that the results may not be generalizable to the opinion of all adult patients on RRT and nephrologists in Europe.

In general, patients on RRT were satisfied with the information provision (on different forms of dialysis, kidney transplantation and CCM) and decision-making. However, patients from low GDP countries reported to receive the information later and to receive less information about home dialysis and kidney transplantation than patients from middle and high GDP countries. Also according to professionals, information provision and decision-making could be optimized in certain countries bearing in mind that patients in different countries might have different needs and wishes. Limited availability of certain treatment modalities or CCM may hamper optimal information provision and decision-making, which can create a vicious circle: due to limited availability of treatment modalities, nephrologists may not discuss the treatment with patients, which may lead to the perception that patients are not interested and thus keeps availability low.

In general, patients reported to have a good experience with the treatment modalities. Insight in the importance of treatment specific reasons for patients (e.g. those related to attitude and fears) may help nephrologists to empower patients (extra discussion, demonstration of home dialysis) when choosing a modality. Several reasons for not having a modality were, according to the patients, related to the availability supporting the hypothesis of limited access to some treatments.

European nephrologists and kidney transplant surgeons usually have a positive attitude to and want higher uptake of most treatments, which are currently less accessible for patients. Nevertheless, we should not presume that all nephrologists want increased uptake, as for example a quarter of our respondents were satisfied with the uptake of kidney transplantation. Nephrologists were notably limited by healthcare system related barriers (practical, financial, legal), particularly if a treatment was unavailable in their center. According to nephrologists, patient related barriers (knowledge, housing, comorbidity) were most frequently experienced when a treatment was already available. Several barriers reported by nephrologists or patients (e.g. knowledge, attitude) could be targeted by policy measures.

The results of the EDITH Nephrologist survey and EDITH kidney patient survey suggest that factors influencing modality choice, including barriers, when providing RRT and CCM to patients with ESKD differ across the GDP categories. Therefore, a single European policy may not be effective. Besides variation in GDP, European countries show variation in other aspects (for example healthcare organization and legislation) which may influence uptake of RRT and CCM as well. Therefore, we suggest that measures to improve access to treatment modalities for patients with ESKD should be tailored to clusters of countries with similar aspects where some countries can learn from each other and exchange best practices..

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III.3. Annex:

Annex 1: Acknowledgements

EDITH Nephrologist survey

The authors wish to thank all nephrologists and kidney transplant surgeons who filled out the EDITH Nephrologist survey. In addition, we would like to thank all colleagues who pre-tested the survey, provided advice about the ethical approval in their country or helped to distribute the survey in their country or personal network.

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EDITH Kidney patient survey

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Annex 2: Non-medical barriers reported by nephrologists when providing renal replacement therapy or comprehensive conservative management to ESKD patients – a systematic review

The review is published in a scientific paper:

de Jong RW, Stel VS, Heaf JG, Murphy M, Massy ZA, Jager KJ. Non-medical barriers reported by nephrologists when providing renal replacement therapy or comprehensive conservative management to end-stage kidney disease patients: a systematic review. Nephrol Dial Transplant. 2020 Jan 3:gfz271. doi: 10.1093/ndt/gfz271. Epub ahead of print. PMID: 31898742.

Abstract

Background: Large international differences exist in access to renal replacement therapy (RRT) modalities and comprehensive conservative management (CCM) for patients with end-stage kidney disease (ESKD), suggesting that some patients are not receiving the most appropriate treatment. Previous studies mainly focused on barriers reported by patients or medical barriers (e.g. comorbidities) reported by nephrologists. An overview of the non-medical barriers reported by nephrologists when providing the most appropriate form of RRT (other than conventional in-centre haemodialysis) or CCM is lacking.

Methods: We searched in EMBASE and PubMed for original articles with a cross-sectional design (surveys, interviews or focus groups) published between January 2010 and September 2018. We included studies in which nephrologists reported barriers when providing RRT or CCM to adult patients with ESKD. We used the barriers and facilitators survey by Peters et al. [Ruimte Voor Verandering? Knelpunten en Mogelijkheden Voor Verbeteringen in de Patiëntenzorg. Nijmegen: Afdeling Kwaliteit van zorg (WOK), 2003] as preliminary framework to create our own model and performed meta-ethnographic analysis of non-medical barriers in text, tables and figures.

Results: Of the 5973 articles screened, 16 articles were included using surveys (n = 10), interviews (n = 5) and focus groups (n = 1). We categorized the barriers into three levels: patient level (e.g. attitude, role perception, motivation, knowledge and socio-cultural background), level of the healthcare professional (e.g. fears and concerns, working style, communication skills) and level of the healthcare system (e.g. financial barriers, supportive staff and practice organization).

Conclusions: Our systematic review has identified a number of modifiable, non-medical barriers that could be targeted by, for example, education and optimizing financing structure to improve access to RRT modalities and CCM.

Keywords: CAPD; ESKD; chronic haemodialysis; kidney transplantation; peritoneal dialysis.

Annex 3: Beyond comorbidity related barriers: factors to limit the access to RRT modalities and conservative care

The abstract is published in:

Rianne de Jong, Vianda Stel, Ziad Massy, Kitty Jager, FP672
Beyond comorbiditiy related barriers: factors to limit the access to RRT modalities and conservative care. Nephrology Dialysis Transplantation, Volume 33, Issue suppl_1, May 2018, Page i272, https://doi.org/10.1093/ndt/gfy104.FP672

Introduction and aims: Large international differences exist in the access to dialysis, kidney transplantation and conservative care for patients with end-stage kidney disease (ESKD). Unfortunately, a number of patients with ESKD may not receive their most suitable treatment. So far, comorbidity related barriers to receive the most suitable treatment have been studied extensively and include for instance patient size, cardiovascular status and manual dexterity. We aimed for the first time to provide a systematic overview of other patient (not comorbidity-related) barriers, healthcare professional related barriers and health system related barriers as experienced by nephrologists when attempting to provide the most suitable treatment (i.e. different types of dialysis, kidney transplantation and conservative care) to adult patients with ESKD.

Methods: Systematic literature search was performed in EMBASE and Medline in June 2017. Publications that represented original research published between 2010 and June 2017, used a quantitative or qualitative cross-sectional design (surveys, interviews or focus groups) and reported other than comorbidity related barriers experienced by nephrologists when providing renal replacement therapy (RRT) or conservative care for adult patients with ESKD were included. All retrieved abstracts were reviewed independently by two authors.

Results: Of the 4965 articles screened, 13 articles met the inclusion criteria and provided information on barriers for home haemodialysis (home HD, n=4), peritoneal dialysis (PD, n=3), home HD as well as PD (n=3) kidney transplantation (n=1) and conservative care (n=2). Methodology used consisted of surveys (n=8), focus groups (n=1) and interviews (n=4). Sample sizes varied between 13 and 431 respondents. Most studies were performed in high-income countries. Inadequate (pre-dialysis) education and inadequate funding were reported as barriers for all four modalities. Reported barriers mentioned for home HD, PD as well as conservative care were lack of experience and training for nephrologists, lack of confidence in discussing the treatment option, difficulty in identifying suitable patients and lack of evidence on outcomes. Reported barriers for both PD and home HD included competing alternative programs and easy access to center haemodialysis, lack of skilled staff, fear of complications and therapy specific problems (i.e. with training facilities or PD-catheter placement). Barriers specifically reported for home HD consisted of unsuitable living circumstances (e.g. housing) and demographics, and concerns about burdening patients and carers. Lack of social support was a barrier for both PD and kidney transplantation.

Conclusions: This systematic review identified other than comorbidity related barriers as experienced by nephrologists related to education, personal beliefs, reimbursement and practical issues which may limit the access to RRT modalities and conservative care. This overview may help in developing successful interventions aiming to improve access to specific treatment modalities for patients with ESKD.

Annex 4: The EDITH Kidney Patient Survey on Modality Choice Among More Than 8000 European Dialysis and Transplant Patients

The abstract is published in:

Rianne W. de Jong, Vianda S. Stel, Raymond C. Vanholder, Ziad A. Massy, Kitty J. Jager. The EDITH kidney patient survey on modality choice among more than 8000 European dialysis and transplant patients.
J Am Soc Nephrol 30: 2019

Background: Renal replacement therapy (RRT) modality selection may be challenging for both patients and nephrologists. Within the EDITH project we surveyed adult European dialysis and kidney transplant patients on factors influencing modality choice and their satisfaction with the modality choice made.

Methods: The EDITH kidney patient survey (online and on paper) was translated into 30 languages. European adults with end-stage kidney disease treated by dialysis or kidney transplantation were eligible to participate between November 2017 and November 2018.

Results: 8133 patients from 40 European countries participated. Age, gender and modality characteristics (56% male, mean age 59 years (SD 14), 66% on haemodialysis (HD), 6% on peritoneal dialysis (PD), 29% on transplantation (Tx)) reflected the European RRT population in the ERA-EDTA Registry.

A quarter of the patients did not receive any information on any modality before the start of RRT. 44% received no information on home haemodialysis (HHD), 24% nothing on PD and resp. 23% and 20% nothing on living and deceased kidney donor Tx. The majority of those who received information, were (very) satisfied with the information (range 57% for HHD to 86% for deceased kidney donor Tx).

Two-thirds of the patients reported that decision making was shared with their doctor and most patients (83%) were satisfied with way the decision was made.

The main reasons for patients not having a particular treatment are listed in Table 1. Most important factors influencing modality choice were quality of life, survival and safety (resp. 97.3%, 96.6% and. 92.2% rated as (very) important). Results were similar by age group, sex, educational level and start of RRT time period.

Table 1: main reasons not to have a ceraa certain treatment	
HHD	Don't want treatment at home (34%) Treatment is not available in my hospital (26%) Discomfort with no supervision (24%)
PD	Don't want treatment at home (34%) Dislike of abdominal catheter (23%) Fear of peritonitis (22%)
Living Tx	No living kidney donor available (37%) Don't want to ask potential donors (31%) Concerns about the health of the donor (18%)
Deceased donor Tx	Not healthy enough (25%) Currently on waiting list (22%) Too old (18%)

Conclusions: Though most patients seem to be satisfied with the information provision and modality choice, there remains room for improvement as a quarter of all patients did not receive any

information on treatment modalities before start of RRT. Better education may also influence patients to choose a home-based form of dialysis or empower them to find a living donor.

Evaluation and analysis of impact of costs of different treatment options for cronic kidney disease

IV. Report on current practice in CKD and its financial impact (D4.4)

Responsible partner: CNT
Document. EDITH_ Deliverable 4.4_final_Oct2020 of 02.11.2020

IV.1. Introduction

About 10% of the population in Europe is affected by Chronic Kidney Disease (CKD) that may eventually lead to end stage renal disease (ESRD). The number of European Union patients affected by CKD is expected to grow as CKD is connected to risk factors such as age, diabetes, hypertension and obesity.

The Italian National Transplant Centre (CNT) is co-leader with the Academisch Medisch Centrum (AMC) of EDITH Work-package (WP) 4 and in particular is in charge of task n. 4, which is aimed at evaluating and analysing the costs of different treatment options related to CKD and their impact on health care policies for this kind of patients.

Renal replacement therapy (RRT) includes haemodialysis (extracorporeal) in its various types and modalities (at hospital, out centre, self care, at home), peritoneal dialysis and the transplantation either from a living or a deceased donor. The study conducted by CNT was mainly focused on a collection of data related to the costs of each therapeutic option for CKD and in particular to haemodialysis, peritoneal dialysis and transplantation.

Haemodialysis (HD) and peritoneal dialysis (PD) are the main dialysis modalities for patients with ESRD. Haemodialysis is typically performed 3 times weekly at a dialysis center, with each treatment taking 3 to 5 hours; nocturnal HD and short daily home HD are also available. In contrast, PD uses the lining of the abdomen (the peritoneal membrane) instead of a dialyzer to filter the blood. The abdomen is filled with dialysis solution (a combination of minerals and sugar designed to draw wastes and excess fluids from the body into the solution) and is then drained several hours later (a process known as “exchange”). There are 3 different types of PD: continuous ambulatory PD (CAPD), automated PD (APD), and combination CAPD and APD. In CAPD, patients undergo the exchange process usually 4 to 5 times during a 24-hour period; no machine is required. In APD, the patient uses an automated cycler to perform 3 to 5 exchanges during the night while sleeping (the abdomen can remain filled with dialysis solution throughout the day) [Berger 2009].

On the other end, as it is widely acknowledged, kidney transplantation, performed with organs retrieved from either deceased or living donors, gives to ESRD-affected patients the chance of leading a nearly normal life in terms of quality of life and survival, and it is considered as the optimal treatment for eligible patients.

The purpose of this study is therefore to evaluate and analyse the impact of different treatment options for ESRD on costs as well as report on current practices from the financial point of view.

IV.2. Methodology

The costs of the different RRT treatment modalities applied in EU Member States have been evaluated. Reimbursement tariffs / DRG revenues applicable in each European Union country served as basis for comparison. Annual expenditure has been calculated on the basis of the number of prevalent patients at the date of December 31st and those of transplanted patients for the year object of the study, namely 2016. There are limitations associated with reimbursement tariffs as they

are often fixed by insurance companies or even federally established. Limitations arise due to variations regarding the scope of services that are covered by certain tariffs. For this study, reimbursement tariffs were chosen as they are considered to orientate on direct medical costs.

During the study design stage, the feasibility of performing a collection of data related to real costs in a smaller number of countries was explored. As far as this specific study is concerned, during the EDITH intermediate meeting, held in Mainz in June 2019, and in the light of issues emerged during the first-eighteen months of activity, mainly related to the lack of homogeneous information, the consortium in agreement with DG SANTE representative, decided not to perform this collection. The reasons for this lies in the lack of volunteer countries/hospitals and necessary resources to conduct the study under EDITH as well as in the already emerged difficulties in collecting even tariff data.

The work was divided according six different phases, here listed with specific timings:

1. Review and analysis of available relevant literature from January 2018 to June 2019;
2. Analysis of the organization of different Health systems in single European Union Countries involved in the EDITH project as well as in the other Member States plus UK
    - Collection of information for profile elaboration: February 2018-July 2018;
    - processing of profiles: September-December 2018;
    - validation of single profiles by CAs during January-February 2019);
3. Collection of the absolute figures and relative numbers (pmp, per million population) regarding the prevalence and incidence of adult patients (20 years and older) undergoing haemodialysis and peritoneal dialysis at day 91 (Incident patients were taken into account at day 91, since mortality and hospitalization risks are proved to be heightened during the first 90 days after start of dialysis [Chan 2011]);
4. Production of a questionnaire, apt to categorize the reimbursed therapies in the different countries as well as to collect the DRG/tariffs applied to each therapeutic option
    - Production of questionnaire February 2017-August 2017;
    - the methodology of the study and the questionnaire were shared with DG SANTE first and then Health Technology Assessment (HTA) group, the final approval on the methodology and the content of the questionnaire was received at the end of January 2018)
5. Data collection
    - Start: February 2nd 2018;
    - Reminder: March 2018;
    - Protraction to April 2018.
6. Data Validation
    - The first validation phase started in July 2018 ending in December 2018;
    - From January 2019 to July 2019 the responding countries were asked to provide further clarifications on costs provided and the request of revision of the country profile on the organisation of national Health system).
    - Final data validation (table of costs for dialysis treatment for general revision and enquiry on details of single items included in the reported tariffs related to transplantation: September-October 2019).

The adopted questionnaire was shared with the European HTA group to be sure that the analysis conducted in the framework of EDITH project would be fully recognized by the HTA community. In February 2018 CNT circulated the questionnaire for the first time to 31 countries (the 28 European Competent Authorities for organ transplantation plus Iceland, Norway and Lichtenstein). Twenty out of 28 countries submitted the questionnaire (BE, BG, CZ, DE, EE, FR, GR, HR, HU, IE, IT, LT, LV, MT, NL,

PT, RO, SI, SK, UK). According to its National organisation, UK sent three different questionnaires for the three regions Wales, England and Scotland. Three countries, namely Denmark, Finland and Spain declared from the very beginning that they would not contribute to the study either for the lack of requested information or that for internal difficulties to provide such info in terms of time and resources. No feedback at all were received from Cyprus, Poland, Iceland and Norway. Austria, Denmark, Finland, Malta and Sweden revised the country profile only.

All the collected answers have been validated the first time and 15 countries out of 20 provided further details and clarifications. After the first validation step it was decided to continue the analysis focusing on those country whose data were validated.

In those countries where the reimbursement systems are mixed (public/private) we invited the Competent Authorities to send the questionnaire to the proper respondent, or to share the contact of key person with CNT.

Preliminary cost tables were circulated to those 15 countries asking them to double-check, integrate or validate the results (for calculation please refer to the methodology chapter). Due to the complexity of the analysis especially the one related to the cost of transplantation from deceased and living donor, it was decided to ask additional information related to the amount of the tariff or DRG provided and to specify which costs related to the overall process were included or not. At the end of this second validation phase, 7 countries out of 15 sent their comments, suggestions and the requested supplementary information.

During the validation phase, Lithuania asked not to be included in the analysis for the costs related to dialysis activity, since the National Health Insurance Fund under the Lithuanian Ministry of Health was not able to specify the way annual costs of such therapy were calculated in their country. Therefore, the subsequent results could not be considered as accurate and comparable to the data delivered by other participating countries that followed a more standardised approach.

IV.2.1 Data sources

For this specific study, CNT performed different data collections drawing from separate data source:

1. Available relevant literature was retrieved through devoted research on the major international databases (PubMed, Sciverse SCOPUS, Ovid and Google Scholar) and, additionally, consortium partners were also asked to report devoted national published papers on the topic;
2. Information on the organization of different health systems in the EU was mostly drawn from the European Observatory on Health Systems and Policies, which supports and promotes evidence-based health policy-making through comprehensive and rigorous analysis of the dynamics of health care systems in Europe. Eventually some specific questions were also inserted in the questionnaire circulated to Member States through Competent Authorities (see point 4). Each country report was therefore validated and revised for its correctness by each CA;
3. Activity data on the number of subjects per therapy, who have been treated in different EU countries in 2016:
    - all the data related to the dialysis treatment were provided by the ERA-EDTA Registry (see specification in Annex 1),
    - the number of organs transplanted were taken from the Newsletter Transplant issued every year by the Council of Europe-EDQM in cooperation with the Spanish Organización Nacional de Transplantes (ONT) on the basis of the data provided by each National Competent Authority for its country.

4. Information on how to categorize the amounts reckoned for the different DRG/tariffs have been supplied either directly by the National Competent Authorities or by devoted national bodies to which CNT was addressed by the CA itself (see complete list of suppliers in Annex 1)

IV.2.2 Review and analysis of relevant literature

CNT conducted a systematic review of about 130 papers published from the year 2000 to 2019 (the complete list is attached as Annex 2). All the papers were classified according to the relevance of the study and the reference country. As stated in the EDITH methodology description document [EDITH WP4 task 4], papers were classified as

- "general study publication";
- ”country-oriented publication";
- "therapy-based"; "publication with limited relevance".

Some publications were considered as not relevant to our analysis. These publications were classified as “publications with limited relevance” and excluded from the study after reading the abstract. Among the remaining publications, it was decided to focus on those with most scientific relevance, that is, those providing information of previous analyses conducted in countries who did not reply to the devoted project questionnaire. The most relevant information drawn from the selected papers and considered as essential for the sake of cost analysis and evaluation are summarized hereinafter.

In countries like **the Netherlands**, where several studies have been conducted over the years the burden of dialysis costs on the Health care system has been seriously taken into account. Taking advantage of the claim data collected by the health insurance, Mohnen et al. [Mohnen 2019] referred to the years from 2001-2014. The study presented the average annual healthcare costs for the Dutch RRT patients for 7 treatment modalities, 5 related to dialysis (CHD, HHD, CAPD, APD, and mix group) and 2 to transplantation procedures (from living and deceased donors). Despite all the limitations declared by the authors for this study, it is however relevant to report some meaningful conclusions.

According to the calculation, the total average annual costs in 2014 ranged from 77.566€ for CAPD to 105.833 for patients in the mix group (multiple dialysis modalities in one year) in 2014. CAPD patients had the lowest costs compared to other dialysis modalities (CAPD = €77.566; HHD = €87.051; APD = €89.932; CHD = €92.616; mix Group = €105.833). Reasons behind the differences could be found in the frequency of treatments and the fact that the largest portion of the costs is directly related to RRT, instead of, for example, primary care or transportation.

The costs related to kidney transplantation were € 85.127 in the year of transplantation with a substantial decline in the following years. Transplantation costs related to the donation from deceased donor appeared to be higher than those from living donors (€ 99.450 vs. € 73.376). This difference was attributed to higher dialysis and transplant surgery related costs in recipients. Though the annual healthcare costs in the year of transplantation are comparable to the annual healthcare costs of dialysis patients, these costs declined substantially after one year to a level that is 14-19% of annual dialysis costs (€ 29.612 in the first calendar year after transplantation, € 20.156 second calendar year after transplantation). According to Mohnen’s study, costs decline even faster, if the transplantation was successful in terms of graft functioning in the second year after transplantation. In that case, costs amount to € 15.018, including after care, medication and hospitalization.

The Dutch study confirms CAPD to be the RRT with lowest costs among dialysis treatments, it also confirms that despite some additional cost for the donor (i.e. preparatory research, guidance, and

donor expenses) there is a clear cost advantage of transplantation using living kidney donor instead of deceased ones. In countries like Netherlands, where living donation (including pre-emptive transplantation) is actively encouraged by nephrologist, the cost advantages are visible not only long term but already short. In addition to early transplantation, the overall cost for RRT could be reduced if more patients would start treatment with home-based therapies, especially CAPD.

A study conducted by Jensen et al. in **Denmark** and published in 2014 on the Danish Medical Journal aimed at assessing whether kidney transplantation is a cost-effective alternative to dialysis [Jensen 2014]. This study showed also, that transplantation is a favourable option when treating ESRD. The Danish researchers produced a cost-utility analysis (CUA) which measured all relevant costs associated to alternative ESRD treatment against their effect. For this study, data from the Danish Nephrology Registry (DNR) were considered, although it is not possible to distinguish which dialysis patients are eligible for transplantation based on the report of the DNR. Costs were calculated on the basis of 2012 using tariffs from the Danish case-mix system 2012* and converted into Euro from the Danish Krune, according to the average 2012 exchange rate (1 DKK = EUR 0.134342). The cost per treatment for haemodialysis at hospital amounted to € 308,44 (treatments: three times a week, for 52 weeks) while the costs for home-based haemodialysis amounted to € 3.708,64 (which include the treatment for the whole year and bimonthly check-ups). As far as peritoneal dialysis is concerned, the cost per treatment amounted to € 3.489,13 (which included the treatment for the whole year and check-ups every three month for a total of four check-ups a year). Among costs listed for the transplantation procedure, the cost related to the surgical intervention of nephrectomy amounted to € 1.418,92 from deceased donor and to € 7.187,97 from living donor. A normal transplantation procedure costs € 24.278,55 while a complicated one amounts to € 68.769,53. Additional costs are those for the check-ups (€ 128,16 each) which patients attend ten times a year, in the first year after transplantation and quarterly in subsequent years and for the immunosuppressive treatments (group 1: € 17,86 ± € 0,85 per day, group 2: € 7,85 ± € 3,47 per day, group 3: € 0,2 ± € 0,02 per day).

Finally, they performed an economic evaluation measuring health outcomes in quality-adjusted life years (QALYs), which is a composite measure of health-related quality of life (HRQoL) and life expectancy [Drummond 2005]. The cost per QALY was € 138.766 for dialysis compared to € 108.886 for transplantation. When comparing kidney transplantation with dialysis, kidney transplantation was cost-saving and resulted in additional QALYs.

*The Danish case mix system is the combination of the Danish diagnose-related groups (DkDRG) tariffs and the Danish ambulatory groups system (DAGS) tariffs which represent the average public health-care cost for in-patient treatments and ambulatory visits, respectively.

According to the NHS Blood and Transplant 2009 report, the indicative cost of maintaining a patient with end stage renal disease on RRT is around £17.500 (i.e. around €19.728) for one year of patient undergoing peritoneal dialysis and around £35.000 (i.e. around €39.457) per patients per year for a patient on hospital haemodialysis in **Britain** [NHSBT media services 2019]. In 2009, the NHS registered in UK over 37.800 ESRD patients, among these those on dialysis treatment were around 21.000 namely 76% on haemodialysis and the other 24% on peritoneal dialysis. Considering that the average cost of dialysis is about £30.800 (i.e. around €34.722) per patient per year and the indicative cost of a kidney transplant is £17.000 (i.e. around €19.165) per patient per transplant, NHS estimated the yearly cost benefit of kidney transplantation to be £25.800 (i.e. around €29.077) from the second year on.

Another British study was conducted by Li et al. and published on Nephrology Dialysis and Transplantation [Li 2015]. The authors observed the cost differential for patients continuing dialysis after the first year of RRT or receiving a transplant. In conclusion, the study supported the longer-

term economic advantage of transplantation over dialysis. This study was conducted thanks to the linkage of the UK Hospital Episode Statistics to the UK Renal Registry. Aim was to analyse the variation of inpatient/outpatient hospital costs, separately from the RRT costs and to related these costs to different treatment modalities, number of years of treatment, and other factors like age and comorbidities. Although the authors list a series of limitations, mainly relating to patient comorbidities and granularity of the dataset, it was however noticed that hospital costs are higher in the first year and gradually decrease in the following year, in particular for transplanted patients. Catheter-related infections, catheter replacement or fistuloplasty, as well as management of immunosuppression therapy or management of complications after transplant are considered to be the possible explanation for the higher costs, respectively of the first year inpatient and kidney transplant patients costs. The long-term economic advantage of transplantation over dialysis for the health service is therefore recognized because of the considerable differential of costs along the years.

Conclusion of a **Swedish** study by Olsson and Olsson is that growing prevalence rates may lead to an unmanageable cost explosion. In their study, four different treatment modalities have been investigated. The outcome showed that treatment at patient's home have the lowest cost, mainly because of reduced medical staff cost as well as infrastructure cost [Olsson 2016]. Olsson and Olsson conclude that treating patients at home will give the possibility to treat a larger number of patients. Frequent home haemodialysis is considered to be the best treatment option not only because of the improved patients' quality of life but also for its economic value.

In 2016, a Swedish research group led by Eriksson compared the health care costs in CKD stage 4 and 5 not on dialysis (estimated glomerular filtration rate <30mL/min/1.73m3), peritoneal dialysis, haemodialysis and transplanted patients [Eriksson 2016]. The study group examined the annual costs assessed by nationwide healthcare registers related to hospital days, out-patients care visits and prescription of drugs and then put the cost in relation to matched general population comparators. In this study a number of 2.432 prevalent patients were included. Among these, there were 1.046 patients with CKD stage 4 and 5 not on dialysis, 101 on peritoneal dialysis, 460 on haemodialysis and 825 transplanted. The highest mean annual cost was observed in the haemodialysis group with €87.600, out of which 71% were accounted for outpatients care cost (€62.500), with 97% (€60.400) related to visit listing dialysis. Patients on peritoneal dialysis had a mean annual cost of €58.600, out of which €29.900 (51% of the total amount) were related to fluids, while costs related to inpatient and outpatient care were similar. Annual costs of drug prescription for transplanted patient were very low (€6.800),while the mean annual cost for this group of patients was estimated to be €15.500, a fourth of the estimated cost in patients on peritoneal dialysis.

To complete the North Europe countries panorama, a **Finnish** study published on the American Journal of Kidney Diseases analysed the costs of RRTs in the country [Salonen 2003]. According to the paper, cadaveric transplantation is less costly than both, HD and CAPD dialysis, since annual costs decline significantly, after the transplant procedure is performed. The costs were identified and valued using the year 2003 currency for the US dollar and they were converted into Euro, according to the average 2003 exchange rate (1 USD = 0,8833 EUR). Direct health care costs for the first year in the HD, CAPD and Transplant groups were, respectively, € 51.972, € 43.919 and € 40.354. During subsequent years, health direct costs calculated every six months, were € 47.860,68 and € 48.170,08 in the HD group, € 40.012,38 and € 43.581,15 in the CAPD group, and € 10.118,46 and € 8.830,45 in the transplant group. The cost of the cadaveric transplant procedure, in 1996, amounted to € 8.823 and living transplant procedure to € 10.110.

Another study published on Nephrology Dialysis Transplantation investigated the costs of home and self-care satellite haemodialysis and concluded that the total costs of Home haemodialysis (€ 38.477) are very similar to those of self-care satellite dialyses (€ 39.781) [Malmstrom 2008].

When comparing different treatments modality costs, it is interesting to note that the same conclusions have been achieved by two different studies: According to Vaccaro 2018 and Mohnen 2018, CAPD seems to have a clear cost advantage compared to other dialysis therapies.

With reference to this, a recent **Spanish** study was also taken into consideration. Villa et al. published in the journal Nephrology Dialysis Transplantation an analysis, which estimated the average annual costs of RRTs per patient in Spain both, for incidence and prevalence figures as follows [Villa 2011]:

- The weighted average cost for HD were € 2.651 (incidence) and € 37.968 (prevalence). From the perspective of the public administration, indirect costs amounted to € 8.929 due to losses of labor productivity.
- The weighted average cost for PD (CAPD and APD) amounted to € 1.808 (incidence) and € 25.826 (prevalence), while the indirect costs were € 7.429 €.
- The estimated cost for kidney transplantation was €38.313 in the first year, going down to € 6.283 in the subsequent years. Kidney transplantation indirect costs amounted to € 4.483.

IV.2.3 Proposed mechanisms to maintain sustainability of renal replacement therapies in literature

Some of the analysed publication tackle the issue of finding possible ways to maintain financial sustainability of RRTs that can be proposed to policy makers. It is a fact that the treatment of kidney disease, consumes a substantial amount of the health budget for a relatively small fraction of the overall population.

First among this is the 2016 paper written by Vanholder et al. in which several mechanism have been proposed to maintain the sustainability of RRT costs. The proposed options are listed as follow:

1) Encourage both living and deceased kidney donation
2) Stimulate alternative dialysis strategie
3) Promote educational activities guiding the patients towards therapies tailored for their health statu
4) Consideration of one or more cost containing incentives
5) Strategically planned adaptations to the exceed growth of the ageing population in need of RRT
6) Support new research studies
7) Increase patience-centered approaches.

The French study conducted in 2012 by the Agence de la biomédecine (ABM) in cooperation with the Haute Autorité de santé (HAS) had the main aim to perform a medico-economic evaluation of management strategies of patients with end-stage renal disease [Couillerot-Peyrondet 2017]. The objective of the French study, was to assess the clinical and economic impact of renal replacement therapies in France with a specific focus on hospital-based haemodialysis, out-center, self-care unit, home HD, automated peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD) assisted or not assisted by a nurse, kidney transplant from deceased or living donor. According to the registry of Epidemiology and Information in Nephrology (REIN) which register the people under replacement therapy in France, at the 31/12/2012 a total number of 73.491 patients (about 0.1% of French population) were receiving replacement therapy. The overall costs declared by the National Health Insurance in 2007 were equal to 4 billion euros for a total number of 61.000 patients. Thus

number were considered as increasing due to the regular increase in the number of patients treated noted by the French REIN registry. The medico-economic evaluation conducted by HAS and ABM is based on a model allowing to describe the changes over 15 years in the distribution of patients treated in ten treatment modalities since the start of their replacement therapy. It made it possible to simulate changes in the care trajectories of patients by modifying the relative share of the various modalities of locum treatment received over time and to evaluate their consequences in terms of cost and efficiency (life expectancy). The change simulations were carried out according to six groups of patients: 18-44 years, 45-69 years and 70 years and over, and according to diabetic status. The average cost of taking care of a patient with ESRD over the first 15 years after starting a replacement therapy varied from € 2.684 per month for young people aged 18 to 45 years non-diabetic at € 7.361 per month for people over the age of 70 with diabetes [Couchoud 2015].

A special focus on renal transplantation costs was published in 2014 by Sainsaulieu et al the objective of this study is to determine for a renal transplant the total amount for health insurance of the stages preceding and peripheral to the transplantation, by distinguishing the case of living and deceased data. This work will shed a primordial light on the cost of renal transplantation which is the subject of a measure of national priority and recommendations on different development issues [Sainsaulieu 2014]. As presented in the study, successful organ transplantation relies on several ancillary activities such as the identification of a compatible donor, organ allocation and procurement and the coordination of the transplant process, for all of these identified steps, three for the donation from deceased and three from living donor the French group had determined the total additional costs of ancillary transplantation activities by comparing the costs of kidney transplantations with living donors against those using deceased donors. The data used are drawn from the 2013 public healthcare tariff calculations, National Hospital discharge database recorded activity and transplant activity in 2012 as assessed and reported by the Agence de la biomédecine. The results show that, in 2012, additional transplant cost varied from € 13.835,44 to € 20.050,67 for a deceased donor and were € 13.601,66 for living donation. In the following Tables 19 and 20 the selected papers from which relevant information of costs per therapy were retrieved are reported and the observed tendency of costs is synthetically reported, for dialysis and transplantation respectively.

In the DOPKI study conducted by the leadership of Hungarian National Blood Transfusion Service in the framework of another European Union funded project, it was constructed a Markov model capable of estimating the net present value cost savings and additional quality-adjusted life years (QUALYs) in renal transplantation that occur as the result of improved organ donation activities in terms of additional organ and improved organ allocation. Starting from the assumption that only five additional part-time donor coordinator in large district hospitals with low historical donation rates and one additional donor coordinator in the National Organ Coordinator Office were needed, the aim of this study was to provide the Hungarian Ministry of Health reliable information to increase the number of donor coordinators. To implement the program the total investment required was approximately about 68.000 euro (23mil HUF) plus € 6.000 (2mil HUF) for training with a final outcome of 15 additional donor reported per year and 24 more kidney transplant from deceased donor performed. With such implementation a substantial saving of 2.417.442 USD (€ 2.163.210) over a total expenditure of 7.557.811 (€ 6.762.970) could be highlighted with a projection in ten years of 19.706.254 UDS (€ 17.633.800) savings over a total expenditure of 61.383.445 (€ 54.927.900). DOPKI study focused on the direct medical costs and benefits without considering societal perspective and at the end of it, the main reported conclusion was that even if the program had resulted in only one additional kidney transplantation, the value of the program would have considered as positive, as its benefits exceed its costs.

The organ donation initiative is cost saving regardless how long it is sustained, according to the study it results in substantial health care value and it is therefore highly recommended.

The most relevant conclusion drawn from the selected papers and considered as essential for the sake of cost analysis and evaluation are summarized Tables 19 and 20.

Table 19: List of references for selected papers on dialysis costs, with summarized main conclusions

Authors	**HD (HHD/CHD)**	**APD**	**CAPD**	**Observed tendency of costs**
Babolal 2008	Yes	Yes	Yes	CAPD < APD HD > PD
Tediosi 2001	Yes	Yes	Yes	CAPD < APD HD > PD
Mohnen 2019	Yes	Yes	Yes	CHD > HHD CAPD < APD
Vaccaro 2017	Yes	Yes	Yes	CAPD < APD Among extracorporeal treatment (HD, HDF/AFB, HDF/MID/HFR) HD is the more affordable treatment
Villa 2011	Yes	Yes	Yes	CAPD and APD cost effective when compared to HD
Jensen 2014	Yes	Not specified	Not specified	HD at hospital < HHD PD < HD
Salonen 2003	Yes	Yes	Yes	HHD > CAPD
Couillerot-Peyrondet 2017	Yes	Yes	Yes	CAPD < HDD < self-care < APD < out center < hospital based

Table 20: List of references of selected papers on transplantation costs, with summarized main conclusions

Authors	**Transplant from Living Kidney Donor (LKD)**	**Transplant from Deceased Kidney Donor (DKD)**	**Observed tendency of costs**
Mohnen 2019	Yes	Yes	In the year of Transplantation (Tx) from LKD 25% < than DKD After successful transplantation, Tx costs < 14/19% of annual dialysis costs
Fondazione CENSIS 2013	Yes	Yes	Cost of Tx 55,2% of total cost related to transplant itself, 44,8% to post transplant costs in the first year. Post-transplant costs are divided as follow: 29,2% immunosuppressive therapy, 16,5% to specific follow-up costs , 28,5% to complications and other pathologies and 25,8% to decease of graft failure
Villa 2011	Yes	Yes	Cost of Tx almost equal to one year of HD for the first year with a decrease subsequent years

Jensen 2014	Yes	Yes	DKD < LKD Normal Tx procedure < complicated Tx Additional costs for checkups are higher in the first year after Tx and decrease in the second year
Salonen 2003	Yes	Yes	Tx costs < HD and CAPD after six months
Couillerot-Peyrondet 2017	Yes	Yes	Monthly Tx costs < HD and PD after four months

IV.3. Overview on health systems in EU countries

Differences among EU countries find their root in the organization of national health system. The following report is a summary of the overview of EU health systems produced as part of WP4 - task 4 of the EDITH project. The aim of both work-package and task is to evaluate and analyze the impact of ESRD treatment modalities on national health expenditure and their impact on health care policies. This brief overview has its source of information in the EU Observatory on Health Systems and Policies. Further, all the country report have been shared to the CAs which have validated the collected information. Despite not all countries answered to the questionnaire, the overview was prepared on all 28 EU MS.

EU Health system overview – EDITH countries Austria

The Austrian system acts on two levels: the federal and the regional one. Each of the nine Länder has its own regional health fund. The country has a two-tier health care system in which virtually all individuals receive publicly-funded care, but they also have the option to purchase supplementary private health insurance. Austrian health service providers may be both, public and private with the majority being public.

EU Health system overview – EDITH countries Belgium

The health system in Belgium is funded both, nationally and by compulsory and non-compulsory private insurance companies. Insurance in Belgium is compulsory for its citizens and it covers nearly the whole Belgian population. Insurance in Belgium is universal and financed through various ways of taxation. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the public health system.

EU Health system overview – EDITH countries Bulgaria

Bulgaria's health system is mixed and based on both national system and private insurance companies. The health system is centralized and all citizens are provided with public insurance by the National Health Insurance Fund. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the public health system. It is possible for Bulgarian citizens to purchase voluntary health insurance from voluntary health insurance providers.

EU Health system overview – EDITH countries Croatia

Croatia's health system is based on a compulsory health insurance, managed by Croatian Health Insurance Fund (CHIF), a quasi-public body, that has the position of Sole insurer, and main purchaser of health services. Citizens pay 16,5% of their payroll for working families, while various vulnerable groups are excluded from this deduction. In Croatia both public and private health care providers operate, out of which some have, and some other have not a contract with the CHIF. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the public health system.

EU Health system overview – EDITH countries Cyprus

The health system of Cyprus is highly centralized and relies strongly on the public administration system. The public health fund does not cover all Cypriots, and thus some of them resort to private insurance or out of pocket payments. Public insurance is financed through tax revenue, with total healthcare being 41.5% funded by the government, with the remainder being privately funded, through unions or other organizations

EU Health system overview – EDITH countries Czech Republic

The Czech health system is based on compulsory health insurance, administered by self-governing health insurance funds, under the aegis of the Ministry of Health. It provides universal coverage with a generous benefit basket. The entitlement to coverage in the Czech Republic is based on permanent residence rather than on direct statutory health insurance contributions. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the public health system.

EU Health system overview – EDITH countries Denmark

Denmark's health system is considered mostly public, with the largest percentage of healthcare spending (84%) being public. Additionally, 14% of spending is out of pocket, and the remaining 2% is private or voluntary health insurance. The Danish health system is decentralized, with the main healthcare responsibilities being present at the regional and local level. RRTs are funded by the public health system according to different DRGs.

EU Health system overview – EDITH countries Estonia

Estonia's health system is national. It is based on compulsory, solidarity-based insurance and universal access to health services made available by providers that operate under private law. 94.5% of the population is covered by mandatory health insurance offered by the EHIF. Chronic haemodialysis is funded by the public health system.

EU Health system overview – EDITH countries Finland

In Finland there are three different health care systems which receive public funding: municipal health care, private health care and occupational health. The largest share of health care services is provided by the municipal health care system.

EU Health system overview – EDITH countries France

France's health system is mixed and based on compulsory and non-compulsory private insurance. It primarily operates as a public system, controlled by the Ministry of Health. The statutory health insurance (SHI) is the main insurance body and it covers almost all French citizens. It is however possible to buy additional insurance to cover a wide range of healthcare services outside of the SHI. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the public health system.

EU Health system overview – EDITH countries Germany

Germany's health system is a mixed one with two parallel systems for health insurance, namely SHI and PHI. Below a certain income level SHI is mandatory, supplementary private health insurance can be obtained on a voluntary basis. Above the aforementioned income level, citizens can choose to be part of either SHI or PHI – the PHI has to cover a minimum service level. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the SHI and PHI. Both systems are using predominantly the same infrastructure, i.e. healthcare providers.

EU Health system overview – EDITH countries Greece

The Greek healthcare system is a mix of various public systems. The combination of social health insurance (SHI) and the financing of the national health system comes as result from the financial

crisis. The EOPYY is a newly created body fully responsible as main purchaser of healthcare services. Coverage is universal due to recent legislation and there is a public health fund to cover health expenses of citizens, even with the inability to provide healthcare contributions, citizens are still eligible for the health benefits package. The fund covers a fixed amount of costs per treatment, with all outside costs being out-of-pocket.

EU Health system overview – EDITH countries Hungary

Hungary's health system is primarily public and focused on a single payer system. The entire Hungarian population should be covered for healthcare, which they pay based on taxes on income. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the public health system.

EU Health system overview – EDITH countries Italy

Italy's National Health Service is regionally based, with the central government sharing responsibility for health care with the country's 19 regions and two autonomous provinces. Italy has universal coverage, thus the National Health Service is responsible for health coverage of all citizens and foreign residents. Chronic haemodialysis is all publicly funded, 70% of service is delivered directly by the public health system structures, and 30% by private centres, which are later reimbursed by national public health system, while peritoneal dialysis and kidney transplantation (both living and deceased) are funded by the public health system.

EU Health system overview – EDITH countries Ireland

Ireland's health system is national and has a high level of centralization. It is primarily mixed, with a national non-compulsory insurance, and additionally, a wide range of private insurances available. Around 70% of healthcare costs are publicly funded, and thus covered by the national health insurance fund. The Irish health care system is predominantly tax-funded, although about half the population has also voluntary health insurance. Chronic haemodialysis and peritoneal dialysis are funded by the public health system.

EU Health system overview – EDITH countries Latvia

Latvia's health system is public. It is based on general tax-financed statutory health care provision, with a purchaser–provider split and a mix of public and private providers. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (living) are all funded by the public health system.

EU Health system overview – EDITH countries Lithuania

The Lithuanian health-care system is predominantly publicly financed. It is based on compulsory private insurance companies. Compulsory health insurance provides a standard benefits package for all beneficiaries. Emergency care is provided free of charge to all permanent residents irrespective of their insurance status. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the public health system.

EU Health system overview – EDITH countries Luxembourg

Data unavailable.

EU Health system overview – EDITH countries Malta

The Maltese health system is strongly centralized and primarily public with complementary roles for private healthcare. Private healthcare does however play a significant role, and stands connected to out-of-pocket payment costs. With the strong presence of public/compulsory insurance, the Maltese have access to a wide range of treatments and care. Patients can make free use of healthcare services, which is financed through general taxation.

EU Health system overview – EDITH countries The Netherlands

Since 2006, the Dutch health system has been considered private, though a minor part of the system and some healthcare responsibilities are placed on local governments and municipalities. Dutch people are free to choose from a wide range of insurance covering companies. This results in around 20% of healthcare spending being out of pocket, while 80% of spending is publicly funded.

EU Health system overview – EDITH countries Poland

Health services in Poland are financed from public funds, in order to ensure equal access to all citizens. Approximately 98% of the population is covered by the system of compulsory health insurance. Compulsory health insurance formally guarantees access to a very broad range of health services, with no need for the patients to pay out of pockets or to go to private health sector services.

EU Health system overview – EDITH countries Portugal

The health system in Portugal is national and acts on different levels: the National Health Service, special public and private insurance schemes for certain professions (noted as health sub-systems) and private voluntary health insurance. The Portuguese health system can be considered a mixed model which focuses on universality and solidarity. Portugal has adopted a social insurance system, under which all residents in Portugal are covered. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the public health system.

EU Health system overview – EDITH countries Romania

Romania's health system is public and it acts on two prominent levels: national and regional. The health system is highly centralized, and is mixed with both public and private insurance being available. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the public health system.

EU Health system overview – EDITH countries Slovakia

Slovakia's health system is based on compulsory private insurance, universal coverage, a basic benefit package and a competitive insurance model with selective contracting of health care providers and flexible pricing of health services. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the public health system.

EU Health system overview – EDITH countries Slovenia

Slovenia's health system is national and it is based on a Bismarck-type social insurance system, which is fully regulated by national legislation and administered by the Health Insurance Institute of Slovenia, which provides universal compulsory health insurance. Three private companies (Adriatic-Slovenica, Triglav and Vzajemna) provide voluntary health insurance which is mainly used by patients to cover co-payments. Chronic haemodialysis, peritoneal dialysis and kidney transplantation (both living and deceased) are all funded by the public health system.

EU Health system overview – EDITH countries Sweden

The Swedish health care system is organised on three levels: the national, regional and local. The publicly financed health system covers public health and preventive services. The market for Voluntary Health Insurance in Sweden is small if compared to other European countries. Private insurance in health care is supplementary.

EU Health system overview – EDITH countries Spain

The Spanish healthcare system is mainly public and decentralized, with a varying availability and presence of private insurance in the different regions in Spain. Spain has compulsory healthcare for its citizens, with an option to opt-out for a very small amount of citizens. 99.9% of the population is

covered, with the exception of opted-out civil servants and restrictions for non-registered immigrants.

EU Health system overview – EDITH countries United Kingdom
The Health system in the United Kingdom is complex and decentralized in the various regions of the UK. The country follows public healthcare systems, with every region having its own publicly funded healthcare. The NHS provides healthcare for all UK citizens, as long as they are ordinary residents in the country. Non-UK citizens like immigrants often pay full costs of treatment, with the exception of EU citizens

IV.4. Collection of data on number of patients per therapy

Thanks to the fruitful collaboration between AMC (the body managing the ERA-EDTA Registry) and CNT, during technical meetings, a dataset needed as denominator in EDITH cost analysis was agreed upon. Such data are only those referring to dialyzed patients, whereas data for transplanted patients were drawn from the Newsletter Transplant, in light of the higher coverage of this source. All data sets referred to the year 2016, since this was taken as reference year for comparison with costs.

Data retrieved from the ERA-EDTA Registry are the following (for 2015 and 2016 - per single EU country):

- absolute and relative number (pmp, per million population) number of prevalent adult patients (20 years and older) undergoing haemodialysis;
- absolute and pmp number of incident adult patients (20 years and older) undergoing haemodialysis;
- absolute and pmp number of prevalent and incident adult patients (20 years and older) undergoing peritoneal dialysis,
- absolute number of prevalent patients that perform treatment in hospital, as out-centre patient or at home.

Data for incident patietns were taken into account at day 91, since mortality and hospitalization risks are proved to be heightened during the first 90 days after start of dialysis [Chan 2011].

Data retrieved from Newsletter Transplant included the following (Newsletter Transplant 2017, referring to 2016 data):

- absolute and pmp number of kidney transplants performed from living donors
- absolute and pmp number of kidney transplants performed from deceased donors
- absolute number of patients on kidney waiting list at December 31 2016

IV.5. Questionnaire on reimbursement of modalities and costs of therapies

During the stage of methodology definition, a cost-effectiveness analysis was selected as preferable approach. The idea was to make a comparison between the costs of different RRTs, under the assumption that the benefits of these therapies are equivalent in terms of efficacy. Questions were formulated broadly in order to gather comprehensive information on reimbursement tariffs foreseen for different treatment modalities (haemodialysis, peritoneal dialysis, transplantation) and contexts (public or private service, out-patient centres, home care). Some supplementary information on healthcare system organization were also requested.

In particular, the RRTs taken into account are the following:

- Haemodialysis
    - Haemodialysis (HD)
    - Haemodiafiltration (HDF)
    - Haemofiltration (HF)
- Peritoneal Dialysis
    - CAPD
    - APD
- Transplant
    - Kidney transplant from Living Donor
    - Kidney transplant from Deceased Donor

The complete set of posed questions is attached as Annex 3. All Competent Authorities of EU Member States plus Norway, Iceland and Lichtenstein have been asked to supply data, suggesting them to forward the questions to devoted authorities. The complete list of data suppliers is reported in Annex 1. A preliminary analysis on data availability showed the necessity to focus on reimbursement tariffs instead of real costs.

The questionnaire was shared with the European HTA group to be sure that the analysis conducted in the framework of EDITH project would be fully recognized by the community. In February 2018, it was circulated for the first time to 31 countries (the 28 European Competent Authorities for organ transplantation plus Iceland, Norway and Liechtenstein). Twenty out of 31 countries submitted the questionnaire (BE, BG, CZ, DE, EE, FR, GR, HR, HU, IE, IT, LT, LV, MT, NL, PT, RO, SI, SK, UK). According to the its national organisation UK sent three different questionnaires for the three regions Wales, England and Scotland. Three countries namely Denmark, Finland and Spain declared from the very beginning that they would not contributed to the study either for the lack of requested information or for the internal difficulties to provide such information. No feedback at all was received from Cyprus, Austria, Sweden, Poland, Iceland and Norway. All the collected answers have been therefore validated the first time and 15 countries out of 20 provided further details and clarifications. After the first validation step it was decided to continue the analysis focusing on those countries whose data were validated.

In those countries where the reimbursement systems are mixed (public/private) we invited the Competent Authorities to send the questionnaire to the proper respondent, or to share the contact of key person with CNT.

Preliminary cost tables were circulated to those 15 countries asking them to double-check, integrate or validate the results (for calculation please refer to the methodology chapter). Due to the complexity of the analysis especially the one related to the cost of transplantation from deceased and living donor, it was therefore decided to ask additional information related to the amount of the tariff or DRG provided and to specify which costs related to the overall process were included or not. At the end of this second validation 7 countries out of 15 sent their comment, suggestion and the requested supplementary information. As already mentioned above, Lithuania asked not to be included in the analysis for the costs related to dialysis activity, since the National Health Insurance Fund under the Lithuanian Ministry of Health was not able to specify the way annual costs of such therapy were calculated in their country

IV.6. Analysis

IV.6.1 Analysis of reimbursement tariffs for dialysis treatments

Analysis of tariffs

Though partial and influenced by the diversity of health systems across countries, the analysis of the 2016 tariffs, allows for a comparison between the different treatments available to CKD patients also in terms of dedicated economic resources.

The following summary tables are based on different sources:

- the data collected and verified were employed for the part of the study related to tariffs per treatment;
- 2016 data from the ERA-EDTA Registry was applied for the part related to the number of prevalent patients per type of treatment.

The high variability in responses was taken into account during the first evaluation of results and raises the need for further clarification.

In general, the data obtained refers to two main types of extracorporeal dialysis: standard haemodialysis (HD) and convective haemodialysis (HF+HDF), both performed in out-patient centres. More specifically, the data taken into account might also consist, for those countries which identified it, of a simple arithmetic mean of the different tariffs foreseen for the different regimes public/private and out-patient centre, self-care unit and home care. However, in most countries, the tariffs provided refer to dialysis in public out-patient centres. As far as peritoneal dialysis is concerned, CAPD (Continuous Ambulatory Peritoneal Dialysis) and APD (Automated Peritoneal Dialysis) have been taken into consideration, both performed at the patient's home. Sometimes, the tariff examined might be an average of the tariffs related to public and private regime. Moreover, in some other cases, the countries involved, did not provide the data related to the specific methodology but rather one tariff for the two sub-groups, making it hard to produce a detailed comparison on the specific methods. Table 21 gives a summarized picture of the different reimbursement tariffs identified for the main renal function replacement treatments.

Table 21: Reimbursement tariff for single treatment by country (€)

	Standard Haemodialysis	**Convective (HF + HDF) Haemodialysis**	**CAPD (continuous ambulatory peritoneal dialysis)**	**APD (automated peritoneal dialysis)**
Belgium	€ 292,33	€ 292,33	€ 145,00	€ 145,00
Croatia	€ 122,51	€ 132,54	€ 45,00	€ 45,00
Czech Republic	€ 130,00	n/a	€ 65,00	€ 155,00
Estonia	€ 212,86	n/a	n/a	€ 60,40
France	€ 277,93	€ 277,93	€ 77,24	€ 99,22
Germany	€ 182,85	€ 179,58	€ 80,86	€ 88,99
Hungary	€ 64,88	€ 64,88	€ 64,88	€ 64,88
Ireland	€ 287,65	€ 309,68	€ 95,89	€ 109,59
Italy	€ 142,03	€ 232,40	€ 46,48	€ 54,74
Latvia	€ 115,28	€ 104,55	~ € 53,00	~ € 73,00
Portugal	€ 150,23	€ 150,23	€ 9,20	€ 9,20
Romania	€ 100,00	€ 233,33	€ 33,33	n/a
Slovakia	€ 159,00	€ 158,50	€ 53,00	€ 63,00
Slovenia	€ 171,58	€ 228,31	€ 83,23	€ 113,62
Min.	€ 64,88	€ 64,88	€ 9,20	€ 9,20
Max	€ 292,33	€ 309,68	€ 145,00	€ 155,00

Source: EDITH – Centro Nazionale Trapianti
Note: In the survey, each country was asked to identify tariffs per single treatment (Standard, HF+HDF, CAPD and APD) differentiating between public and private and by regime (out-patient centres, self-care units and home care) in order to calculate the weighted average for the amount of services provided in the various regimes. The ERA-EDTA registry does not allow to determine the number of patients treated per each type of regime (public/private and out-patient centres, self-care units and home care). Therefore, the tariffs shown by the table were obtained considering the simple mean of the different tariffs indicated, except for France which provided data related to patients treated in each particular regime that allowed ponderation. In some countries tariffs varies with number of patients treated by a dialysis center assuming the effect of economies of scale. In such cases averages were used, too.

As far as a single standard dialytic treatment is concerned, the tariff ranges from € 64,88 indicated by Hungary, to € 292,33 in Belgium, with values exceeding € 200 per treatment, also in Ireland (€ 287,65), in France (€ 277,93) and in Estonia (€ 212,86).

With reference to convective techniques, which on average have higher tariffs (around € 195 compared to around € 170 for standard hemodialysis), there is a greater variability between the maximum and minimum tariff value. However, in this case, this could depend also on Hungary's outliner position, indicating a single reimbursement rate (€ 64,88) for all the analyzed methods. The highest value of € 309,68 was provided by Ireland, while neither Czech Republic nor Estonia provided data on the tariffs of these methods. Leaving out Hungary's single tariff, the lowest value is the one presented by Latvia (€ 104,55). In some cases, the rate indicated is (slightly) lower than the one for standard dialysis (Germany, Latvia, Slovakia) while Belgium, France and Portugal indicated a single rate for both these methods and standard dialysis.

If we consider the first type of peritoneal treatment, CAPD, Portugal indicated a decidedly low value per treatment (€ 9,20), but also Romania, Croatia and Italy have a reduced tariff value (€ 33,33 , € 45 and € 46,48 respectively) compared to the maximum value of Belgium (€ 145,00). The average value per treatment reported (approximately € 61) is lower than the average value for APD (around € 77). The highest tariff for this second type of dialysis were reported by Czech Republic (€ 155,00) and the lowest (excluding the peculiar value identified by Portugal) by Croatia (€ 45) and Italy (€54,74).

The comparison of tariffs per single treatment provided by the respondent to the questionnaire, proves to be a partial data, which does not take into account the frequency of treatment. Therefore, in order to calculate the average tariff cost per patient per year, we assumed an average of 3 weekly treatments for extracorporeal dialysis and a daily treatment for peritoneal dialysis. The annual value was then obtained by multiplying, for the first type of dialysis, the rate indicated for each treatment 3 (time/week), by 52 (weeks/year) while for peritoneal dialysis, the daily rate was multiplied by 365 (days/year).

In the evaluation of the summary data, it shall be taken into account that, obviously, the annual tariff costs per patient are highly variable, reflecting the large fluctuations in the input data and the lack of differentiation of some tariffs (see Table 22).

Variability in annual cost between countries also relates to the fact that different services may be included in the tariff. For example, in France, erythropoietin-stimulating agent and injectable iron supplement are included in the overall amount, whereas, in some countries, medical consultations during the dialysis session may be not included in the tariff. Differences in tariff should also be interpreted in the light of GDP in each country, and subsequent high variability of staff costs and consumables across Europe

Table 22: Annual tariff per patient by treatment type (€)

	HD			PD		
	Totale HD*	**Standard**	**HF-HDF**	**Totale PD***	**CAPD**	**APD**
Belgium	€ 45.604,00	€ 45.604,00	€ 45.604,00	€ 52.925,00	€ 52.925,00	€ 52.925,00
Croatia	€ 19.893,90	€ 19.111,56	€ 20.676,24	€ 16.425,00	€ 16.425,00	€ 16.425,00
Czech Republic	€ 20.280,00	€ 20.280,00	-	€ 40.150,00	€ 23.725,00	€ 56.575,00
Estonia	€ 33.206,16	€ 33.206,16	-	€ 22.046,00	€ 22.046,00	€ 22.046,00
France	€ 40.113,84	€ 40.113,84	€ 40.113,84	€ 32.203,43	€ 28.192,08	€ 36.214,78
Germany	€ 28.523,82	€ 28.523,82	€ 28.014,48	€ 30.912,70	€ 29.433,04	€ 32.388,72
Hungary	€ 10.121,28	€ 10.121,28	€ 10.121,28	€ 23.681,20	€ 23.681,20	€ 23.681,20
Ireland	€ 46.591,74	€ 44.873,40	€ 48.310,08	€ 37.500,00	€ 35.000,00	€ 40.000,00
Italy	€ 29.205,70	€ 22.156,37	€ 36.255,02	€ 18.472,65	€ 16.965,20	€ 19.980,10
Latvia	€ 17.146,74	€ 17.983,68	-	€ 22.995,00	-	-
Portugal	€ 23.435,36	€ 23.435,36	€ 23.435,36	€ 3.356,96	€ 3.356,96	€ 3.356,96
Romania	€ 26.000,00	€ 15.600,00	€ 36.400,00	€ 12.166,26	€ 12.166,26	-
Slovakia	€ 24.765,00	€ 24.804,00	€ 24.726,00	€ 21.170,00	€ 19.345,00	€ 22.995,00
Slovenia	€ 31.191,42	€ 26.766,48	€ 35.616,36	€ 35.925,13	€ 30.378,95	€ 41.471,30
Min.	€ 10.121,28	€ 10.121,28	€ 10.121,28	€ 3.356,96	€ 3.356,96	€ 3.356,96
Max	€ 46.591,74	€ 45.604,00	€ 48.310,08	€ 52.925,00	€ 52.925,00	€ 56.575,00

(*) Average tariff of the individual tariffs indicated for standard hemodialysis and convective (HF + HDF) Hemodialysis (**) Average tariff of the individual tariffs indicated for CAPD and APD
The annual patient amount is calculated as follow: HD=total mean tariff * 3*52; PD= total mean tariff * 365
Source: EDITH – Centro Nazionale Trapianti

For standard HD, the minimum annual value is featured by Hungary (€ 10.121,28) and the maximum one, by Belgium (€ 45.604,00).

The Hungarian numbers represent also minimum rates for the more complex methods like HF+HD (€10.121,28), while the highest average annual cost per patient is noticed for Ireland (€ 48.310,08).

We then calculated an overall average annual cost for all HD techniques, since the detail on the number of prevalent patients undergoing the different treatments is not always available.

In addition to the particularly low figures of Hungary, also countries like Latvia, Croatia and Czech Republic range in the lower cost segment of around € 20.000 per year and patient. Germany, Italy, Slovenia and Estonia lie above, at approximately, € 30.000. France reaches around € 40.000 euros per year and the highest values, as already mentioned, are featured by Belgium and Ireland with more than € 45.000.

Considering the average annual tariff cost for CAPD, there is a very strong variation between the minimum and the maximum rate. This could be a result of the very low tariff values in Portugal and Croatia. Belgium indicated the maximum value, equal to € 52.925,00, while the values relating to one year of CAPD per patient from Romania, Italy, Slovakia, Estonia, Hungary and the Czech Republic range from around € 12.000 to € 24.000. For countries such as France, Germany and Slovenia the amounts are closer to a value of € 30.000, while Ireland reaches € 35.000.

Also for APD, there are important variations, but again, in evaluating the data, we have to consider that four countries (Belgium, Estonia, Hungary and Portugal) have provided the same tariffs for both peritoneal treatments. The highest value is indicated by Czech Republic (€ 56.575,00) and the lowest by Portugal.

Considering the average value of both types of peritoneal dialysis, the data from Belgium stands out with almost € 53.000 per year per patient, while seven countries lie in the range of € 20.000 to € 24.000. Values from € 30.000 to € 40.000 were reported by Germany, France, Slovenia and Ireland.

Estimate of direct costs of dialytic therapies

The next step in the analysis, is to evaluate the different overall cost, based on the reimbursement rate data and, therefore, not on the real cost, that countries bear to meet the needs of people affected by chronic kidney disease.

The number of prevalent patients who undergo the different types of dialysis treatment has been taken from the ERA-EDTA Registry and it refers to the year 2016 (see Table 23).

Table 23: Prevalent patients on dialysis in 2016 by country (number)

	HD			PD			TOTAL HD+PD
	Total HD (a)+(b)	**Standard (a)**	**HF-HDF (b)**	**Total PD (c)+(d)**	**CAPD (c)**	**APD (d)**	
Belgium	7.726	4.930	2.796	620	369	251	8.346
Croatia	2.051	1.767	284	156	51	105	2.207
Czech Republic	6.310	1.595	4.715	429	-	-	6.739
Estonia	343	332	11	55	42	13	398
France	43.680	29.718	13.962	3.030	1.193	1.835	46.710
Germany	72.943	-	-	4.615	-	-	78.089
Hungary	5.560	-	-	868	-	-	6.428
Ireland	1.867	-	-	208	-	-	2.075
Italy	13.579	10.192	3.387	1.692	854	838	15.271
Latvia	385	385	-	97	-	-	482
Portugal	11.836	304	11.532	720	315	405	12.556
Romania	17.300	17.206	94	1.348	89	1.255	18.648
Slovakia	3.295	888	2.407	75	46	29	3.370
Slovenia	1.376	-	-	52	-	-	1.428
Min.	343	304	11	55	42	13	398
Max	72.663	29.718	13.962	4.564	1.193	1.835	77.219

Source: ERA-EDTA Registry Annual Report 2016, Germany: GBA report 2016, Ireland: National Renal Office, Dublin, Slovakia: USRDS, Slovenia: data from Dialysis Services Reimbursement survey (personal communication with professor Raymond Vanholder

However, also in this case, not all countries provided detailed data: Germany, Hungary and Ireland only indicated the number of prevalent patients undergoing HD and peritoneal dialysis, without differentiating between the different methods, and in the case of Slovenia, the data are completely missing.

In order to evaluate the significance of the disease, a prevalence figure compared to the population was used, which highlights a greater presence of people with chronic kidney disease in Portugal with 1.212,2 prevalent patients undergoing dialysis per million population (pmp). The lowest figure has been recorded in Estonia with 302.5 patients pmp. In Germany and Romania there are more than 900 patients pmp undergoing dialysis while Latvia, just as Estonia, recorded around 300 patients pmp (see Table 24).

Table 24: Prevalent patients on dialysis in 2016 by country (pmp)

	HD			PD			TOTAL HD+PD
	Total HD	**Standard**	**HF-HDF**	**Total PD**	**CAPD**	**APD**	
Belgium	681,8	435,1	246,7	54,7	32,6	22,2	736,5
Croatia	546,2	470,6	75,6	41,5	13,6	28,0	587,8
Czech Republic	614,9	155,4	459,5	41,8	-	-	656,7
Estonia	260,7	252,3	8,4	41,8	31,9	9,9	302,5
France	653,3	444,5	208,8	45,3	17,8	27,4	698,6
Germany	892,3	-	-	56,0	-	-	948,4
Hungary	566,5			88,4			655,0
Ireland	392,6	-	-	43,7	-	-	436,7
Italy	649,1	487,2	161,9	80,9	40,8	40,1	730,0
Latvia	246,8	-	-	62,2			309,0
Portugal	1.142,7	29,3	1.113,3	69,5	30,4	39,1	1.212,2
Romania	886,9	882,1	4,8	69,1	4,6	64,3	956,0
Slovakia	606,3	163,4	442,9	13,8	8,5	5,3	620,1
Slovenia	666,3	-	-	25,2	-	-	691,5
Min.	246,0	29,3	4,8	13,8	4,6	5,3	302,5
Max	1.142,7	882,1	1.113,3	88,6	40,8	64,3	1.212,2

Source: ERA-EDTA Registry Annual Report 2016, Germany: GBA report 2016, Ireland: National Renal Office, Dublin, Slovakia: USRDS, Slovenia: data from Dialysis Services Reimbursement survey (based on Van der Tol et al. An international analysis of dialysis services reimbursement. Clin J Am Soc Nephrol. 2019:14;84-93. and personal communication with professor Raymond Vanholder).

The number of patients represented the basis for carrying out the calculation reported in Table 25, which compares the direct costs of RRT. This is an overall value obtained by multiplying the annual cost per patient by type of treatment, by the number of prevalent patients in 2016 referring to the different types of treatment. In the absence of distinct data per type of dialysis, we multiplied the average annual cost per method (HD and PD) by the total number of patients who underwent these treatments.

Clearly, the strong variability of the data is affected not only by the different annual average tariff but also by the large variability in the number of patients treated (Table 25)

Table 25: Total amount for all patients on dialysis by type of treatment and country in 2016 (€)

	HD			PD			TOTAL HD+PD
	Totale HD (a)	**Standard**	**HF-HDF**	**Totale PD (b)**	**CAPD**	**APD**	
Belgium	€ 352.336.504,00	€ 224.827.720,00	€ 127.508.784,00	€ 32.813.500,00	€ 19.529.325,00	€ 13.284.175,00	€ 385.150.004,00
Croatia	€ 39.642.178,68	€ 33.770.126,52	€ 5.872.052,16	€ 2.562.300,00	€ 837.675,00	€ 1.724.625,00	€ 42.204.478,68
Czech Republic	€ 127.966.800,00	€ 32.346.600,00	-	€ 17.224.350,00	-	-	€ 145.191.150,00
Estonia	€ 11.389.712,88	€ 11.024.445,12	-	€ 1.212.530,00	-	€ 286.598,00	€ 12.602.242,88

France	€ 1.893.815.602,58	€ 1.288.470.972,47	€ 605.344.630,11	€ 100.087.268,41	€ 33.633.149,74	€ 66.454.118,68	€ 1.993.902.870,99
Germany	€ 2.080.613.002,26	-	-	€ 142.662.110,50	-	-	€ 2.223.275.112,76
Hungary	€ 56.274.316,80	-	-	€ 20.555.281,60	-	-	€ 76.829.598,40
Ireland	€ 86.986.778,58	-	-	€ 7.800.000,00	-	-	€ 94.786.778,58
Italy	€ 348.613.468,94	€ 225.817.702,66	€ 122.795.766,29	€ 31.231.604,60	€ 14.488.280,80	€ 16.743.323,80	€ 379.845.073,54
Latvia	€ 6.923.716,80	€ 6.923.716,80	-	€ 2.230.515,00	-	-	€9.154.231,80
Portugal	€ 277.380.920,96	€ 7.124.349,44	€ 270.256.571,52	€ 2.417.009,14	€ 1.057.441,50	€ 1.359.567,64	€ 279.797.930,10
Romania	€ 271.835.200,00	€ 268.413.600,00	€ 3.421.600,00	€ 16.400.119,98	€ 1.082.797,24	-	€ 288.235.319,98
Slovakia	€ 81.541.434,00	€ 22.025.952,00	€ 59.515.482,00	€ 1.556.725,00	€ 889.870,00	€ 666.855,00	€ 83.098.159,00
Slovenia	€ 42.919.393,92	-	-	€ 1.868.106,76	-	-	€ 44.787.500,68
Min.	€ 6.923.716,80	€ 6.923.716,80	€ -	€ 1.212.530,00	€ 837.675,00	€ 286.598,00	€ 9.154.231,80
Max	€ 2.080.613.002,26	€ 1.288.470.972,47	€ 605.344.630,11	€ 142.662.110,50	€ 33.633.149,74	€ 66.454.118,68	€ 2.223.275.112,76

The total amount by type of treatment (in case of availability of single tariff) is obtained by multiplying the patient annual cost per patient for each treatment with the total number of patients treated.
In cases where the tariff for HF-HDF or PD was missing, the total amount was calculated multiplying the total number of patients undergoing convective treatment for the standard tariff available. In cases where the patient's HD or PD specification was missing, the total cost was calculated by multiplying the average annual tariff by the total number of patients on HD respectively PD.
Source: EDITH – Centro Nazionale Trapianti and ERA-EDTA Registry Annual Report 2016

Essentially, when compared to the resident population, direct costs shows a lower incidence of this expenditure (always linked to tariffs) for CKD in Latvia (€ 4.7 per capita) with respect to € 34 in Belgium (see Table 26). However, higher values are also reported by France (€ 29,9) and Germany (€ 27 per capita), while Latvia, Italy, Hungary, Estonia and Croatia range between € 5 and € 10.

Table 26: Total annual cost for dialytic treatment by country in 2016 (per capita)

	Total cost HD + PD	**Costs per capita**
Belgium	€ 385.150.004,00	€ 33,99
Croatia	€ 42.204.478,68	€ 10,12
Czech Republic	€ 145.191.150,00	€ 13,74
Estonia	€ 12.602.242,88	€ 9,58
France	€ 1.993.902.870,99	€ 29,88
Germany	€ 2.223.275.112,76	€ 27,00
Hungary	€ 76.829.598,40	€ 7,83
Ireland	€ 94.786.778,58	€ 19,93
Italy	€ 379.845.073,54	€ 6,27
Latvia	€ 9.154.231,80	€ 4,67
Portugal	€ 279.797.930,10	€ 27,10
Romania	€ 288.235.319,98	€ 14,63
Slovakia	€ 83.098.159,00	€ 15,30
Slovenia	€ 44.787.500,68	€ 21,69
Min.	€ 9.154.231,80	€ 4,67
Max	€ 2.223.275.112,76	€ 33,99
Source: EDITH – Centro Nazionale Trapianti, ERA-EDTA Registry Annual Report 2016 and Eurostat		

IV.6.2 Analysis of tariffs reimbursed for transplantation

The evaluation of the costs of kidney transplantation implies, both in case of living and deceased donor, the identification of a certain amount of data related to:

1. The costs for procurement of the organ to be transplanted,
2. The costs for the surgical intervention on the recipient,
3. The costs for the recipient's follow-up.

We consider the costs for the living donor's follow-up to be, for the most part, irrelevant.

The survey elaborated and circulated for this purpose, has been returned by fifteen countries: Belgium, Bulgaria, Croatia, Czech Republic, Estonia, France, Germany, Hungary, Ireland, Italy, Latvia, Portugal, Romania, Slovakia and Slovenia.

These countries all feature different types of national health systems; however, they all foresee some form of compulsory insurance which finances from a national fund that covers healthcare costs. Healthcare is provided by public health structures, partner private structures and accredited private structures.

In the countries examined, the reimbursement of living and deceased transplant procedures is carried out based on predetermined tariffs, except for Bulgaria where a remuneration reimbursement system is implemented. It is based on the submission of the related receipts.

At first sights, tariffs seemed to refer mainly to the hospital stay for the transplant surgical intervention. In order to validate the collected data, the countries participating to the study were therefore asked to declare whether the tariff / DRG, included all the steps related to the donor and recipient costs. Table 8 and 9 in Annex 4 and Annex 5 summarize the collected answers highlighting in green the cost declared as included in the Tariff/DRG column costs and in red those not included. For some countries (Belgium, Bulgaria, Hungary, Latvia, Portugal and Romania) this information was not provided.

Based on the answers received, it has not been feasible to accurately determine the entity of the costs for the procurement of a kidney retrieved from a deceased donor, and in some cases neither from a living donor.

Tariffs applied to kidney transplant procedures across the countries examined, show a wide dispersion and range from a minimum of € 8.188 in the Slovak Republic to a maximum of € 73.000 in Slovenia. Due to the huge difference between Slovenia and other countries, CNT investigated the reason behind the declared tariff. According to the explanation provided, the transplantation reimbursement in Slovenia is unique in comparison to other European countries. The National Insurance Company define the reimbursement of transplantation procedures. The same amount is paid for deceased-donor and living-donor kidney transplantation. The Slovenian reimbursement model includes complete recipient assessment, waiting list management, surgical transplant procedure, hospital stay immediately after the transplantation procedure and follow-up during the first year (including potential complications and re-hospitalizations). In case of a living donor kidney transplantation, the same reimbursement also includes complete donor assessment, donor operation procedure and hospital stay after donation. As Slovenia is a small country (population 2 million), there is only one national transplant centre situated at the University Medical Centre Ljubljana, where all pre- and post-transplant recipients management and procedures are taking place. Therefore, the University Medical Centre Ljubljana receives the whole reimbursement for each kidney transplant. The reimbursement is paid every time a transplantation procedure is realized.

The average reimbursement rate for a kidney transplant from all countries responding to the questionnaire amounts to €26.685,91 for a deceased donor transplant and to €25.073,69 for a living donor transplant.

The costs for the procurement of a kidney from a deceased donor range from a minimum of € 1.285 (Slovakia) to a maximum of € 12.500 (Portugal). Similarly, for the procurement procedure of a kidney from a living donor, a minimum rate of € 887 (Latvia) and a maximum rate of € 24.100 (Slovenia) have been reported.

Data collected for the follow-up of living donors and recipients have proved to be fragmentary. There is no general consensus what should be included in the cost calculation for the follow-up care. Therefore the data provided do not allow consistent conclusions.

EDITH analysis, does not include data from Portugal. Portugal's system multiplies a basal value of € 2.285 by a factor that varies based on the complexity of the activity performed by the single healthcare structure where the transplant is performed.

Tables 8 and 9 of Annex 4 and Annex 5 were therefore summarized in table 27.

Table 27: Summary table of Transplant costs from deceased and living donor (€)

	Deceased Tx costs	Procurement costs of deceased Tx donor	Living Tx costs	Procurement costs of living Tx donor	Recipient follow-up	Living Donor follow-up
Belgium	€ 26.196	€ 2.329	€ 16.352	€ 3.698		€ 244
Croatia	€ 8.632	€ 4.538	€ 8.632	€ 4.538		
Czech Republic	€ 8.400	€ 1.706	€ 8.400			
Estonia	€ 14.362	€ 4.769	€ 14.015	€ 4.423	€ 3.057	
France	€ 34.618		€ 27.241		€ 1.128	
Germany	€ 36.086	€ 6.992	€ 32.959	€ 11.355		
Hungary	€ 12.990		€ 12.990			
Ireland	€ 27.287		€ 27.287	€ 5.030		
Italy	€ 33.162	€ 2.482	€ 33.162	€ 7.137		
Latvia	€ 14.016		€ 14.016	€ 887		
Portugal	€ 2.285	€ 12.500				
Romania	€ 15.000	€ 3.000	€ 15.000	€ 400	€ 400	
Slovakia	€ 8.188	€ 1.285	€ 8.770	€ 1.726	€ 5.700	
Slovenia	€ 73.000		€ 73.000			
Min.	€ 2.285	€ 1.285	€ 8.400	€ 400	€ 400	€ 244
Max	€ 73.000	€ 12.500	€ 73.000	€ 11.355	€ 5.700	€ 244
Source: EDITH – Centro Nazionale Trapianti						

Transplantation activity data were extrapolated from the Newsletter Transplant [EDQM 2017] summarizing the international data on organ donation and transplantation activity in 2016 (Table 28) provided by the European Competent Authorities for organ donation and transplantation.

Table 28: Number of Kidney transplantation by donor type in 2016 (number)

	Total Tx (all patient ages)	Tx from deceased donor	Tx from living donors	Tx from living donor / Total tx (%)
Belgium	520	453	67	12.9
Croatia	190	183	7	3.7
Czech Republic	458	412	46	10.0
Estonia	42	38	4	9.5
France	3.615	3.039	576	15.9
Germany	2.094	1.497	597	28.5
Hungary	342	308	34	9.9
Ireland	172	122	50	29.1
Italy	2.076	1.796	280	13.5
Latvia	59	49	10	16.9
Portugal	499	434	65	13.0
Romania	265	224	41	15.47
Slovakia	143	124	19	13.3
Slovenia	46	44	2	4.3
Min.	42	38	2	3.7
Max	3.615	3.039	597	28.5
Source: Newsletter Transplant 2017				

The overall direct costs for deceased and living kidney donor transplantation were multiplied with the volume of transplant activity performed for each country. As table 29 shows the total direct costs

for transplantation from DKD in 2016 ranges from a minimum of € 686.784 (Latvia) to a maximum of € 105.204.102 (France) with average direct costs per million inhabitants that ranging from € 213,59 in Romania to € 1.317,79 in France.

With reference to the total costs for transplantation from LKD in 2016 the lowest expenditure was record in Estonia with a total amount of € 71.044 and the highest costs were recorded in Germany with an overall expenditure of € 19.544.687.

Table 29: Total direct costs by type of treatment and country in 2016 (€)

	DKD Tx costs	**Total cost DKD tx**	**LKD Tx costs**	**Total costs LKD tx**
Belgium	€ 28.525,00	€ 12.921.825,00	€ 20.050,00	€ 1.283.200,00
Croatia	€ 13.169,87	€ 2.410.086,21	€ 13.170,00	€ 92.190,00
Czech Republic	€ 10.106,00	€ 4.163.672,00	€ 8.400,00	€ 352.800,00
Estonia	€ 22.877,00	€ 869.326,00	€ 17.761,00	€ 71.044,00
France	€ 34.618,00	€ 105.204.102,00	€ 27.241,00	€ 15.581.852,00
Germany	€ 39.839,00	€ 59.638.983,00	€ 32.959,00	€ 19.544.687,00
Hungary	€ 12.990,00	€ 4.000.920,00	€ 12.990,00	€ 441.660,00
Ireland	€ 27.287,00	€ 3.329.014,00	€ 32.317,00	€ 1.615.850,00
Italy	€ 35.644,00	€ 64.016.624,00	€ 40.299,00	€ 11.203.122,00
Latvia	€ 14.016,00	€ 686.784,00	€ 14.903,00	€ 149.030,00
Portugal*				
Romania	€ 18.500,00	€ 4.144.000,00	€ 15.500,00	€ 635.500,00
Slovakia	€ 16.345,00	€ 2.026.780,00	€ 17.368,00	€ 329.992,00
Slovenia	€ 73.000,00	€ 3.212.000,00	€ 73.000,00	€ 146.000,00
Min	€ 10.106,00	€ 686.784,00	€ 8.400,00	€ 71.044,00
Max	€ 73.000,00	€ 105.204.102,00	€ 73.000,00	€ 19.544.687,08
Source: EDITH – Centro Nazionale Trapianti				

As far as the incidence of costs per capita is concerned (see Table 30), it ranged from € 0.21 (per capita) in Romania to € 1.56 in Slovenia for kidney transplantation from deceased kidney donor and from € 0.02 (per capita) in Croatia to € 0.34 in Ireland.

Table 30: Total amount by type of treatment in 2016 per capita

	DKD cost per capita	**LKD costs per capita**
Belgium	€ 1,14	€ 0,11
Croatia	€ 0,58	€ 0,02
Czech Republic	€ 0,39	€ 0,03
Estonia	€ 0,66	€ 0,05
France	€ 1,58	€ 0,23
Germany	€ 0,72	€ 0,24
Hungary	€ 0,41	€ 0,05
Ireland	€ 0,70	€ 0,34
Italy	€ 1,06	€ 0,18
Latvia	€ 0,35	€ 0,08
Portugal*		
Romania	€ 0,21	€ 0,03
Slovakia	€ 0,37	€ 0,06
Slovenia	€ 1,56	€ 0,07
Min	€ 0,21	€ 0,02
Max	€ 1,58	€ 0,34
Source: EDITH - Centro Nazionale Trapianti, Newsletter Transplant 2017 and Eurostat		

IV.6.3 Comparison of reported tariffs for dialysis and transplantation

A large amount of scientific studies show that transplantation, compared to dialyses, is the best treatment option currently available for chronic ESRD in terms of patient survival and quality of life for patients eligible for transplantation. Considering the notable economic scope of both treatment options, it seems understandable that there is an interest in comparing the costs of transplant and dialysis. However, even by excluding from the analysis the costs related to the complications that often occur directly or indirectly during both treatments, such comparison does not come as an easy and immediate task: dialysis is, in fact, a replacement treatment which only makes up partially and temporarily for the lack of renal function. Therefore, dialysis has to be performed periodically in order to keep a sufficient level of blood purification. All costs thus represent a *recurring* cost. Transplant, on the other hand, is a replacement treatment which restores renal function and, therefore represents a *lump sum* cost. It obviously is a much more expensive procedure than a single dialysis session, to which the costs for pharmacological treatment and periodical clinical checkups shall also be added.

It is, however, possible to calculate for a "standard" patient, the difference between the cost of transplant and the cost that would have been afforded for that same patient over a fixed period of time, i.e. one year, had that patient not undergone transplantation. By doing so, outset data can be obtained and employed to calculate how long it is going to take for the potential surplus of costs over the first year after transplantation, to counterbalance the costs of dialysis. From that moment on, the costs sustained for dialysis, will be considered as "savings" generated by transplantation compared to dialysis. Such initial saving which, starting from the second year after transplantation, coincides with the total cost of dialysis, assuming that costs for immunosuppressive therapy are negligible compared to the costs of dialysis treatment.

If data on survivals for transplanted patients and for patients undergoing dialysis had been available in the cost reporting countries, we would have been able to estimate in an adequate and reliable manner, the total "savings" produced by transplant compared to dialysis. These could have been added to the better results indexes, in terms of survival and quality of life, which have already been extensively proven. Unfortunately, for this specific study, survival rates were only available for countries that were unable to provide information on costs of patient follow-up and immunosuppressive therapy. France was the only responding country that provided the cost of follow-up (recipient and living donor). For this reason the authors decided to discard the option of adding a table on long terms effects.

However, we were able to estimate the variation between the costs of dialysis (in each of its different alternatives) and transplant, for each country examined. Tables 31 and 32 show for each country the transplant costs respectively from deceased and living kidney donor, calculated using the tariffs or DRG provided for these interventions to which, when available, the total costs related to kidney procurement by the respective donor, donor evaluation and recipient waiting list maintenance have been added, if appropriate.

As far as the kidney transplantation from deceased donor is concerned (Table 31) , it is possible to notice that already in the first year of a functioning graft Belgium, Croatia, Czech Republic, Estonia, France, Ireland, Latvia, Romania and Slovakia record transplant savings compared to standard dialysis, from a minimum of € 3.131 (Latvia) to a maximum of €17.079 (Belgium). For Germany, Italy and Slovenia show costs of a successful kidney transplant are higher than standard dialysis treatment in the first year. The additional cost for the first year range from a minimum of € 2.869 (Hungary) to a maximum of € 41.809 (Slovenia).

Whereas, when comparing kidney transplantation from deceased donor and one year cost of peritoneal dialysis, in the first year of functioning graft Belgium, Croatia, Czech Republic, Hungary, Ireland, Latvia and Slovakia show an economic advantage from a minimum of € 4.825 (Slovakia) to a maximum of € 30.044 (Czech Republic).

Estonia, Germany, Italy, Romania and Slovenia incur costs for transplantation from deceased donor that are higher than those of peritoneal dialysis in the first year ranging from a minimum of € 831 (Estonia) to a maximum of € 37.075 (Slovenia).

Table 31: Estimation of differences of costs per patient - Transplantation from Deceased Kidney Donor VS 1 year of Dialysis

	Deceased Kidney Transplantation (DKD	**Deceased donor procurement cost**	**Immunosuppresive therapy costs**	**DKD Tx costs**	**HD costs**	**PD costs**	**Δ DKD Tx HD**	**Δ DKD Tx PD**
Belgium	€ 26.196	€ 2.329		€ 28.525	€ 45.604	€ 52.925	-€ 17.079	-€ 24.400
Bulgaria*	€ 23.936	€ 2.965						
Croatia	€ 8.632	€ 4.538		€ 13.170	€ 19.894	€ 16.425	-€ 6.724	-€ 3.255
Czech Republic	€ 8.400	€ 1.706		€ 10.106	€ 20.280	€ 40.150	-€ 10.174	-€ 30.044
Estonia	€ 14.362	€ 4.769	€ 3.746	€ 22.877	€ 33.206	€ 22.046	-€ 10.329	**€ 831**
France	€ 34.618			€ 34.618	€ 40.114	€ 32.203	-€ 9.496	**€ 2.415**
Germany	€ 36.086	€ 6.992		€ 43.078	€ 28.524	€ 30.913	**€ 14.554**	**€ 12.165**
Hungary	€ 12.990			€ 12.990	€ 10.121	€ 23.681	**€ 2.869**	-€ 10.691
Ireland	€ 27.287			€ 27.287	€ 46.592	€ 37.500	-€ 19.305	-€ 10.213
Italy	€ 33.162	€ 2.482		€ 35.644	€ 29.206	€ 18.473	**€ 6.438**	**€ 17.171**
Latvia	€ 14.016			€ 14.016	€ 17.147	€ 22.995	-€ 3.131	-€ 8.979
Portugal*	€ 2.285	€ 12.500						
Romania	€ 15.000	€ 3.000	€ 500	€ 18.500	€ 26.000	€ 12.166	-€ 7.500	**€ 6.334**
Slovakia	€ 8.188	€ 1.285	€ 6.872	€ 16.345	€ 24.765	€ 21.170	-€ 8.420	-€ 4.825
Slovenia	€ 73.000			€ 73.000	€ 31.191	€ 35.925	**€ 41.809**	**€ 37.075**
Min	€ 2.285	€ 1.285	€ 500	€ 10.106	€ 10.121	€ 12.166	-€ 19.305	-€ 30.044
Max	€ 73.000	€ 12.500	€ 6.872	€ 73.000	€ 46.592	€ 52.925	**€ 41.809**	**€ 37.075**
Source: EDITH - Centro Nazionale Trapianti								

When considering the costs of kidney transplantation from living donor (Table 32) compared to one year of standard dialysis, in the first year of functioning graft Belgium, Croatia, Czech Republic, Estonia, France, Ireland, Latvia, Romania and Slovakia show an economic advantage of the transplantation from a minimum of € 2.244 (Latvia) to a maximum of € 25.554 (Belgium).

Germany, Hungary, Italy and Slovenia incur costs for transplantation from living donor higher than those of standard dialysis in the first year from a minimum of € 2.869 (Hungary) to a maximum of € 41.809 (Slovenia).

Whereas, when comparing kidney transplantation from living donor and one year cost of peritoneal dialysis, in the first year of functioning graft Belgium, Croatia, Czech Republic, Estonia, France, Hungary, Ireland, Latvia and Slovakia show an economic advantage from a minimum of € 3.802 (Slovakia) to a maximum of € 32.875 (Belgium).

Germany, Italy, Romania and Slovenia incur costs for transplantation from living donor higher than those of peritoneal dialysis in the first year from a minimum of € 3.334 (Romania) to a maximum of € 37.075 (Slovenia).

Table 32: Estimation of differences of costs per patient - Transplantation from Living Kidney Donor VS 1 year of Dialysis

	Living Kidney Transplantation (LKDTx)	Living donor procurement costs	Immunosuppresive therapy costs	LKD Tx costs	HD costs	PD costs	Δ LKD Tx HD	Δ LKD Tx PD
Belgium	€ 16.352	€ 3.698		€ 20.050	€ 45.604	€ 52.925	-€ 25.554	-€ 32.875
Bulgaria*								
Croatia	€ 8.632	€ 4.538		€ 13.170	€ 19.894	€ 16.425	-€ 6.724	-€ 3.255
Czech Republic	€ 8.400			€ 8.400	€ 20.280	€ 40.150	-€ 11.880	-€ 31.750
Estonia	€ 14.015		€ 3.746	€ 17.761	€ 33.206	€ 22.046	-€ 15.445	-€ 4.285
France	€ 27.241			€ 27.241	€ 40.114	€ 32.203	-€ 12.872	-€ 4.962
Germany	€ 32.959	€ 11.355		€ 44.314	€ 28.524	€ 30.913	**€ 15.790**	**€ 13.401**
Hungary	€ 12.990			€ 12.990	€ 10.121	€ 23.681	**€ 2.869**	-€ 10.691
Ireland	€ 27.287	€ 5.030		€ 32.317	€ 46.592	€ 37.500	-€ 14.275	-€ 5.183
Italy	€ 33.162	€ 7.137		€ 40.299	€ 29.206	€ 18.473	**€ 11.093**	**€ 21.826**
Latvia	€ 14.016	€ 887		€ 14.903	€17.147	€ 22.995	-€ 2.244	-€ 8.092
Portugal								
Romania	€ 15.000		€ 500	€ 15.500	€ 26.000	€ 12.166	-€ 10.500	**€ 3.334**
Slovakia	€ 8.770	€ 1.726	€ 6.872	€ 17.368	€ 24.765	€ 21.170	-€ 7.397	-€ 3.802
Slovenia	€ 73.000			€ 73.000	€ 31.191	€ 35.925	**€ 41.809**	**€ 37.075**
Min	€ 8.400	€ 887	€ 500	€ 8.400	€ 10.121	€ 12.166	-€ 25.554	-€ 32.875
Max	€ 73.000	€ 11.355	€ 6.872	€ 73.000	€ 46.592	€ 52.925	€ 41.809	€ 37.075
Source: EDITH - Centro Nazionale Trapianti								

Obviously, for every country, starting from the second year a successful transplant, net of any possible complications, entails a saving of costs equivalent to those of dialysis.

IV.7. Conclusions

The EDITH Pilot Project intended to take a picture of the costs sustained for RRT in the European Union Member States and to estimate the impact of such costs on the health expenditure of different EU countries.

Despite all the limitations encountered in this study and highlighted in each part of this deliverable, the final analysis of collected data shows some commonalities, especially with previously-analysed publications, that are all limited to single countries. In particular:

- Most authors list a series of limitation for each of the conducted studies;
- Most authors declared difficulties in collecting information on real costs;
- Most publication were related just to estimation of costs;
- Most publications stated that although costs for transplantation are very high in the first year, they decreased in the following one;
- Transplantation should be then prioritized over dialysis although self-sufficiency cannot be achieved only through deceased donation. Living donation should be promoted and presented as possible treatment despite the risk of long term complication for the living donor.

We need to stress that some limits were also inherent to the nature of the study. As it is the case with a pilot project, a methodology was laid down- that was also validated through contacts with HTA group at European level - that is susceptible to be improved and perfected, if a devoted

properly-funded analysis on reimbursement costs and real costs should be performed at European level in the years to come. For the sake of accuracy, access to national/main health insurance registers should be ensured as well as the possibility to double check such information with clinical databases and prescribed drug registries.

Concerning the systematic review of papers, especially the most significant ones about which we reported in this document, they were mainly related to countries not participating in EDITH data collection. Furthermore, some papers focused their analysis on claimed costs that were collected through national insurance companies [Mohnen 2019, HAS 2012], others - like the case of Denmark [Jensen 2014], UK [Li 2015] and Sweden [Eriksson 2016], - referred to tariffs or DRG costs; and a third group – including Finland [Salonen 2003], Italy [Vaccaro 2017, CENSIS 2013, Tediosi 2001] - and France referred to real costs [HAS 2012]. Finally, the Spanish study, provided just an estimation of costs based on available literature and health care costs database [Villa 2011].

Despite this, the overall results and conclusions quoted figures that are in line with EDITH analysis and underline that starting from the second year a successful transplant, net of any possible complications, entails a saving of costs equivalent to those of dialysis.

Additionally, it is worthwhile to stress that, despite the fact that the EDITH study does not investigate the issues related to advantages for transplanted patients in terms of quality of life and survival, this important aspect is largely explored and confirmed in the available international and national literature and should be taken in due consideration for proper policy-making.

Variability in annual costs between countries also relates to the fact that different services may be included in the tariff, e.g. administered drugs and medical consultations may be not included, or in the case of transplantation, different phases of the whole process from organ donation to transplant follow-up are included in the tariff, e.g. in Slovenia the overall tariff seems to be meant to include all phases of the process, whereas in other countries, the surgical intervention alone. In addition, as mentioned before, differences in tariffs should also be interpreted in the light of GDP in each country, and subsequent high variability of staff costs and consumables across Europe.

Eventually, based on collected data, an estimation of the impact of RRT on health expenditure was made for the year 2016. As Table 33 shows, dialysis costs accounted for a range from 0,25% (Italy) to the 2,21% (Romania) of national health expenditures. Total costs of transplantation from living and decease donor, in contrast, ranged from the 0,3% of Ireland to the 0,09% of Slovenia.

Table 33: Total health expenditure by type of RRT (2016)

	HD + PD	HD+PD costs % health expenditure	DKD + LKD	DKD + LKD costs % health expenditure
Belgium	€ 385.150.004,00	0,83	€ 14.205.025,00	0,03
Croatia	€ 42.204.478,68	0,97	€ 2.502.276,21	0,06
Czech Republic	€ 145.191.150,00	0,95	€ 4.516.472,00	0,03
Estonia	€ 12.602.242,88	0,85	€ 940.370,00	0,06
France	€ 1.993.902.870,99	0,87	€ 120.785.954,00	0,05
Germany	€ 2.223.275.112,68	0,73	€ 79.183.670,00	0,03
Hungary	€ 76.829.598,40	0,95	€ 4.442.580,00	0,06
Ireland	€ 94.786.778,58	0,51	€ 4.944.864,00	0,03
Italy	€ 379.845.073,54	0,25	€ 75.219.746,00	0,05
Latvia	€ 9.154.231,80	0,57	€ 835.814,00	0,05
Portugal*	€ 279.797.930,10	1,55		-
Romania	€ 288.235.319,98	2,21	€ 4.779.500,00	0,04
Slovakia	€ 83.098.159,00	1,17	€ 2.356.772,00	0,03
Slovenia	€ 44.787.500,00	1,25	€ 3.358.000,00	0,09
Min	€ 9.154.231,80	0,25	€ 835.814,00	0,03
Max	€ 2.223.275.112,68	2,21	€ 120.785.954,00	0,09
Source: EDITH - Centro Nazionale Trapianti and Eurostat				

The limitation of Table 33 is that it does not reflect the real access to transplantation for all patients with end-stage kidney disease (ESKD). As a matter of a fact, some patients with ESKD are not eligible for transplantation, often due to age limits or comorbidities that prevent them to be enrolled in transplant waiting lists.

In the light of above-mentioned results and considerations and respecting all possible limitations, we can conclude that this attempt for international comparison is the first of this kind, and that this pilot effort to collect data from different countries offers room for further considerations and subsequent due actions at policy-making level.

IV.8. References

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IV.9. Annex

Annex 1: Data sources

Country	Population data	Incidence	Prevalence	Transplantation rate	Waitlist
Belgium	midyear 2016, Eurostat	ERA-EDTA Registry[1]	ERA-EDTA Registry[1]	Transplant Newsletter	Transplant Newsletter
Bulgaria	midyear 2016, Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	Transplant Newsletter	Transplant Newsletter
Croatia	midyear 2016, Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	Transplant Newsletter	Transplant Newsletter
Czech Republic	midyear 2016, Eurostat	ERA-EDTA Registry[2,3]	ERA-EDTA Registry	Transplant Newsletter	Transplant Newsletter
Estonia	midyear 2016, Eurostat	ERA-EDTA Registry[4]	ERA-EDTA Registry	Transplant Newsletter	Transplant Newsletter
France	midyear 2016, Eurostat	ERA-EDTA Registry[4]	ERA-EDTA Registry	Transplant Newsletter	Transplant Newsletter
Germany	midyear 2016, Eurostat	GBA report[2, 5] Eurotransplant Annual report	GBA report[2]	Transplant Newsletter	Transplant Newsletter
Hungary	midyear 2016, Eurostat	USRDS[6]	USRDS	Transplant Newsletter	Transplant Newsletter
Ireland	midyear 2016, Eurostat	not available	National Renal Office, Dublin	Transplant Newsletter	Transplant Newsletter
Italy	midyear 2016, Eurostat	ERA-EDTA Registry[7]	ERA-EDTA Registry[7]	Transplant Newsletter	Transplant Newsletter
Latvia	midyear 2016, Eurostat	ERA-EDTA Registry	ERA-EDTA Registry	Transplant Newsletter	Transplant Newsletter
Portugal	midyear 2016, Eurostat	ERA-EDTA Registry[8]	ERA-EDTA Registry	Transplant Newsletter	Transplant Newsletter
Romania	midyear 2016, Eurostat	ERA-EDTA Registry	ERA-EDTA Registry[9]	Transplant Newsletter	Transplant Newsletter
Slovakia	midyear 2016, Eurostat	ERA-EDTA Registry[2]	USRDS	Transplant Newsletter	Transplant Newsletter
Slovenia	midyear 2016, Eurostat	Eurotransplant Annual Report	survey Vanholder[2]	Transplant Newsletter	Transplant Newsletter

1 Patients younger than 20 years of age are not reported
2 Incidence data for dialysis patients only
3 Incidence data for day 1 instead of day 91
4 Day 91 incidence data are estimated
5 Unknown if incidence data are for day 1 or day 91
6 Only RRT incidence is included
7 Based on 6 of 20 regions
8 Only pre-emptive transplantations (at day 1) are included
9 The overall prevalence of RRT is underestimated by approximately 3% due to an estimated 30% underreporting of patients living on a functioning graft

Country	Specifications/ remarks
Belgium	Patients younger than 20 years of age are not reported
Bulgaria	
Croatia	
Czech Republic	No incident counts for day 91, so counts for day 1 used
Denmark	No distinction made between between HD and HDF
Estonia	The incident counts at day 91 are estimated (see methods)
France	The incident counts at day 91 are estimated (see methods)
Germany	Data via Eurotransplant, GBA Jahresbericht, Transplant Observatory Prevalence numbers: only dialysis patients
Hungary	Incidence and prevalence data via USRDS data report
Iceland	
Ireland	Prevalence data via National Renal Office Transplant rates via Newsletter Transplant
Italy	Incidence and prevalence numbers and rates based on 6 of 20 regions from Italy Transplant and waitlist numbers and rates via Newsletter Transplant based on complete country
Latvia	
Portugal	Only pre-emptive transplantation (at day 1) are included
Romania	The overall prevalence of RRT is underestimated by approximately 3% due to an estimated 30% underreporting of patients living on a functioning graft The transplantation activity reflects 70% of the total transplantation activity in the country, because there is an underreporting of preemptive transplantation
Slovenia	Incidence of transplantation via (pre-emptive Tx) via Eurotransplant https://www.eurotransplant.org/cms/mediaobject.php?file=Eurotransplant+JV+PDF.pdf page 71, table 5.3 (iii) Transplant rates via Newsletter Transplant

Annex 2: List of countries answering to the questionnaire

This table contains the people responding to the questionnaire circulated by CNT and that have validated the information contained in it.

Country	Organisation	Name of rappresentative	Role/position of rappresentative
Belgium	National Institute for Health Insurance	Legrand Jean	Responsible health care insurance
Bulgaria	Bulgarian Executive Agency for Transplantation	Dr. Maryana Simeonova	Executive Director
Croatia	Croatian Health Insurance Fund Ministry of Health	Dubravka Pezelj Duliba, Mirela Bušić, Stela Živčić Ćosić	
Czech Republic	Ministry of Health	Mr. Tomas Troch	Analyst
Estonia	Estonian Health Insurance Fund	Malle Avarsoo,	Head specialist, specialized care benefit package,
France	Agence de la biomédecine	Couchoud Cécile	Epidemiologist Coordination REIN registry
Germany	Federal Ministry of Health DSO	Bettina Ruoff-Ruellich Marie Lingemann, Axel Rahmel	
Greece	EOM - national competent authority	Konstantina Tsaroucha	
Hungary	Hungarian National Blood Transfusion Service, Organ coordination Office	Dr. Sándor Mihály	Director
Ireland	Health Service Executive	Professor Liam Plant	National Clinical Director, National Renal Office
Italy	CENSIS Foundation Centro Nazionale Trapianti	Maria Concetta Vaccaro Vito Sparacino	National Experts National Experts
Latvia	Latvian Transplantation centre	Jānis Jušinskis	Head of the Latvian Transplantation centre
Lithuania	National Transplant Bureau under the Ministry of Health	Audronė Būziuvienė Vita Petronytė	Acting Director, Deputy Director Senior specialist
Malta	Ministry of Health	Patrcia Galea	Director- Healthcare standards
Netherlands	Baxter	Melanie van Riemsdijk	Head of Market Access Netherlands
Portugal	ACSS IPST	Alexandra Cerqueira Ana Franca	Senior Technician Director General
Romania	National Transplant Agency	Luscalov Dan Adrian	Councilor/Regional Transplant Coordinator
Slovakia	Všeobecná zdravotná poisťovňa Ministry of Health	Dominika Holubjakova Blahová Nataša	Data Analyst EU Affairs Department International Relations and EU Affairs
Slovenia	University Mecial Centre Ljubljana	Miha Arnol; Jakob Gubenšek	Head – Centre of kidney transplantation Head of dialysis centre
England	NHS England (NHSE)	Jon Gulliver	Lead Commissioner, Renal Services, NHSE

Country	Organisation	Name of rappresentative	Role/position of rappresentative
Northern Ireland	Department of Health Northern Ireland (DoH) Health and Social Care Board (HSCB)	Joe Magee John Russell	Head of Policy and Legislation Branch, Secondary Care Directorate Senior Accountant
Scotland	Scottish Government	Pamela Niven OBE	Programme Manager for Organ Donation and Transplantation

Annex 3: Overview of costs deriving from the analysed literature and the answer to EDITH questionnaire

Country	Source	Reference year	Notes	Dialyses - costs per year						Cost of Transplantation		
				HD	CentreHD	HomeHD	PD	CAPD	APD	Tx	DD	LD
NL	Monhen et al. 2019	**2001-2014**	average annual healthcare costs		92.616 €	87.051 €		77.566 €	89.932 €		99.450 €	73.376 €
DK	Jensen et al. 2014	**2012**	cost per quality-adjusted life year		48.118 €	22.252 €		13.957 €			25.697 €	31.467 €
UK	NHSBT 2009	**2009**	indicative costs	39.457 €				19.728 €		19.165 €		
UK	Li et al. 2015	**2003-2006**	hypothetical average over a 4 year period	41.392 €			34.728 €			30.264 €		
UK	Baboolal et al. 2008	**2009**			39.471 €	23.401 €		17.547 €	24.405 €			
SE	Olsson, Olsson 2016		industrial study		81.807 €	57.126 €		64.442 €				
SE	Eriksson 2016	**2009**	mean annual cost	87.600 €			58.600 €					
SI	Salonen et al. 2003	**1991-1996**			48.131 €			43.919 €			40.354 €	
FI	Malmström et al. 2008	**2004**			39.781 €	38.477 €						
ES	Villa et al. 2011	**2010**	Average prevalence costs	37.968 €				25.826 €			38.313 €	
FR	ABM/HAS 2012	**2012**	average cost over 15 years	58.686 €								
IT	Vaccaro, Sopranzi	**2017**	medical direct costs and nonmedical in 2 hospitals direct costs	33.804 €				21.977 €	32.007 €			
IT	Tediosi et al. 2008	**1994-1996**						18.927 €	33.099 €			
Belgium	EDITH questionnaire	**2016**		45.604 €			52.925 €	52.925 €	52.925 €		26.196 €	13.977 €
Bulgaria	EDITH questionnaire	**2016**									23.936 €	16.873 €
Croatia	EDITH questionnaire	**2016**		19.894 €			19.389 €	5.449 €	33.328 €		8.632 €	8.632 €
Czech Republic	EDITH questionnaire	**2016**		20.280 €			40.150 €	23.725 €	56.575 €		8.400 €	8.400 €
Estonia	EDITH questionnaire	**2016**		33.206 €			22.046 €	22.046 €	22.046 €		14.362 €	14.015 €
France	EDITH questionnaire	**2016**		38.823 €			32.203 €	28.192 €	36.215 €		34.618 €	27.241 €
Germany	EDITH questionnaire	**2016**		28.524 €			30.913 €	29.433 €	32.389 €		36.086 €	32.959 €
Hungary	EDITH questionnaire	**2016**		10.121 €			23.681 €	23.681 €	23.681 €		12.990 €	12.990 €
Ireland	EDITH questionnaire	**2016**		46.592 €			37.500 €	35.000 €	40.000 €		27.287 €	27.287 €
Italy	EDITH questionnaire	**2016**		29.206 €			18.473 €	16.965 €	19.980 €		33.162 €	33.162 €
Latvia	EDITH questionnaire	**2016**		17.147 €			22.995 €	-	-		14.016 €	14.016 €
Portugal	EDITH questionnaire	**2016**		23.435 €			3.357 €	3.357 €	3.357 €		2.285 €	2.285 €
Romania	EDITH questionnaire	**2016**		26.000 €			12.166 €	12.166 €	-		15.000 €	15.000 €
Slovakia	EDITH questionnaire	**2016**		24.765 €			21.170 €	19.345 €	22.995 €		8.188 €	8.770 €
Slovenia	EDITH questionnaire	**2016**		31.191 €			35.925 €	30.379 €	41.471 €		73.000 €	73.000 €
			Maximum	87.600 €	92.616 €	87.051 €	58.600 €	77.566 €	89.932 €	30.264 €	99.450 €	73.376 €
			Minimum	10.121 €	39.471 €	22.252 €	3.357 €	3.357 €	3.357 €	19.165 €	2.285 €	2.285 €
			Mean	**34.685 €**	**58.321 €**	**45.661 €**	**29.139 €**	**27.571 €**	**35.275 €**	**24.714 €**	**28.525 €**	**24.321 €**
			Median	**32.199 €**	**48.125 €**	**38.477 €**	**27.297 €**	**22.864 €**	**32.744 €**	**24.714 €**	**25.697 €**	**15.000 €**

Annex 4: Deceased donor kidney Transplant Costs (€)

	Tariff/DRG	Breakdown of reported tariffs by donation process phase					Breakdown of reported tariffs by recipient management phase					
		Death declaration procedure	Donor assessment procedure	deceased donor management	Donor kidney retrieval		recipient assessment	recipient wl manteinance	Surgical intervention	Recipient hospital stay after surgical intervention	Post transplant immunosuppressive therapy	Patient follow-up
Belgium	€ 26.196			€ 1.006,00	€ 1.323,00				€ 2.375,00			
Croatia	€ 8.632				€ 4.538,00				€ 8.631,00			
Czech Republic	€ 8.400			€ 1.446,00	€ 260,00				€ 8.400,00			
Estonia	€ 14.362			€ 4.769,00					€ 9.593,00		€ 3.746,00	€ 3.057,00
France	€ 34.618			€ 9.172,00	€ 5.182,00		€ 5.264,00		€ 15.000,00			€ 1.128,00
Germany	€ 36.086	*/**	*/**	*/**	€ 3.753,00		€ 3.239,00		€ 18.365,00	***		
Hungary	€ 12.990											
Ireland	€ 27.287											
Italy	€ 33.162				€ 2.482,00				€ 33.162,00			
Latvia	€ 14.016											
Portugal	€ 2.285			€ 5.000,00	€ 7.500,00				€ 6.239,97			
Romania	€ 15.000			€ 3.000,00					€ 15.000,00		€ 500,00	€ 400,00
Slovakia	€ 8.188				€ 1.285,00				€ .481,18		€ 6.872,00	€ 5.700,00
Slovenia	€ 73.000								€ 14.500,00		€ 4.600,00	€ 4.900,00
Min	€ 2.285	-	-	€ 1.006	€ 260		€ 3.239	--	€ 1.325	-	€ 230	€ 400
Max	€ 73.000	-	-	€ 13.835	€ 7.500		€ 3.239	-	€ 33.162	-	€ 14.706	€ 6.952,97

Source: EDITH – Centro Nazionale Trapianti

Note: the countries participating to the study were asked to declare whether the amount provided as tariff or DRG for deceased donor kidney transplantation included all the steps related to the donor and recipient costs, or not. This table summarizes the collected answers highlighting in green the cost declared as included in the Tariff/DRG column costs and in red those not included.

Annex 5: Living donor kidney Transplant costs (€)

	Tariff/DRG	Breakdown of reported tariffs by donation process phase					Breakdown of reported tariffs by living donor recipient management phase					
		Living donor assessment	Living donor kidney retrieval	Living donor hospital stay	Living donor follow-wp		Living recipient assessment	Recipient wl maintennance	Surgical intervention	Recipient hospital stay after sur.intervention	Post transplant immunosuppressive treatments	Patient follow-up
Belgium	€ 13.977,00	€ 2.983,00	€ 715,00		€ 244,00				€ 2.375,00			
Croatia	€ 8.631,87		€ 4.538,00						€ 8.631,87			
Czech Republic	€ 8.400,00								€ 8.400,00			
Estonia	€ 14.015,00		€ 4.423,00						€ 9.593,00		€ 3.746,00	€ 3.057,00
France	€ 27.241,00	€ 4.584,00	€ 4.313,00		€ 3.344,00				€ 15.000,00			€ 1.128,00
Germany	€ 32.959,00	€ 2.850,00	€ 8.505,00				€ 3.239,00		€ 18.365,00			
Hungary	€ 12.990,00											
Ireland	€ 27.287,00	€ 5.030,00										
Italy	€ 33.162,00		€ 7.137,00						€ 33.162,00			
Latvia	€ 14.016,00		€ 887,00									
Portugal	€ 2.285,00	€ 548,68	€ 5.000,00						€ 6.239,97			
Romania	€ 15.000,00				€ 400,00				€ 15.000,00		€ 500,00	
Slovakia	€ 8.770,00		€ 1.726,08						€ 4.481,18		€ 6.872,00	€ 5.700,00
Slovenia	€ 73.000,00	€ 15.100,00	€ 9.000,00		€ 500,00				€ 14.500,00		€ 4.600,00	€ 4.900,00
Min	€ 2.285	€ 365	€ 715	-	€ 88		€ 3.239	-	€ 1.325	-	€ 230	€ 1.128,00
Max	€ 73.000	€ 15.100	€ 9.000	-	€ 9.612		€ 3.239	-	€ 33.162	-	€ 14.706,00	€ 6.952,97

Source: EDITH – Centro Nazionale Trapianti

Note: the countries participating to the study were asked to declare whether the amount provided as tariff or DRG for deceased donor kidney transplantation included all the steps related to the donor and recipient costs, or not. This table summarizes the collected answers highlighting in green the cost declared as included in the Tariff/DRG column costs and in red those not included.

Annex 6: Acknowledgements

The Italian National Transplant Centre pays special thanks to Dr Maria Concetta Vaccaro and Dr Vittoria Coletta of CENSIS Foundation for their outstanding contribution to the work conducted for this analysis. We thank Dr Cecile Couchoud for sharing her insight and experience in the field and the French Agence de la biomédecine for being collaborative partner in the EDITH project. We are grateful to Vito Sparacino, Niels Voets, Valentina Caramia, Margherita Gentile, Alessandro Nanni Costa and all the colleagues of the European Competent authorities who supported this work in the last two years.

European Transplant Registries

Existing registries

V. Report on outcomes of questionnaire about willingness to participate among EU Member States (D5.1)

Responsible partner: NTS
Document. EDITH_D5_1_Report on the current activities in living donor registration of 10.10.2018

V.1. Introduction

This report is the first planned deliverable of EDITH Work Package 5 (WP5). EDITH stands for The Effect of Differing Kidney Disease Treatment Modalities and Organ Donation and Transplantation Practices on Health Expenditure and Patient Outcomes. This project, which is co-financed by the European Commission, aims to assess the different treatment modalities for End Stage Kidney Disease (ESKD) currently used throughout the EU and to examine the factors that influence the different treatment choices. EDITH supports the establishment of follow-up registries in order to collect crucial information to increase the quality and safety of living donors as well as all transplant recipients. EDITH WP5 will build upon the recommendations of the former EU Joint Action "Achieving Comprehensive Coordination in Organ Donation" (ACCORD).

Work package 5 of EDITH is aimed at the establishment of a European Living Donor follow-up Registry (ELDR). Furthermore, EDITH WP5 will provide support to EU Member States that are building, or adapting their national living donor registries in order to enable them to share information with the ELDR.

The rationale for EDITH WP5 is to collect crucial information, on a (supra)national level, to increase the quality and safety of living kidney donors.

V.1.1 Living donation

Living donation is an important source of available kidneys for organ transplantation. In many countries living donation has been introduced to fill the gap between the demand and availability of organs for transplantation. Moreover, the transplant outcomes in recipients of living donor kidneys in comparison with a deceased donor transplantation are superior. In some countries the balance between deceased and living donor organs has changed, maybe partly because of successfully functioning living donor programs. Worldwide the proportion of living donations as donor source for kidney transplantation is approximately 40%.

V.1.2 Living donor follow-up registration

In order to protect current and future living donors, a good follow-up registration and analysis is very important. Although many publications, suggest that donors can donate a kidney with minimal health risks, this usually refers to short-term risks, while long term consequences remain unclear. In fact, recently, two matched cohort studies from the USA and Norway have raised some concerns with regard to the long-term safety of living kidney donation [Muzaale 2014, Mjoen 2014]. Furthermore, earlier research results might not apply to new donors when donor selection criteria are changed (e.g. when older and less healthy donors are accepted for kidney donation). The general assumption behind living kidney donor programs is that (absolute) long-term health risks are acceptable, but long-term follow-up registries are still very rare. Adequate sample sizes and long-term follow-up duration are needed to be able to answer research questions with regard to the detection of risks attributable to kidney donation. Therefore, to be able to fully answer questions regarding long-term safety, it is desirable to establish a European Living Donor Registry.

V.1.3 European living donor registry (ELDR)

The advantage of a European living donor registry is the scale of the registry. With an ELDR it would be much easier to answer questions about long-term risks for living donation, where this would be a challenge for country registries (especially for small countries, or countries starting a living donor program). Furthermore, results from different countries could be compared. If this benchmark shows any differences in long-term outcomes, best practice analysis might lead to better general protection and/or selection and/or care of living donors in Europe.

V.2. Inventory on current living donor registration activity and willingness to participate in an ELDR

In order to start WP5, we needed insight in the current practices on living donor registration and to make an inventory on which MS are willing to participate (and on what conditions) in an ELDR.

V.2.1 Methods

After approval by the EDITH Steering Committee, in June 2017 a questionnaire was sent to all EU Member States to investigate their current experience with living donation and living donor follow-up registration, as well as their ability and willingness to participate in an ELDR. The questionnaire is attached to this report as Annex 1.

The questionnaire was divided into 5 focus areas:

- General information
- Actual information on national living donor follow-up registries
- Willingness to participate in a European Living Kidney Donor Follow-up Registry
- Detailed specification on the content of the database
- Detailed information of the local registries (for countries that have no national registry and do not intend to develop one)

V.2.2 Outcomes

In this paragraph a summary of the completed questionnaires is given, divided by the focus areas mentioned in paragraph 2.1.

General information

- A total of 24 of the 28 EU MS completed and returned the questionnaire. 3 MS (Denmark, Malta and Sweden) have not yet completed the questionnaire;
- Denmark and Sweden register their living donor patients in Scandiatransplant and have indicated that they would need to discuss participation in EDITH with their executive boards and relevant health authorities before providing any answers. There has been a board meeting with Scandiatransplant and a meeting with the Competent Authorities of the Nordic countries in the beginning of October; the conclusion from these meetings was that the Scandinavian countries (among which EU Member States Denmark, Sweden and Finland) are for the time being not willing to participate in EDITH, but will follow it closely. Sweden is not willing to participate because they have to make a national registry, implement this, and validate the amount of data and completeness first. Also Scandiatransplant prefers to use time and resources on getting better compliance with use of the Scandiatransplant Living Donor Registry. Nevertheless Scandiatransplant is prepared for future collaboration as overall the variables and follow-up frequencies match quite well with EDITH (except for religion/ethnicity) according to the representative of Scandiatransplant.

- Malta also performs follow-up for living donors, but the data are not comprehensive and there currently is no registry. Willingness to complete the questionnaire was expressed, but this was not returned yet. From 1 MS (Cyprus) no reaction was received until now.

Actual information on national living donor follow-up registries

All respondents (24 MS) reported having experience with living donation, but the number of living donor transplant per year varies over the countries:

Table 34: Respondents with experience in living donation

Living donor transplants per year	Number of respondents (N=24)
1-10	5 (Estonia, Latvia, Lithuania, Luxembourg, Slovenia)
10-50	9 (Bulgaria, Croatia, Czech Republic, Finland, Greece, Hungary, Poland, Republic of Ireland, Romania)
50-200	4 (Austria, Belgium, Portugal, Slovak Republic)
>200	6 (France, Germany, Italy, Netherlands, Spain, United Kingdom)

Next to the number of yearly living donor transplants, also the relative use of living donors versus deceased donors varies in European countries, as can be illustrated by the figures from the Newsletter Transplant 2017 (Figures 35 and 36):

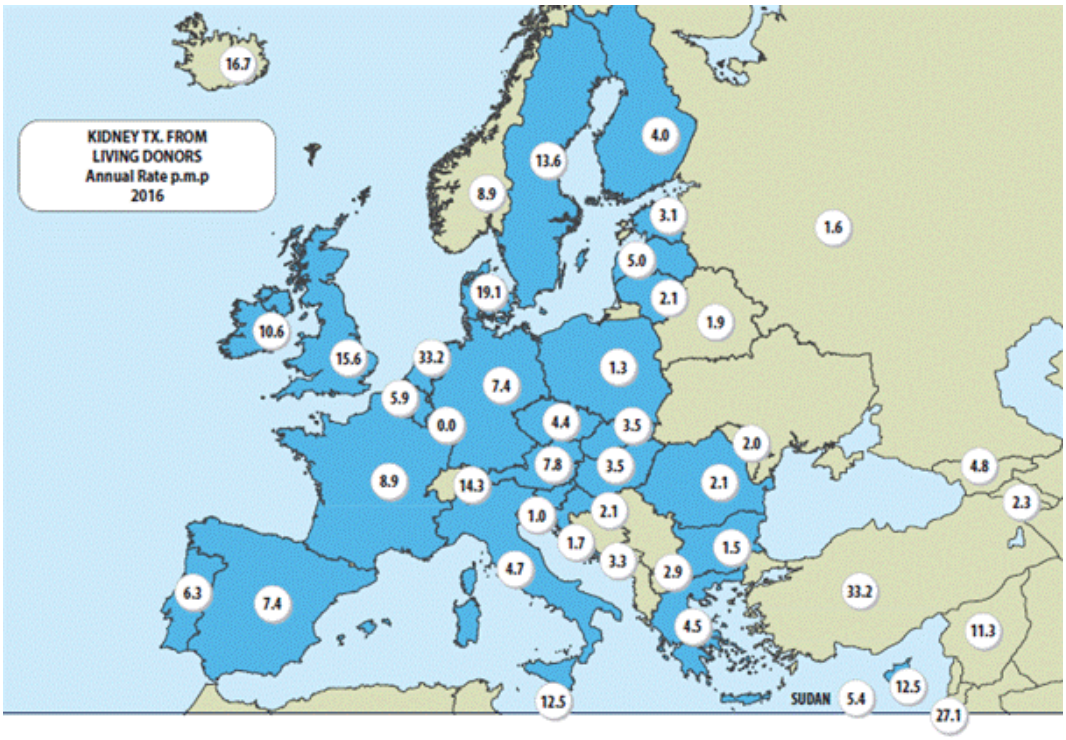

Figure 35: Kidney transplants from living kidney donors. Annual rate pmp 2016

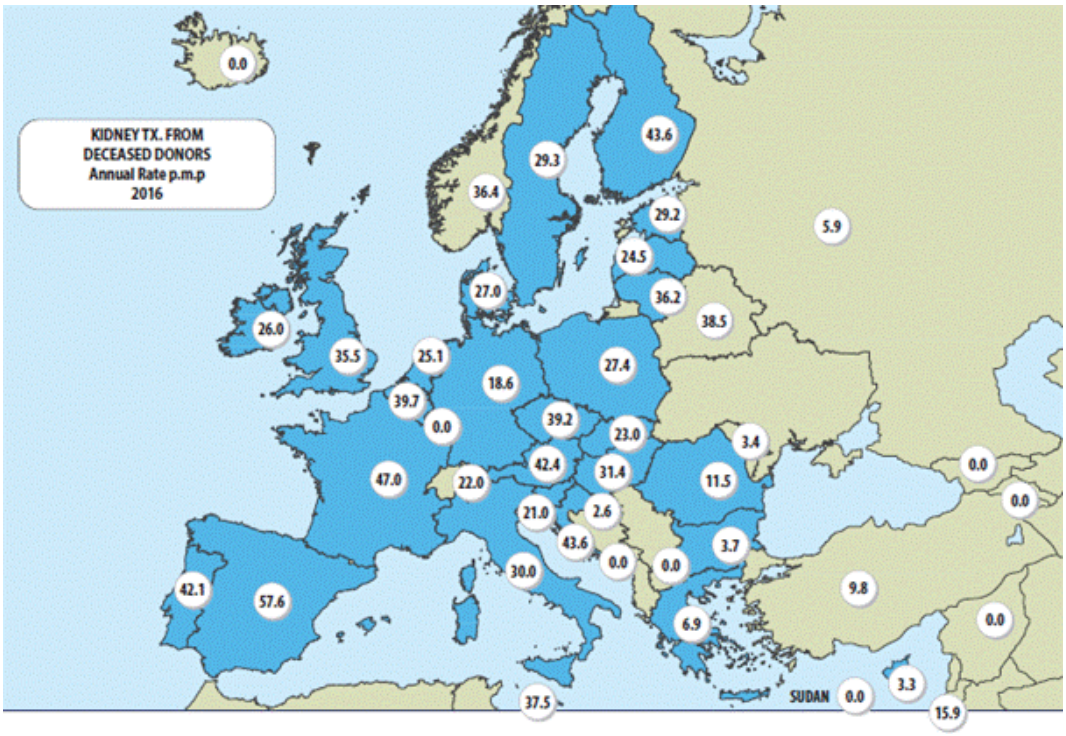

Figure 36: Kidney transplants from deceased donors. Annual rate pmp 2016

The questionnaire results further provide insight in current experience with living kidney donor follow-up registration among EU countries (Table 35, Figure 37):

Table 35: Respondents with experience in living kidney donor registries

Living donor follow-up registration	**Living donor follow-up registration**
National system	5 (Finland, France, Poland, Republic of Ireland, United Kingdom)
National and local systems	5 (Hungary, Italy, Netherlands, Slovak Republic, Spain*)
Local systems	11 (Belgium, Croatia, Czech Republic**, Estonia, Germany, Greece, Latvia, Lithuania***, Portugal, Romania, Slovenia)
No registration (yet)	3 (Austria****, Bulgaria, Luxembourg)
*Spain has an official National registry that receives information from transplant centers except in the case of two regions, that report data from their regional registries **Czech Republic has a local system in Prague, which is covering approximately 95% of all national data ***Lithuania has a local system in Vilnius, covering 98% of all living donors **** Austria recently started with local registries	

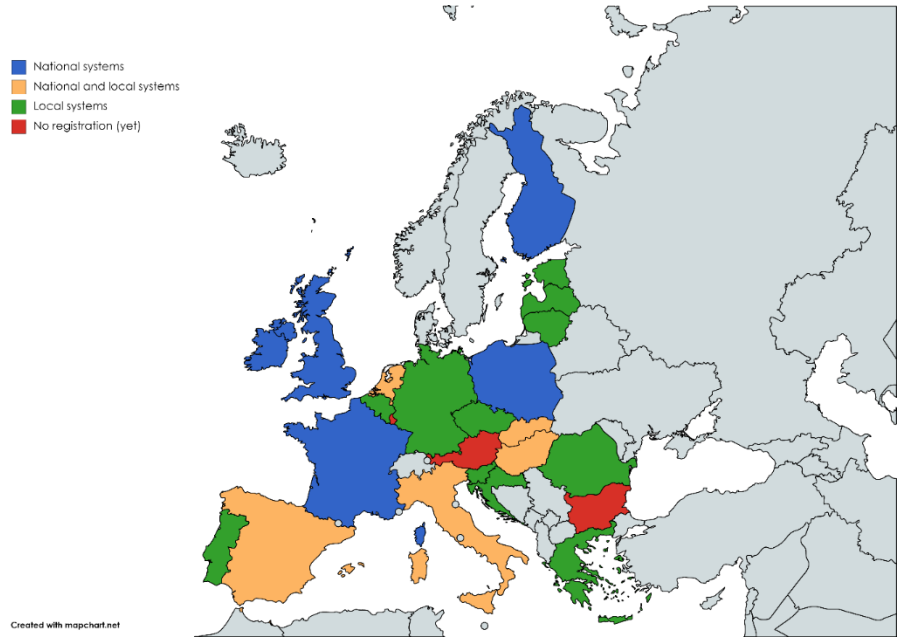

Figure 37: Overview living donor registrations in EU countries

*National registries (N=10)

The starting dates of the national registries lie between 1/1/1996 and 14/11/2016 and all national registries are digital registries (i.e. a database or electronic file); most databases (7/10) are Oracle.

Additionally, 6 of the 14 MS that do not have a national registry yet (Austria and Bulgaria without any registration and Germany, Greece, Portugal, Romania currently with local registries only) reported that they are planning to start a national registry:

- Austria (currently working with local registries) stated to need help from the EDITH project to raise the awareness to the relevant persons (e.g. on political level) that a follow-up registry is necessary and that every EU MS needs to have one. However recently, based on Austrian law, living kidney donor follow-up transplant centres are obliged to establish an individual follow-up plan.
- Bulgaria (currently no registry) needs time to collect the available data from hospitals and to work on the establishment of a national program, providing an organizational model and financing. Bulgaria will follow ELDR specifications when building a national living donor registry (intention to establish this soon, although no starting date is mentioned yet), although also some deviations at data-level were mentioned.
- The national registry for Germany (only local registries) is currently under development (planned realization beginning 2019) and it is uncertain at this moment whether living donor registration will be a part of it. Furthermore, several remarks were made with regard to the ELDR-dataset.
- Greece (local registries) is planning to start a national registry, but a date for this is not known yet
- In Portugal (local registries) a national registry is being implemented and will gather national information on living kidney donor follow-up
- Romania (local registries) is planning a national registry (intended starting date 1/1/2018)

The number of hospitals/centres that share data in the national registries varies between 4 and 40. The Republic of Ireland has only one living donor transplant centre, data is collected from other hospitals for follow up, but would only be shared in the form of an annual report.

The follow-up frequency is only limited to the one-year follow-up in 2 countries (Hungary, Slovak Republic). Most often there is yearly follow-up in the first years after transplantation; thereafter the frequency in most country decreases e.g. till one follow-up for every 2 or 5 year. This indicates that the proposed follow-up frequency in EDITH (immediately after donation, 3 months, 1 year, 5 year and further every 5 year (unlimited)), should be no problem for the majority of the countries. United Kingdom and Italy will not be able to change the follow-up frequency of the national registry, but their follow-up frequencies are not so much different from the proposed ELDR follow-up frequency. Most deviations indicate more frequent follow-up collection, and most countries with a more limited follow-up (like Hungary and Slovak Republic) answered to be able to elaborate the frequency in their country. On the other hand two countries with no national registry yet (Bulgaria and Germany), foresee that deviations from the preferred frequency in their country will be difficult.

Of the 10 countries with a national living donor registry, 5 declared to already use a consent form for living donors to express their approval for registration (Italy, Netherlands, Slovak Republic, Spain, United Kingdom). In Poland the registry is required by law, in France approval is only obtained by information, and in the Republic of Ireland there is no consent form, but all donors consent that their information is recorded for audit purposes. Further Hungary and Finland don't currently use a consent form.

The estimated completeness varies a lot, generally with a lower completeness for the longer follow-up intervals (>one-year follow-up is approximately 50% in most MS). Nevertheless, it's hard to compare the completeness as the follow-up frequencies and definitions for completeness might differ between the countries.

Requests for information are most frequently granted by an officer of the national organization who is in charge of the registry or a scientific committee with persons from in- and/or outside the registry.

Willingness to participate in a European Living Kidney Donor Follow-up Registry

Table 36: Willingness to participate in a European Living Kidney Donor Follow-up Registry

Willingness and ability to participate	**Number of questionnaire respondents (N=24)**
Yes, willing and able	13 (France, Greece, Hungary, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Republic of Ireland, Romania, Spain, United Kingdom)
Willing but not able yet	6 (Bulgaria, Croatia, Czech Republic, Germany, Slovak Republic, Slovenia)
No, not willing	3 (Belgium, Estonia, Finland)
Unknown (not answered in questionnaire)	2 (Austria, Luxembourg)

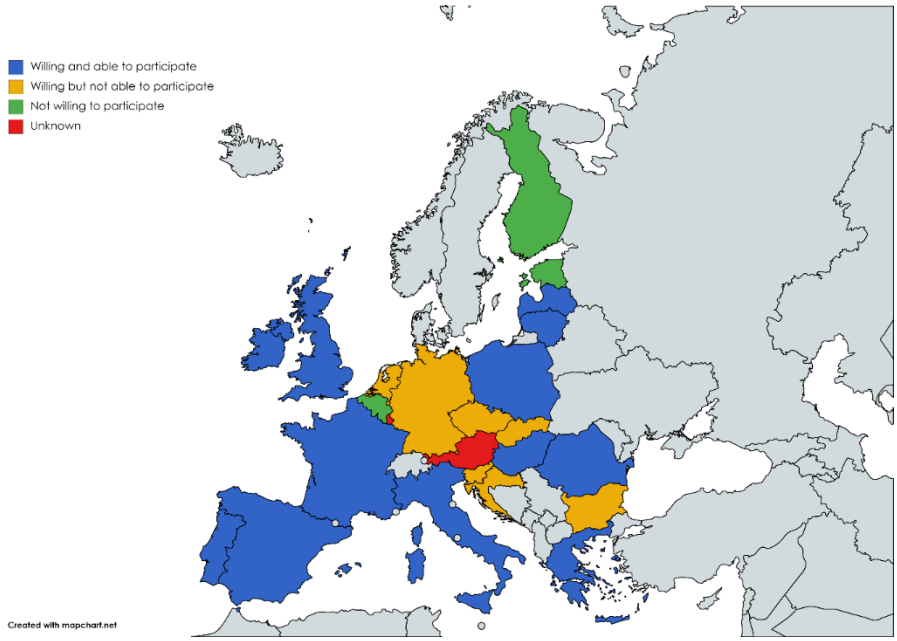

Figure 38: Overview EU countries and willingness/ability to participate in an ELDR

13 countries are willing and able to cooperate in an ELDR:

- France, currently has a national system; will be able to deliver all data-elements and frequencies preferably via file upload; no help needed
- Greece, currently has local systems; will be able to deliver all data elements and frequencies preferably via direct data entry (for file upload it is mentioned that for post living kidney donors a unique identification code is missing); help from WP project organization is needed, but not further specified
- Hungary, currently has both national and local systems, will be able to deliver all data-elements and frequencies preferably via file upload; no help needed
- Italy, currently has both national and local systems (there is one national registry managed by the Italian National Transplant Centre in Rome; part of the information and data are originally collected regionally or locally and merged in the national registry), prefers file upload, but will not be able to deliver all data elements and frequencies (a number of items is missing and will not be added, also one item differs in definition, and will not be changed, further Italy has yearly follow-up, this would mean that follow-up immediately post donation and 3 month follow-up is missing, but this cannot be elaborated due to additional work overload; no help needed
- Latvia, currently has local systems; will be able to deliver all data elements and frequencies preferably via direct data entry; help from WP project organization is possibly needed at the start of ELDR data delivery. Note: transplant centre re-organization on short-term might (temporarily) impact participation possibilities.
- Lithuania, currently has local systems; will be able to deliver all data elements and frequencies preferably via direct data entry; technical and organizational advice from WP project organization is needed
- Netherlands, currently has both national and local systems; will be able to deliver all data elements and frequencies preferably via file upload; no help needed
- Poland, currently has a national system; will be able to deliver all data elements and frequencies preferably via file upload (currently only up to 10 years follow-up based on legal regulations, but this will be elaborated to longer follow-up periods); no help needed

- Portugal currently has local systems, but a national registry is being implemented and will gather national information on living kidney donor follow-up; will be able to deliver all data elements and frequencies preferably via direct data entry; no help is needed
- Republic of Ireland, currently has a national system; will be able to deliver all data elements and frequencies preferably via file upload; no help needed
- Romania, currently has local systems; will be able to deliver all data elements and frequencies preferably via direct data entry; help from WP project organization is possibly needed, depending on the type of the registry
- Spain, currently has a national system that receives information from transplant centers and two regional registries. They will be able to deliver all data elements and frequencies preferably via file upload; the follow-up frequency is 3 months, 1, 2, 4, 6, 8, 10 years and further every 5 years. Information immediately post donation is available only before discharge; no help needed
- United Kingdom, currently has a national system; prefers file upload, but will not be able to deliver all data elements and frequencies; in current data collection forms some items are missing and there are no plans to add additional variables to the forms; the follow-up frequency is 1, 2, 5 and further every 5 years, so information immediately post donation and at 3 months are missing, but the current schedule cannot be altered; no help needed

There were 6 countries willing but not able yet, 3 not willing (yet) and 2 indecisive.

Reasons for the 6 MS that are willing, but not able (yet) are:

- At the moment time is needed to collect the available data from hospitals and to establish a national program providing an organizational model and financing (Bulgaria); - Lack of administration resources and technical capacities (Croatia);
- Coverage of the local registry is 95%, rest is in other centres (Czech Republic);
- Cooperation is dependent on the realization of the National Registry, which is currently under development (Germany);
- Differences in databases, although this can be solved in time (Slovak Republic);
- Would need additional administrative support (Slovenia).

Note: these reasons give insight in possible hurdles that have to be addressed in WP5; they don't automatically imply that cooperation isn't possible.

Indecisive answers: Austria didn't answer this question yet, because "Participation depends on decision of the applicant of the project", and Luxembourg replied with "We bring a national Organ Donation and Transplantation Agency into being".

Help from the project (technical or organizational advice to help realizing data delivery to the ELDR) would be appreciated by 3 of the 6 MS that are willing but not able yet to cooperate in the ELDR:

- Croatia would need technical help;
- Czech Republic would need technical help;
- Slovak Republic would need technical specification of different or missing fields in database.

So 3 out of the 6 countries that are willing, but not able (yet) to participate, could eventually participate in the ELDR after receiving help by the WP5 project organization. The other 3 countries don't see possibilities yet to deliver information to the ELDR despite eventual help, mainly because the issues they have raised are organizational issues that should be solved on a national level (Bulgaria, Germany, Slovenia).

Reasons for the 3 MS not willing to participate:

- The reason for Belgium is the fact that first agreement of national council and collaboration with Eurotransplant is needed; NOTE: this reason (first part) could also be mentioned as "willing, but not able, to participate yet". This should be arranged by the MS as soon as possible, at least before the ELDR development is finished and actual data delivery to the ELDR starts.
- For Estonia the reason is that there is only one transplantation centre with low living donor transplant activity, whereby there is a complete picture and data on all living donors already. There is no need or plan to have a special register on living donors, and there is no believe in an all European register, in its possibility and rationale;
- For Finland the reason is the fact that they still have to work on improvement of their local registry, the amount of data and completeness. The first and last explanation suggest that these reasons might be solved in time, so willingness for participation might be reconsidered in a later stage.

12 of the 19 countries that are willing to participate (with or without eventual help from the project) will be able to deliver the complete dataset for all possible follow-up frequencies in time (Croatia, France, Greece, Hungary, Latvia, Lithuania, Netherlands, Poland, Portugal, Republic of Ireland, Romania, Slovenia). In Spain every follow-up except the 5-year follow-up, as 4 and 6 year follow-ups are collected. The 5 countries that are not able to do so (Bulgaria, Czech Republic, Italy, Slovak Republic, United Kingdom) have mentioned possible discrepancies; these are summed in section D. From 1 country (Germany) it is unknown whether it is/will be able to deliver the complete dataset.

The preferred method of data delivery has been filled in by the countries that are willing to participate in an ELDR. The countries that already have a national system prefer file upload. The countries with local registries generally prefer direct data entry; one exception is Germany that currently has only local registries, but is only willing to participate from a national registry, and then also prefers file upload. Greece is also planning to start a national registry; once this is implemented, Greece would also prefer file upload instead of direct data entry.

Most countries (9/10) that prefer file upload are able to make necessary adaptations in their national registries to comply with the ELDR dataset. One of them (Greece) mentioned that they will not be able to make the necessary adaptations and code transformations (yet) to realize this. In fact, this only applies to the historical data; they just recently started with giving unique identification codes to their living donors and this unique donor identifier is lacking for past living kidney donors. Greece mentioned that they would need advice from the project organization to adapt their registry to the ELDR needs.

17 countries answered the question on possible differences on the process of long-term follow-up data collection; all think that data collection for both short- and long-term follow-up can be arranged via the donor centre.

Follow-up frequency synchronization between national and supranational registries is no problem for 12 countries; 3 countries cannot easily adapt their current frequencies to the ELDR frequencies:

- Bulgaria states that the organization is a subject of a national level decision making and the way of financing the process has to be discussed and specified;
- Italy states that elaboration of follow-up frequencies would lead to additional workload for transplant centres, but as the follow-up frequency currently is yearly, this is in concordance with the frequencies determined for EDITH;

- the United Kingdom states that the elaboration of the follow-up frequencies is not possible due to the fact that they have a set data collection schedule, which cannot easily be altered.

Furthermore, in Poland follow-up is currently collected up to 10 years, as this is legally required, but there is an intention to collect follow-up longer than 10 years.

Finally, most (17) countries stated that they are willing to be involved in EDITH WP5: Croatia, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Republic of Ireland, Romania, Slovak Republic, Slovenia, Spain and United Kingdom. 2 are not interested in active involvement (Bulgaria and Czech Republic) and for 5 MS this is unknown (Austria, Belgium, Estonia, Finland, Luxembourg). Active contribution by the EU MS to help us reaching our WP5 goals is very welcome. Countries that are interested in participation can be consulted on several issues that we might encounter during the project; they can be involved in reading/commenting on our deliverables and further we would like to invite some countries (if our budget allows this) to actively participate in one or more technical meetings from WP5 (with the possibility to reimburse travel costs).

Detailed specification on the content of the database

Deviations from the ELDR specifications are reported by Bulgaria and Germany (both with future systems), Czech Republic, Italy, Republic of Ireland, Slovak Republic, Spain and United Kingdom (current systems). The deviations regarding the current living donor registries are:

- Czech Republic reports that ethnicity, country of residence, complications during operation and complications after operation are missing in their living donor registrations. As the EDITH dataset is too detailed according to Czech Republic, they will not be able to deliver the complete dataset to the ELDR.
- Italy reports that date of birth, ethnicity, ethnicity-specification, antihypertensive medication, proteinuria, medical history data, data on complications during operation, complications after operation until first discharge, and follow-up data items 6-13 (weight, antihypertensive medication, creatinine, proteinuria, RRT, date of RRT-start, pregnancy and pregnancy-specification) and health issue data are not available in their registry. Further the cause of death is registered differently from the ELDR (cause related to transplant or not related to transplant = related to transplant Y/N), and this cannot be changed.
- The Republic of Ireland is restricted to providing dates in YYYY format only, due to data governance.
- Slovak Republic reports a number of items that are currently missing from the national system, but will be added from 30/9/2018 (mandatory items in EDITH marked *): country of residence*, nationality*, nationality_2, ethnicity, ethnicity specification, antihypertensive medication*, proteinuria*, MEDICAL HISTORY: any significant comorbidity* (a-v), operation technique, other operation technique specification, complications during operation* (a-h), complications after operation until first discharge* (a-g), other severe complications, specify…, other severe complications specification, length of hospital stay (LOS), number of days in ICU, RRT*, date of RRT-start*, pregnancy, pregnancy specification, health issues (a-x). Reason for the fact that they are currently not collected is most often that the information is stored only locally and for some items the reason is that deviations of the usual are very unusual (like ethnicity and nationality).
- Spain reports that the items Nationality, Ethnicity, Renal replacement therapy (RRT) and Date of RRT start are registered with different definitions. It intends to adapt RRT and date of RRT definitions in 2018.
- The United Kingdom reports that dates are not collected; they are restricted in providing dates due to information governance, but are able to provide YYYY as a substitute. Ethnicity

specification is not collected, as a breakdown is not registered. For proteinuria a urine dipstick is collected. Only a small selection of diseases is registered: additional cardiac investigations, any significant comorbid condition, any regular drug therapy. Further detailed complications, besides the ones currently collected in the UK, will not be available. There are no plans to extend the current data collection forms for the UK.

Detailed information of the local registries (for countries that have no national registry and do not intend to develop one)
There are currently 9 countries with local registries;

- 4 are willing and able to participate in the ELDR; in one case there are 2 local registries; in one other case there are 4 different local registries and from 2 we did not get information on the local registries.
- 3 are willing but not able yet to participate, without further information about the number of local registries.
- 2 are not willing to participate in the ELDR

V.2.3 Concluding remarks

Almost all EU Member States have completed the questionnaire on current living donor follow-up practices and willingness to participate in an ELDR. This provides us with the sufficient information to proceed the EDITH project. The fact that 12 MS are willing and able to participate in an ELDR is in our opinion an excellent starting point for the development and implementation of an ELDR.

Based on the analysis of the results we can conclude that

- Most (19) MS are willing to participate in an ELDR; *13 are willing and able (4 with a national system, 4 with both, and 5 with local systems (from whom 1 already planned a national system); *6 are willing but not able yet (4 local systems only, 1 both, and 1 with no system yet)
- The ELDR should, as already proposed, both support file upload and data entry; the first option is mainly desired by countries with a national registry (11 of the 19 countries willing to participate (9 with national systems, and 2 with local systems), and the second only by countries with local systems (8 of the 19 countries willing to participate);
- Most countries will be able to report the follow-up frequencies as proposed by EDITH; however a few countries indicated that they probably will not be able to deliver all requested frequencies; this might require attention in the development of the ELDR.
- No countries have indicated the need for a separate functionality, or a different registration practice, for long-term follow-up registration. In all countries both short-term and long-term follow-up information is, or will be, collected via the donor centre. On the other hand we noticed that the long-term follow-up registration currently is far from complete. Therefore, it might still be useful to explore the desirability of a separate functionality for long-term follow-up collection (via general practitioner or donor) later on in the project, as this might be one possible solution to enhance follow-up completeness.
- 11 MS have indicated that they would appreciate help from the WP5 project organization, either on a practical level (e.g. to adapt current registries or realize data delivery to the ELDR) or to raise awareness of the importance of the ELDR and living donor follow-up registration in order to start a national registry (8 and 2 MS respectively, 1 unspecified).
- Many MS (17 in total) are interested in involvement in WP5 participation. Some of them are already involved, but other interested countries might be invited to read proposals from the project to discuss possible choices. Some countries might also be asked to participate in one

or more future technical meetings, if they are expected to be able to specifically contribute to topics on the agenda.

V.3. Conclusion

From the questionnaire results we conclude that 19/24 EU member States that have a living kidney donor registration are willing to participate in an ELDR; 13 are willing and able, 6 are not able yet. File upload is preferred by MS with a national registry and data entry by the MS with local registries. Currently long- and short-term follow-up are both collected in the donor centres, but long-term follow-up collection is far from complete. Help from the EDITH project is wanted by 11 MS. 17 MS are interested in involvement in WP5.

V.4. References

Mjoen G, Hallan S, Hartmann A, Foss A, Midtvedt K, Oyen O, Reisaeter A, Pfeffer P, Jenssen T, Leivestad T, Line PD, Ovrehus M, Dale DO, Pihlstrom H, Holme I, Dekker FW, Holdaas H: Long-term risks for kidney donors. Kidney Int 2014, 86: 162-167.

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V.5. Annex

Annex 1: Questionnaire WP5 EDITH

The questions below are designed to help us review the current situation on living donor follow-up registration in all Member States that are participating in the EDITH project. We would also like to identify the Member States that need support from the project to enable them to establish such a registry. We very much hope that you will be able to complete this questionnaire and return it to a.hemke@transplantatiestichting.nl by July 13th 2017. Thank you for your cooperation.

A. General information

Country	
Name of representative (person who filled in this questionnaire)	
Role/position of representative	
Email address	

B. B. Actual information on national living donor follow-up registries

1. Does your country have experience with living kidney donation? 0 YES 0 NO
2. How many living kidney donor transplants were performed in your country in 2016? 0 none → *if 1=NO and 2=none, this questionnaire is completed* 0 1-10 0 10-50 0 50-200 0 >200

3.	Does your country systematically gather information on living kidney donor follow-up in a national system, in local systems, or both? 0 YES, a national system 0 YES, local systems→ *please continue with section C* 0 YES, both a national system and local systems → *please answer the next questions for the national system* 0 NO→ *if NO, please continue with section C*
4.	What was the starting date of data-collection in the national registry? …/…/……
5.	Is this living donor follow-up information collected in a digital registry (database or electronic file)? 0 YES → if yes, please continue with question 9 0 NO
6.	If your country does not yet collect data in a digital registry, does your country intend to have such a digital registry? 0 YES → if yes, please fill out 7&8, and then continue with question 9 (and further) with the intended situation in mind 0 NO, reason…….. → please also answer question 11-15, and then continue with section C
7.	If 6 =YES. Please indicate expected date of realization of such a digital registry: --/--/----
8.	IF 6 = YES, Would you need any technical or organizational advice from the EDITH project in order to help you realizing such a digital registry? 0 YES, please specify……. 0 NO
9.	What kind of database does your national registry have? 0 Excel 0 Access 0 Oracle 0 DB2 (IBM) 0 SQL Server (Microsoft) 0 Other, please specify……
10.	How is this database hosted and by whom? (name + email address)
11.	How many hospitals / transplant centers share their data in your registry?
12.	What is the follow-up frequency for each donor?
13.	Is there a consent form for living donors to express their consent to be registered in your Living Donor Registry 0 YES 0 NO
14.	Could you estimate the completeness (%) of your national registry and describe how your completeness is calculated?
15.	Who determines if a request for data from your national registry is granted?
16.	Is there a specific person responsible for answering (helpdesk) questions about the database, performing statistical analysis, etc? (name + email address)

C. Willingness to participate in a European Living Kidney Donor Follow-up Registry

17.	Is your country willing and able to participate in the ELDR? 0 YES, willing and able → *please continue with 19* 0 Willing, but not able (yet), reason……→ please also answer 18 0 NO not willing, reason……→ if 17=NO this questionnaire is completed
18.	IF 17 = willing, but not able (yet), Would you need any technical or organizational advice from the project in order to help you realizing data delivery to the ELDR? 0 YES, please specify……. 0 NO

19. Will you be able to deliver (possibly with the help mentioned in 18) the complete dataset (see the attachment) for all proposed follow-up frequencies? 0 YES 0 NO → if no, please also answer section D: detailed information on collected items/follow-up frequency
20. Preferred method of data delivery to the ELDR: 0 File upload → continue with 21 0 Direct data entry→ continue with 22
21. In case of 20 = file upload, will you be able to make the necessary adaptations and code transformations (see dataset) in your system? 0 YES 0 NO, reason…….
22. Would you need any technical or organizational advice from the project in order to help you developing such a registry or adapting an existing registry to the ELDR requirements? YES, please specify…… NO
23. Should the long-term follow-up collection be collected differently from the short term follow-up collection? 0 YES, long term follow-up preferably via donor or general practitioner (direct data entry) 0 NO, all follow-up will be collected via the donor centre 0 OTHER, specify……..
24. If your follow-up frequency is more limited than the proposed ELDR frequency (immediately after donation, 3 months, 1 year, 5 year and further every 5 year (unlimited)), can you easily elaborate this in your country? 0 YES 0 NO, reason……..
25. Do you actively want to contribute to EDITH WP 5 0 YES 0 NO

D. Detailed specification on the content of the database

In the attachment we present the proposed living kidney donor follow-up dataset, based on ACCORD. Note that few items are mandatory. However, completeness of data is essential for data research purposes, and therefore hopefully all items can be collected in your country. The recommended course of action would be that all countries make eventual necessary adaptations in their registries to be able to collect complete follow-up information on record level and on variable level. This should preferably be done in the same period that EDITH WP5 is developing the ELDR. However, if there are specific reasons why this is not feasible, it is important that this is communicated to EDITH. Based on the outcomes of the questionnaire we intend to make an inventory of items that are assumed problematic in all EU countries (also the MS that previously participated in ACCORD); this might lead to some adaptations of the final dataset.

In the next section, please specify which of the items in the dataset (see attachment) you will not (yet) be able to send to the ELDR, either because this item is not collected in your country or the definition differs from the ELDR definition.

Which ELDR items are currently missing in your dataset; please also indicate whether (at what date) they will be added to your registry, or the reason that they will not be available		
Item	Will be added from --/--/yyyy	Reason not collected/available
…		

Which ELDR mandatory items are optional (so occasionally missing) in your dataset; please also indicate whether (at what date) they will be made mandatory in your registry, or the reason that they will not be mandatory		
Item	Will be made mandatory from --/--/yyyy	Reason not mandatory (so occasionally missing)
…		

Do you have collected items with definitions different from the ELDR definitions? Please specify your current definitions, and whether (at what date) you can change these to match the ELDR definitions		
Item	Current definition	Can be changed to ELDR definition from --/--/yyyy
…		

E. Detailed information of the local registries (for countries that have no national registry and do not intend to develop one)

26. How many different local registries does your country have?

    Please specify……

Annex 2: Member States and representatives who have been contacted for information

Austria	Birgit Priebe
Belgium	Luc Colenbie
Bulgaria	Maryana Simeonova, Violetta Marinkova, Evelina Tsvetkova
Croatia	Mirela Busic, Marijana Dragovic
Cyprus	Michalis Hadjigavriel
Czech Republic	Eva Pokorna, Milos Adamec
Denmark	James Heaf, Kaj Joergensen
Estonia	Peeter Dmitriev
Finland	Heikki Makisalo, Kaj Joergensen
France	Camille Legeai, Cécile Couchoud
Germany	Marie Lingemann, Axel Rahmel
Greece	Konstantina Tsaroucha
Hungary	Sandor Mihaly, Orsolya Deme
Ireland	Dilly Little, Yvonne Williams
Italy	Mario Caprio, Claudia Carella
Latvia	Janis Jusinskis
Lithuania	Marius Miglinas, Audrone Buziuviene
Luxembourg	Philippe Remy
Malta	Paul Calleja, Joseph Zarb-Adami
Poland	Jaroslaw Czerwinski
Portugal	Catarina Bolotinha
Romania	Dan Luscalov
Slovakia	Daniel Kuba, Magdalena Kratka
Slovenia	Barbara Ustar, Danica Avsec
Spain	Maria Valentin, Beatriz Dominguez-Gil
Sweden	Helena Ström, Kaj Joergensen
the Netherlands	Cynthia Konijn, Bernadette Haase
United Kingdom	Lisa Mumford, Rachel Johnson

VI. Report on national kidney follow up registries and on variables in a national transplant registry (D6.1/.2/.7)

Responsible partner: ET, NHSBT
Document. WP& Deliverable 1 2 7 FINAL (002) PB_Update Can Meek no table of 26.11.2020

VI.1. Introduction

Previous EU funded projects, particularly EFRETOS (European Framework for Evaluation of Organ Transplants) and ACCORD (Achieving Comprehensive Coordination in Organ Donation throughout the European Union), have described how a national registry of follow-up data from both transplant recipients (EFRETOS) and living donors (ACCORD) can advance European transplant practice. Work package 6, led by NHSBT and Eurotransplant, builds on this expertise to establish an infrastructure for national and European registries of kidney transplant outcomes, and to explore quality of life issues following a kidney transplant.

VI.1.1 Current situation

Work package 6 has begun with a survey to establish the current situation regarding national kidney transplant recipient follow up registries in all Member States. Although this was carried out in the EFRETOS project in 2008, the present situation could be very different, especially in view of scientific and IT developments since that time. This survey enabled an identification of the support that each National Competent Authority of the EU Member States needs to enable it to submit data to a national transplant registry. It was already known that a number of Member States will not need any support, while others may require some sort of methodological support to enable them to submit such data. The survey has also provided us with information on current arrangements for patient consent and governance, to ensure that data confidentiality and protection issues are addressed..

VI.1.2 Establishing national registries

The next step was to specify the variables that need to be obtained in a national registry. These concerned information about the donor, the recipient, the transplant procedure and the patients' treatment outcome. Donor variables included their age and gender and whether they are living or deceased. Recipient variables included age, gender, serum creatinine level and their primary disease. Information about the transplant procedure included data about the time interval between the procurement of the organ to transplantation.

Dataset
A full list of variables was agreed by participants in the EFRETOS project, and all were carefully described. Three tiers of variables were defined. Tier 1 contained those data items that were considered to be a minimum mandatory set, and it was expected that these would need to be obtained by all Member States. Tier 2 contained the variables that were considered necessary for a national registry, but that may not currently be collected. Member States were then expected to move towards having systems that collected information on these variables. Tier 3 variables made up an expanded data set. These variables were deemed to be relevant for a thorough evaluation of transplant outcomes, but not essential. Some of these variables may be of national or regional interest, while others may pertain to population characteristics not prevalent in all other areas, or relate to transplant practices that are country dependent. In Edith Work Package 6, the EFRETOS Tier 1 data was used as the basis for both the European and the National registry, but adapted to current insights. The number and content of variables of Tier 1 have been reviewed by both work package 5

and 6. The revision was agreed upon by the EDITH steering committee. During the first phase of the project agreement will be sought on which variables should now feature in a national and European registry for kidney recipients. Consideration is given on how linkage should be established between a donor and recipients, and the frequency and method for collecting follow up data. Although transplant follow up data should be available for recipients at 1, 3, 5, 10 and 15 years following transplantation, this may not be practical in all Member States, but any barriers to follow-up data collection will be explored. This process will lead to a definition of the variables to adopt in every national registry either as essential or optional, and this in turn will be the basis for the development of the EKKR.

Within the official time frame of the EDITH project, new EU legislation with regard to the privacy of EU citizens came into force. The team of Work package 6 had to make an investigation of the impact of this new legislation for the EKRR. It has become clear and was also discussed during the Eurotransplant annual meeting of 2019 that the EKRR would need a thorough anonymization of the living donor and recipient data because of the fact that without consent of the individual patient or a living donor no identifiable data of a patient/living donor could be legally transmitted to the Registry.

The team of WP 6 therefore evaluated the dataset and has made sure that no exact dates or pseudonomized patient or donor ID's would be used in the final version of the EKRR. In the first quarter of 2020 an independent GDPR expert has performed a Data Privacy Impact Analysis (DPIA). The results of the DPIA are described in a separate report. Most important outcome is the fact that no serious issues were found, but that based on this advice a few adaptations will have to be made to the final version of the EKRR.

Technical requirements and software development

After the first phase of the project where variables, support, availability and commitment of the MS were identified, the technical requirements for the project were defined. Hence the request for offers were at the basis of one of the most important phases, the construction of a European Registry and (upon need) national Registries. In addition to this information the work package intended to lead to a sustainability plan.

The system to be designed had to support:

- Data entry and file upload support for national registries
- Central data storage
- Data download support
- Multi-lingual data entry
- Basic data validation and event logging
- Procedures for security and privacy protection

Reporting

In addition to the above the activities, work package 6 included the definition of basic reporting tools for both the European level and the individual Member States. These reports comprise the following data:

To enable Member States who submit data to the registry to get a comprehensive understanding of the state of transplantation within their country as well as basic comparisons between other European countries twice yearly reports will be created.

In June the full annual report will include data for the previous financial year (April – March) and these will be created separately for individual Member States and a smaller report that compares across all Member States. The full report for Member states will include information on; the number

of transplants performed by type compared to previous financial years, Demographic characteristics of transplants performed compared with previous financial years, waiting time to transplant, and post-transplant outcomes. The full report comparing across Member states will include similar information but will compare across the member states for the previous financial year only.

In December an interim report for the current financial year will be created (April – September) and will replicate the full reports for the six-month reporting period. An example of a six-months report is given in the section X Example Kidney Transplanation Activity Report (D6.1/.2/.7).

Member states will also be able to extract their own data from the registry to create ad-hoc reports.

VI.2. Objectives

Specific objectives for work package 6 included identifying the needs of EU MS in regard to setting up a national follow-up registry of kidney transplant outcomes and agreeing a data set that specifies the variables that should feature in a national registry with a corresponding data dictionary.

VI.2.1 Survey of National Arrangements for Collecting Kidney Transplant Follow-up Data

After approval by the EDITH steering Committee a questionnaire (see Annex) was sent to all EU Member States to understand the current existence of a national kidney follow-up registry, their content and any requirements for future development along with willingness to participate in the EDITH project. Further information was also collected on technical needs and reporting requirements.The results will be presented in four sections:

- The willingness to contribute expertise in the stakeholder group
- The willingness to participate in EDITH
- Details of the current transplant registry if there is one
- Support required from EDITH if no registry in place

Of the 28 EU member states that were sent a survey, a total of 21 were completed and returned. After remittal of the first report no more surveys were sent in by the other countries

Willingness to contribute expertise in the stakeholder group
Of the 21 completed surveys, the following MS were willing to contribute:

- United Kingdom
- Spain
- Poland
- Belgium
- Lithuania
- Italy
- Greece

Willingness to participate in EDITH
17 of the 21 MS that completed the survey reported that they were willing to participate in the EDITH project, these included; The United Kingdom, Spain, Poland, Ireland, Belgium, Slovenia, Bulgaria, Lithuania, Italy, Greece and France. The Netherlands gave a response of maybe due to the reason that it is not yet a national decision in the country and that completeness should be better. Three MS indicated that they were not willing to participate in EDITH, one due to not having enough staff resources, one because they felt they could not participate yet and one as there are no plans for a follow-up registry for recipients until now and as such a contribution of expertise is not reasonable.

After the implementation of the EKRR system on February 17th 2020, the EDITH WP 6 project team sent out a letter to all responding countries to again ask for their participation. The countries that indicated earlier not to support the EKRR received a letter asking to reconsider their previous statement. In addition, all the countries were requested to confirm at least their final standpoint with regard to the EKRR. 27 countries were addressed and 6 responded. France indicated that despite their previously expressed opinion they were willing to contribute data, but would not be able to achieve this before the deadline of Edith. On 26/27th February and once more on 25th March all were again addressed with a reminding letter.

The same was done for the countries that had indicated that they would be willing to support the EKRR with their data. In November 2020 the following countries have contributed their data to the EKRR database:

- Belgium
- Italy
- United Kingdom

Two other countries who desired to remain anonymous also contributed real data.

Due to time limitations it was impossible for some countries to achieve the final data upload within the requested project time frame. The following countries have confirmed their willingness to also contribute data being:

- France
- Latvia
- Lithuania
- Poland

Three other countries, who expressed the desire to remain anonymous, were also in the process to complete data into the EKRR database.

The EDITH project team was in process to obtain the written confirmation of willingness to contribute data by

- Bulgaria
- Greece
- Slovenia
- Switzerland.

Again four other countries expressed their desire to be remain anonymous. They were also internally processing the request of the WP6 project team.

Details of current transplant registry

Of the 17 MS that indicated willingness to participate in EDITH, 11 have already got a follow-up registry in place, all of which have national coverage. Ten of the eleven member states follow-up patients who have received transplants from living and deceased donors: The United Kingdom, Spain, Poland, Ireland, Slovenia, Bulgaria, Italy, Greece and France. One MS only collects follow up data of living donor transplants.

Of the 4 MS that did not indicate willingness to participate in EDITH, 3 have already got a follow-up registry in place, all of which have national coverage. All registries are following up patients who have received transplants from living and deceased donors.

Of the 11 MS who have a national registry, The United Kingdom, Ireland and Bulgaria collect data via paper and web based applications, Poland, Italy, France and 1 other MS collects data via a web based application, Greece collects data on paper, Slovenia and 1 other MS receive their data through excel spread sheets and Spain collects data from regional registries through electronic data transfer.

Each of the 11 MS collect data on the characteristics of the organ donor (e.g. age, gender, cause of death and type (DBD/DCD), the characteristics of the transplant recipient (e.g. age, gender, primary disease), data on the transplant procedure (e.g. cold ischaemic time), and follow-up data on the transplant recipients (e.g. time to graft failure, time to death, delayed graft function).

For Bulgaria, Greece and 1 other MS information was sent by the hospitals and for the United Kingdom, Spain, Poland, Slovenia, Italy, France and 1 other MS data was collected via regular data collection. Four collect the data at transplant and annually thereafter, four only collect data on a yearly basis and 2 are able to collect data on a daily basis.

Table 37 shows the year at which each of the 15 registries started to collect follow-up data and how many kidney transplants were recorded on their registry in the 2016 calendar year.

Table 37: Overview of existing registries

Registry	Date registry started collecting follow-up	Number of kidney transplants in 2016
United Kingdom	1990	3328
Spain	2004	2995
Poland	1998	-
Ireland	-	-
Slovenia	2007	750
Bulgaria	1980	65
Italy	2000	2000
Greece	2012	124
France	1965	3615
Anonymous	2011	20
Anonymous	-	-
Anonymous	2016	34
Netherlands	2002	735
Anonymous	2003	493
Anonymous	1961	-

Of the 7 MS that currently do not have a registry of kidney transplant recipients, three have plans to introduce one. One because it will facilitate and ease the work in the field of transplantation, one because of a law that was passed in November 2016 and one of which the registry is currently in the project stage.

Support required from EDITH if no registry in place

Four of the seven member states were interested in the services that EDITH could offer, and all four indicated to be interested in receiving support in setting up the database and also arranging a web based system for data entry. Only one MS indicated the need for methodological support with regard to defining the technical specifications, and the financial implications.

VI.2.2 Report on variables that need to feature in a national transplant registry

The feedback on the suggested dataset has come from 24 of the 28 countries.

Some suggested data fields did not reach a unanimous consensus. In these cases it was decided by the work package leaders that a 75% votes in favour of a data field was enough to come to a decision.

In section X EKRR Dataset (D6.3/.4/.5) is described per dataset type (donor-, recipient-, transplantation-, follow up) how many countries are not able to supply the data-item requested. It is recommended to delete or redefine all items that less than 75% of the countries are able to supply. This means that we should consider this when at least 6 countries have indicated that a data element is unavailable on a national level.

If we take this into consideration at this point in time we recommend the following:

Donor dataset: Elimination/Redefinition of the following items

- D1.1. ER Donor ID: the project team would like to suggest using coding system that is likely to be adopted by the Joint Research Center of the European Union (EUPID) or the system of the Global Alliance for Genomics and Health
- D1.8. Unified Code of Death: This item could maybe be retrieved by manual mapping.
- D3.4. Ethnic origin
- D3.11 HBV-DNA

Recipient dataset: Elimination/Redefinition of the following items

- R1.4.Recipient age of listing: due to the EU regulations dates can't be used in a European Registry, we would recommend calculation on a national level since this is a crucial value
- R1.5. Unified Primary Diagnosis: This item could maybe be retrieved by manual mapping
- R1.6. Country of Residence
- R1.7. Age in years at listing is requested to not be in the dataset anymore. The field is however available in sufficient countries.
- R1.8. Urgency of candidate at time of transplantation
- R1.9. Age in years at start of first dialysis
- New field: Days between dialysis and listing
- R3.16 Ethnic origin

Transplantation dataset: Elimination/Redefinition of the following items

- T1.1.ER: Transplant ER Id number: the project team would like to suggest using coding system that is likely to be adopted by the Joint Research Center of the European Union (EUPID) or the system of the Global Alliance for Genomics and Health
- T1.5. Height at time of transplantation
- T1.6. Weight at time of transplantation
- T1.14 Unified cause of graft failure
- T1.17 Unified Cause of Death
- T1.18 Donor warm ischemic time
- T1.21 Date last dialysis
- T3.33 Serum creatinine at discharge

New field: Graft function
New field: Days between date of listing and date of transplant
New field: Number of days between transplantation and first discharge
New field Type of multi organ transplant Conditional

Follow up dataset: Elimination/Redefinition of the following items

New ER: Number of days the patient was seen for follow up and the date of transplant: Due to the regulations it might be necessary that the National registries or the centers calculate this number of days manually

New ER: Number of days between the date that the recipient is lost to follow up and the date of transplant: Due to the regulations it might be necessary that the National registries or the centers calculate this number of days manually

- F1.3 Number of days between transplant data and date of Irreversible graft failure
- F1.5. Unified cause of Graft failure: we could recommend that at some level mapping is done between the causes for graft failure that were delivered to the Registry
- F1.8. Unified cause of death: idem
- F1.9. Serum creatinine: maybe we could accept any creatinine value with a quarter indication of a year? Both NHSBT and Eurotransplant are surprised that this many countries are not collecting this field. We advise to query the countries on the methods they use to analyse the graft function of kidney patents.

Quality of life dataset: Availability and future Development

Excursus

The development of Quality of Life fields is a point of interest. Two countries are collecting data on: the experiences of drug compliance, the social and personal life before and after transplantation, activity levels, nutritional aspects and professional life changes.

After the implementation of the technical software, the team of WP6 requested the experiences of the use of the chose SF12 questionnaire with other EU project teams being the EU reference network ERKNET and TransplantChild which are under development.

The SF12 scores for physical and mental health were added to the initial and recurrent follow-up fields to be able to follow these quality of life indicators during the patients followed years.

ERKNET has indicated that the first results on the use of the SF12 questionnaire were an indicator that more promotion was needed to get a higher completion on patient information on Quality of Life. The experience of the EKKR is in line with these findings: none of the participating countries were able to deliver Quality of Life data as it is not in the source dataset. Also parties are unsure how to best implement these indicators in their processes.

Both parties are of the opinion that further EU cooperation could be of benefit and therefore decided that parties will meet at the ERKNET annual meeting mid of May 2020. The EU reference network ERKNET and the team of EDITH envision an incorporation of the use of the SF12 questionnaire in future updates of clinical guidelines.

One of the objectives of EDITH is to investigate whether it is feasible to implement a Quality of Life (QoL) dataset in the registry. So far, to our knowledge almost no EU member state has such a QoL dataset right now in its national registry. Implementing a complete QoL data set in the national registries would require setting up a new procedure to systematically collect these data from patients, during follow-up visits in their transplant center, and have these data delivered to the national registry.

In the EU community, two European Reference networks (ERNs) that are currently being set up, focus on the same patient cohort as EDITH: the Transplant Child and the European Network for Rare Kidney Diseases (ERKNet). Eurotransplant has contacted both ERNs to learn about their plans. Both

of them intend to build patient registries. ERKNet has indicated that they plan to use the 12-Item Short Form Health Survey (SF-12) as quality of life tool. The SF-12 has been developed for the Medical Outcomes Study (MOS). Transplant Child is in the process of defining their needs on registry systems and a possible dataset. After consultation of all EDITH partners, it was decided by the EDITH project team to propose to all countries to start using this relatively low impact but scientifically based QoL questionnaire. The corresponding 12 items have been implemented in the EKRR.

Regarding the present availability of Quality of life fields on a national level, we can conclude that it is definitely a new area of data collection. Only two countries indicated that for the European level it would be possible that their centers collect Quality of life data of kidney transplant patients. Their experiences are worthwhile evaluating and taking into consideration for the dialogue in the next phases of the development of the Edith registry.

Additional general comments
It is indicated by Germany that their National Kidney Transplant Registry is under construction and that the dataset that was sent into the EDITH project is a combination of the possible datasets indicated to be available with three suggested data providers. The final choice of the real dataset will be taken in the near future.

VI.3. Conclusion

At the moment of the previous report the majority of the countries have expressed their willingness to work with the future project of the European Registry for kidney transplant recipients. The majority of the countries would be able to deliver after consent of their patients the majority of the dataset to the EDITH project.

Due to the fact that the new GDPR legislation came into force the EKRR is set up in an anonymised way because of which consent of patients and living donors is no longer required. The NCA's that want to contribute data are able to anonymise all data themselves.

In the final part of the EDITH project a Data Privacy Impact Analysis will be performed in order to assess data privacy issues (if any) and propose improvements to the EDITH registry.

And as a final remark, it is obvious that the datasets collected in national and international registries are not static: as transplant medicine advances, so also the need for (follow-up) data may change. The dataset defined in Edith therefor is subject to regular evaluation and change.

VI.4. Annex: Survey of National Arrangements for Collecting Kidney Transplant Follow-up Data

The questions below are designed to help us review the current situation in regard to the collection of follow-up data on kidney transplant recipients in all Member States that are participating in the EDITH project. We would also like to identify whether any Member States need support from the project to enable them to establish such a Registry. We very much hope that you will be able to complete this short survey and return it to Lisa.mumford@nhsbt.nhs.uk by 31 July 2017. Thank you for your cooperation

Member State:	
Contact person:	
Address of contact:	
Telephone of contact:	

Are you willing to voluntarily contribute your expertise in the stakeholder group for this project?	0 yes 0 no
If yes, what kind of expertise would you like to contribute?	
Does your country want to participate in EDITH?	0 yes 0 no
If no, please indicate the reason for your decision	
Does your Member state have a follow up registry of kidney transplant recipients?	0 yes 0 no
If YES:	
Which groups of patients do you follow-up? (tick all that apply)	0 Transplants from live donors 0 Transplants from deceased donors
What is the coverage of your Registry?	0 National 0 Regional 0 Individual hospitals 0 others (please specify)
What organisation is responsible for maintaining the Registry?	
How are data submitted to the Registry?	0 Paper forms 0 Web based entry 0 Paper / web based entry 0 others (please specify)
Do you collect data on the following (tick all that apply). No need to say what variables are collected.	0 Characteristics of organ donor (eg age, gender, cause of death, type (DBD/DCD)) 0 Characteristics of transplant recipient (eg age, gender, primary disease) 0 Data on the transplant procedure (eg cold ischaemic time) 0 Follow-up data on transplant recipient (eg time to graft failure, time to death, delayed graft function)
How are follow-up data obtained?	0 Regular data collection 0 Linkage to hospital records 0 Information sent by hospital 0 others (please specify)
How frequently is follow-up data obtained?	
In what year did you start collecting follow-up?	
Approximately how many kidney transplants were recorded on the Registry in the 2016 calendar year?	
If NO:	
Do you have plans to introduce a follow-up registry?	0 yes 0 no
If yes, please give details of your plans	
Is your country interested in the service of the EDITH project to help develop a Kidney Transplant Follow-up registry for your country?	0 yes 0 no
If yes, what support do you need to establish a Registry?	0 Setting up the data base 0 Arranging a web based data entry system 0 others (please specify)
What needs would you have related to:	Technical Support (please specify) Methodological support (please specify)

Set-up of the EDITH registries

ELDR

VII. Report on the ELDR specifications (D5.2)

Responsible partner: IDIBAPS
Document. Technical and Functional Design Document from 19.11.2020

VII.1. Introduction

This document describes the functional design of the European living donor registry (ELDR) as well as the technical requirements stablished for the ELDR implementation and accessibility to every member state (MS). These actions are developed by work package 5 (WP5) in the framework of the EDITH project and such design is based on the experience learned and recommendations formulated of the former EU Joint Action “Achieving Comprehensive Coordination in Organ Donation” (ACCORD), which was dedicated to the living donor follow-up registry.

The specific scope that this document will address is in line with the project objectives:

- Development of a European Living Donor Registry (ELDR), following the recommendations defined in ACCORD, for living kidney donors*.
- Implementation and support of a long-term living donor follow-up data delivery to ELDR
- Provide functional and technical advice to support MS in building up their national systems.

*This ELDR will have the scope to be elaborated in the future with living liver donor follow-up. For realization within the scope of the project, however, the focus is on the kidney..

VII.2. Technical requirements for ELDR

VII.2.1 Background

This work package is supporting the establishment of registries to follow-up living kidney donors by EU Member States (MS) following the EU Directive 2010/53/EU on standards of Quality and Safety of human organs intended for transplantation where is written: “Member States shall ensure that a register or record of the living donors is kept and shall endeavour to carry out the follow-up of living donors”. EU Member States will be responsible for building their own national registries and WP5 will support them thru functional and technical advice, based on the structure of the ELDR which will support supranational data collection.

VII.2.2 System Characteristics

The ELDR is intended to be a web-based application approachable by common internet surfing programmes (any HTML5 standard browser); the language used for the ELDR is English. The ELDR is technically designed using the currently available technology; the registry has been developed using Angular frontend and an environment PHP for backend. Communication between frontend and backend is encrypted (SSL) and the authorization is possible by using the token mechanism.

Data persistency is ensured by an open source relational database management system (MySQL). Server infrastructure is functional on windows/Linux OS environment.

As other important features, ELDR support direct data entry as well as file upload by countries/centres, and a data download functionality. As a standard, data delivery is done by the national registries staff(s) of the Member States. Competent Authorities of participating countries decide on how the data delivery is organized. Those possibilities will be discussed in the following paragraphs.

VII.2.3 Direct data entry

The ELDR provides the possibility to enter living donor´s information directly into the registry by direct key entry. The application has clear screens with all the items that need to be collected. Some of the items have drop-down lists to choose from, others will provide the possibility to enter free text. Whether an item is mandatory or optional is clearly visible and the data is validated prior submission to avoid mistakes or flaws. The application is intended to be easy to use and have an attractive feature.

Direct data entry is particularly useful for those countries with a small number of transplant centres or a small number of living donors. On the other side, countries with a well-stablished living donor follow-up registry will probably use the file upload module to upload the data from the existing registry into the ELDR.

VII.2.4 Batch upload module

MS that already have a well-functioning living donor follow-up registry will be able to upload the data to the ELDR as long as the data definitions will be in accordance with the data items and data definitions of the ELDR. The batch upload module is possible via CSV-files (comma separated value). The conversion of the existing data to the ELDR has to be done by the MS themselves, therefore, MS aiming to participate though batch upload will follow the conversion instructions defined in the User Manual, data set and naming conventions in order to be able to transform their data to the ELDR standards. Validation checks of the data included in the batch are performed; only the correct batches will be submitted while the inaccurate information will be avoided and an error message will be displayed mentioning the critical errors.

VII.2.5 Data exportation possibility

The system offers the possibility to export the data from a download facility. The report obtained will have fixed values and its access will depend on the user level and access rights. The document exported will be in .CVS-format.

VII.2.6 Safety and security

Data Access

Co-workers of the ELDR are the only ones who have access for all data in the registry (from every country involved). The access to the ELDR is classified in three different levels; the possibility to change or delete data is only reserved for a limited number of users, also depending on their user's profile and authorisations.

Web Audits

The ELDR system audits all users' activities and actions. The application will log every modification in the data, including time of the modification and the name of the moderator (the user that was logged-in).

General Protection

The registry is protected against any spyware or viral software which can lead to the damage or loss of data. Also, technical defects or power failure may have no influence on the collected data. Daily back-ups of the data and applications are made to facilitate data safety and security.

Summary of Technical requirements:

- Web based application
- Approachable by HTML5 standard browser
- Official language: English
- Angular frontend
- PHP backend
- Communication between frontend and backend encrypted (SSL) and authorized using token mechanism
- MySQL database for data persistency
- Server infrastructure available on windows/Linux OS
- User interface approachable by HTML5 standard browser
- Direct data entry & Batch upload module
- Data download possibility
- Daily backup of the data and applications

VII.3. Functionality of ELDR

VII.3.1 General ELDR Functionalities

The ELDR is hosted by a contracted well-established organisation, experienced in running a registry in the field of transplantation. The project is aimed to perform the ELDR implementation with a web-based application emphasizing the following aspects: data entry in different levels, file upload and file download possibilities and long-term follow-up application.

The ELDR offers a range of features depending on the user level. The authorization system is fine-grained to filter the access to the different functionalities. The baseline characteristics are the following:

- Add Donor
- Add Survey
- Edit Donor
- Edit Survey
- Delete Donor
- Delete Survey
- Export data
- Import data
- Manage Centers
- Manage Users
- Dashboard
- Audit

VII.3.2 Data access levels

The ELDR offers different access levels. Each user access level depends on which permissions are assigned to each account. There are three types of access levels: local, national or global. The user access level is determined by the user logged in. Each participating MS and their competent authorities are responsible to decide the desired user level according to their system or necessities.

- Local (for own center data)
- National (for all centers in the country)
- Global (for all countries and centers)

Data providers

The main data providers are either clinical units or hospitals/transplant centres in the case of individual data entry. Alternatively, data can be entered as "batch upload" from regional or national registries.

Task and responsible

Tasks related to data collection and Data operations related to the ELDR are given in the following Table 38 (the tasks and responsibilities of each party are further described in the Governance Document.).

Table 38: Tasks and responsibilities in the registry organisation (from Governance Document Draft)

Task	Responsible party	Supervision
Data collection		
Specification of valid formats for data entry	European Transplant Registries	Steering Committee
Communication concerning requests for data	European Transplant Registries	Steering Committee
Conversion of data from an existing living donor registry or recipient follow-up registry to EDITH dataset and dictionary	Member State / National Registry	National Competent Authority / Registry
Data entry, review and correction	Member State / National Registry	National Competent Authority / Registry
Data integrity	Member State / National Registry	National Competent Authority / Registry
Data completeness	Member State / National Registry	National Competent Authority / Registry together with ETRs
Overall monitoring and feedback on completeness and integrity of the data	Steering Committee	General Assembly
Data operations		
Daily support, helpdesk, database management, (technical) development and improvements, releases, etcetera	European Transplant Registries	Steering Committee
Data safety and security	European Transplant Registries	Steering Committee
Bugfixes and minor technical improvements in the ELDR/EKRR	European Transplant Registries	Steering Committee
Standardized Reports	European Transplant Registries	Steering Committee
Evaluation of requests for data	Steering Committee	General Assembly
Data analysis	European Transplant Registries	Steering Committee

VII.3.3 Data to be collected

The EDLR has defined a data set based on previous European project recommendations. The system offers a common data set for all the MS; a set of mandatory items is defined with items that should be delivered by all MS. Apart from the minimum dataset a more expanded list of items is also defined, listing optional data that could be delivered by MS.

The data to be collected is described in detail in section VIII ELDR Dataset (D5.2).

Lifelong follow up collection

The ELDR has a key focus on supporting lifelong follow-up collection (at fixed intervals of time) from living kidney donors that have donated in the participants MS.

The initial data collection is based on a retrospective methodology; the countries willing to participate are already informed about the EDITH project, and those who can send the data will register the information based on the following system:

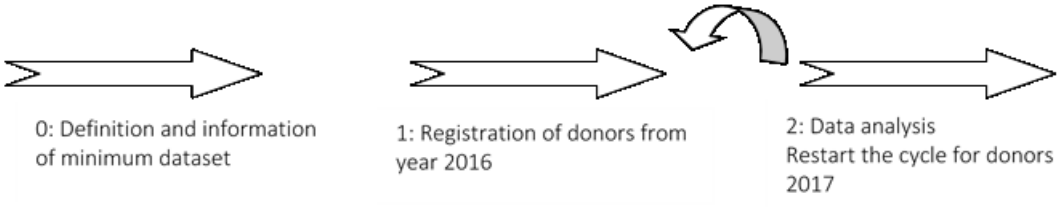


Figure 39: Prospective methodology of data collection

The prospective methodology is also considered and is expected to cover the living donors as of the initial year of the project.

The expected numbers of total donors' records are estimated in 500.000 (1 follow-up eq. 1 record) into 50 years of follow up.

Quality of data
The data quality depends on the national registries (if the data comes via batch upload) and will in this case depend on the quality control mechanisms of the respective national registries or – in case of individual data input – will depend directly on the transplant center or regional authority, which then will be responsible for the quality of the data.

Method of data capture
The registry is a purely electronic registry. There is no paper whatsoever as part of the handling of the registry. Data input is only electronic via file upload or web browser-based individual data entry. Source data has the form that is appropriate for the respective transplant centers and can be electronic or paper-based patient records.

Interoperability
The planned registry will receive data from national registries or individual data from transplant centers or regional authorities. Moreover, in terms of patient safety and potential "data exploitation" the registry needs to have features of interoperability. This is guaranteed for data input, either individual data via a common web browser or batch input via standardized files that can be easily generated or modified using a common program that is able to handle .csv or .xls files such as Excel.

Furthermore, data can be extracted into common formats that later on can be used further in programs like Excel or common statistics applications.

Future developments
Recent advances in electronic and mobile technologies as well as management of patient and donor data warrant an ever-increasing role of these technologies. In this context, a development of donor self-reporting facilities is a realistic objective and could easily developed in the near future.

VII.3.4 Responsibilities

- The participating MS will have the responsibility to introduce their donor's information following the ACCORD recommendations, an ELDR staff (in the assigned host company) will have the responsibility for daily application management.
- The steering committee and assembly (with representatives from the participating Member States) will be responsible for registry management (e.g.: functional management, finance and budget control, data safety and security, data requests).

- In addition, there will be a sustainability plan covering the rest of aspects.

Summary of ELDR functionalities:

- Data access levels
  - Local (for own center data)
  - National (for all centers in the country)
  - Global (for all countries and centers)
- Fine-grained Data-level Access to the following functionalities:
  - Add Donor
  - Add Survey
  - Edit Donor
  - Edit Survey
  - Delete Donor
  - Delete Survey
  - Export/Import
  - Manage Centers
  - Manage Users
  - Dashboard
  - Audit
- Possibility of Lifelong follow up collection data
- Possibility of improving the ELDR following the new available technology

VIII. ELDR Dataset (D5.2)

Responsible partner: IDIBAPS
Document. D5.2_APPENDIX 1_ ELDR_File_specifications of 09.11.2020

Changes from previous version:

1. Unknown options are no longer available for Mandatory items, as otherwise this Mandatory flag has no significance and the Unknown option could be used to skip this item. For data entry this is clear. For file upload, which depends on the available data in the source files, this check will be skipped in order to be able to collect as much ELDR information as possible. Since this is the case, quality checks by ELDR staff are very important; these can result in contacting countries that miss certain Mandatory items in order to persuade them to change their national registries and start collecting these items as well. The unknown option is still available for Optional fields in order to make a difference between not completed ([empty]) and not available in source information (= Unknown).
2. Items added and removed: some free text fields with specification are removed as these would not be useful for reporting purposes. If there were specific examples of these free text fields, the free text field were replaced by separate new fields with Y/N/U options.
3. Free text fields were replaced by specific lists of values (LOV's): in order to get valuable information in the ELDR that can be used in analyses, the comorbidity/complication/health issue specification fields were all replace by LOV-fields..

VIII.1. Donor demographic information

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
1	ExternalID	The unique identification code (ID number) that is given by the national authorities to each person (*Glossary)*	String(50)	M
2	Name	Name of the donor	String(50)	O
3	DOB	Date of birth	Date, format: DD/MM/YYYY	O
4	Age	Actual age at the date of donation	Integer years [99], no decimals	M
5	Gender	Male or Female, or Unknown	String (1); [M,F]	M

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
6	BloodGroup	Menu: - A - B - O - AB	String (2); [A,B,O,AB]	M
7	CountryOfResidence	Country of residence: The country where the person lives during at least 7 months of a year	String(2) [ISO code 3166]]	M
8	Nationality	In case of a double nationality, both should be registered	String(2) [ISO code 3166]	M
9	Nationality_2	In case of a double nationality, here the second nationality should be registered	String(2) [ISO code 3166]	O
10	Ethnicity	Menu: - White=W - Asian=A - Black=B - Oriental=O - Mixed=M - Other=X - Unknown=U	String (1); [W,A,B,O,M,X,U]	O

VIII.2. Pre-donation data

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
0	ExternalID	The unique identification code (ID number) that is given by the national authorities to each person (*Glossary)*	String(50)	M
1	Relation type	Menu (Glossary): - Related - Genetically=RG - Non-genetically=RNG - Unrelated=UR	String (3); [RG, RNG, UR]	M
2	Weight	Last weight before donation	Integer [99], no decimals	M

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
2b	Weight_unit		String(2); [Kg, lb]	M
3	Height		Integer [99], no decimals	M
3b	Height_unit		String(2); Cm or ft	M
4	Antihypertensive medication	Menu: - Yes - No	String (1); [Y,N]	M
5	Creatinine		Numeric (1 decimal) [99.9]	M
5b	Creatinine_unit		String(2); Umol/L or mg/dl	M
6	Proteinuria	- 24 hour urine collection - Spot urine in gram per litre - Dipstick - PCR (protein creatinine ratio)	Numeric (1 decimal) [99.9] +/-	M
6b	Proteinuria_unit		String(2); g/24h g/L Y/N mg/mmol creat	M
Medical history				
7	co-morbidity	Any significant co-morbidity, Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O
a	Abdominal surgery	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
b	Abdominal surgery_specification	Menu: - Appendectomy =AP - Cholecystectomy=CH - Cesarean Section=CE - Bariatric Surgery=BA - Colon Surgery=CO - Hernia Surgery=HE - Synthetic mesh for hernia surgery=SMH - Other=O	String(3); [AP, CH, CE, BA, CO, HE, SMH,O]	O, if abdominal surgery=Y
c	Malignancies	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y
d	Malignancies_specification	Menu: - Colon=CO - Lung=LU - Prostate=PR - Mamma=MA - Hematological=HE - Other=O	String(2); [CO, LU, PR, MA HE, O]	O, if Malignancies=Y
e	Hematological disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y
f	Hematological disease_specification	Menu: - Monoclonal gammopathy of unknown significance=MS - Bleeding disorders=BL - Anemia = AN - Lymphoma=LY - Other=O	String(2); [MS,BL,AN,LY, O]	O, if Hematological disease=Y

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
g	Neurological disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y
h	Neurological disease_specification	Menu: - Epilepsy=EPI - Peripheral nerve lesion=PNL - Non-malignant tumor=NMT - TIA=TIA - CVA=CVA - Other=O	String(3); [EPI, PNL, NMT, TIA, CVA, O]	O, if Neurological disease=Y
i	Cardiovascular disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y
j	Cardiovascular disease_specification	Menu: - Arrhythmia=AR - Ischemic heart disease=IS - Valvopathy=VA - Arterial hypertension=HY - Other=O	String(2); [AR, IS, VA, HY,O]	O, if Cardiovascular disease=Y
k	Respiratory disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y
l	Respiratory disease_specification	Menu: - Clinic obstructive pulmonary disease (COPD)=CO - Lung infection =LI - Other infection=OI - Other=O	String(3); [CO,LI,OI,O]	O, if Respiratory disease=Y

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
m	Gastrointestinal disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y
n	Gastrointestinal disease_specification	Menu: - Peptic ulcer=PU - Inflammatory bowel disease=IBD - Gall bladder problems=GBP - Other=O	String(3); [PU, IBD, GBP, O]	O, if Gastrointestinal disease=Y
o	Psychiatric disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y
p	Psychiatric disease_specification	Menu: - Schizophrenia=SZ - Depression=DE - Addiction=AD - Other=O	String(2); [SZ, DE, AD, O]	O, if Psychiatric disease=Y
q	Psychological disorder	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y
r	Psychological disorder_specification	Menu: - Anxiety syndrome=AS - Other=O	String(2); [AS, O]	O, if Psychological disorder=Y
s	Renal / urinary tract disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y
t	Renal / urinary tract disease_specification	Menu: - Chronic urinary tract infection=CT - Nephrolithiasis=NL - Other=O	String(2); [CT, NL, O]	O, if Renal/urinary tract disease=Y

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
u	Diabetes Mellitus	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y
v	Diabetes Mellitus_specification	Menu: - Diabetes Mellitus type 1= DM1 - Diabetes Mellitus type 2=DM2 - Unknown=U	String(3);[DM1,DM2,U]	O, if Diabetes Mellitus=Y
w	Other disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if co-morbidity=Y

VIII.3. Peri- and post-operative data (until 3 months after donation)

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
0	ExternalID	The unique identification code (ID number) that is given by the national authorities to each person (*Glossary)*	String(50)	M
1	Donation country	Country of donor hospital	String(2); [ISO code 3166]]	M
2	Donation date	Date of donation	Date, format: DD/MM/YYYY	M
3	LRKidney	Left or right kidney Left = L or Right = R kidney is donated	String (1);[L,R]	M

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
4	Operation technique	Menu: - Open technique a. Classic technique 1. Costal resection=CR 2. No costal resection=NC b. Mini-incision=MI - Laparoscopic 3. Standard=LS 4. Hand-assisted laparoscopic=LH - Single port=SP - Transvaginal=TV - Other=O - Unknown=U	String (2); [CR,NC,MI,LS,LH,SP,TV,O,U]	O
Complications				
5	Complications	Complications during/after operation* Menu (*Glossary)*: - Yes - No - Unknown	String (1); [Y,N]	M
a	Blood loss	Blood loss: need for transfusion Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if complications =Y
b	Kidney damaged ?	Kidney damaged during retrieval ? Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if complications =Y

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
c	Kidney damage	Menu: - Kidney can be used for transplantation=A - Kidney is discarded for transplantation =B - Unknown=U	String(1);[A,B,U]	O, if kidney damaged=Y
d	Other organ damaged	Other organ damaged during surgery Menu: - Spleen=SP - Intestine=IT - Other =O - No =N - Unknown=U	String (2); [SP,IT,O,N,U]	O, if complications =Y
e	Switch technique	Switch from laparoscopic procedure to open technique Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if complications =Y
f	Cardiac arrest	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if complications =Y
g	Thrombo complications	Thrombo/embolic complications (DVT, pulmonary embolism) Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if complications =Y
h	Pneumothorax	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if complications =Y

No	Item	Definition	Datatype (length); [validation]	Mandatory/ Optional
i	Anaphylactic reaction	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O if complications =Y
j	Need re-operation	Need for re-operation Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if complications =Y
k	Infection	Infection (urinary, wound, other) Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if complications =Y
l	Renal Replacement Therapy	Acute (temporary) Renal Replacement Therapy* Menu (*Glossary*): - Yes - No - Unknown	String (1); [Y,N,U]	O, if complications =Y
m	Other severe complications	Menu: - Yes - No - Unknown	String (1); [Y,N,U]	O, if complications =Y
6	LOS	Length of hospital stay (LOS): The number of days in hospital during the first admission (from day of surgery until discharge)	Number of days Integer [99]	O
7	ICU	Number of days in ICU: The number of days in Intensive Care Unit during the first admission (until discharge)	Number of days Integer [range: between 0 and LOS]	O

*Only serious adverse events have to be reported. A serious adverse event is defined as follows:

- Hospitalisation or prolonged hospitalisation
- Persistent or significant disability or incapacity
- Intervention to preclude permanent damage or to prevent death

VIII.4. Follow-up data

(frequencies: 3 months after donation, 1 year after donation, 5 year, 10 year, 15 year etc.)

No	Item	Definition	Datatype (length); [validation]	Units	Mandatory/ Optional
0	ExternalID	The unique identification code (ID number) that is given by the national authorities to each person (*Glossary)*	String(50)		M
1	Follow-up date	Date of follow-up; In case of donor lost to follow-up or death, this date should be the same as date lost to follow-up or date of death	Date, format: DD/MM/YYYY		
2	Lost to follow-up	Donor lost to follow-up (*Glossary)* Yes / No	String(1);[Y,N]		
3	Date lost to follow-up	Date lost to follow-up	Date, format: DD/MM/YYYY		
4	Donor Death	Yes / No	String(1);[Y,N]		
5	Date of death	Date of death	Date, format: DD/MM/YYYY		

6	Cause of death	Menu: - Certain infectious and parasitic diseases 5. Neoplasms=NEO 6. Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism=DBB 7. Endocrine, nutritional and metabolic diseases=ENM 8. Mental, Behavioral and Neurodevelopmental disorders=MBN 9. Diseases of the nervous system=DNS 10. Diseases of the eye and adnexa=DEA 11. Diseases of the ear and mastoid process=DEM 12. Diseases of the circulatory system=DCS 13. Diseases of the respiratory system=DRS 14. Diseases of the digestive system= DDS 15. Diseases of the skin and subcutaneous tissue=DSS 16. Diseases of the musculoskeletal system and connective tissue=DMS 17. Diseases of the genitourinary system=DGS 18. Pregnancy, childbirth and the puerperium=PCP 19. Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified=SSA 20. External causes of morbidity=ECM	String(3); [NEO, DBB, ENM, MBN,DNS,DEA, DEM, DCS, DRS, DDS, DSS, DMS, DGS, PCP, SSA, ECM,O,U]		

No	Item	Definition	Datatype (length); [validation]	Units	Mandatory/ Optional
		- Certain infectious and parasitic diseases=INF - Other = O - Unknown=U			
The next items are only filled in case of a regular follow-up for a donor that is still alive and not lost to follow-up					
7	Weight		Integer, no decimals [99]		
7b	Weight_unit		Kg or lb,		
8	Antihypertensive medication	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		
9	Creatinine		Numeric, 1 decimal [99.9]		
9b	Creatinine_unit		Umol/L or mg/dl		
10	Proteinuria	- 24 hour urine collection - Spot urine in gram per litre - Dipstick - PCR (protein creatinine ratio)	Numeric, 1 decimal [99.9] +/-		
10b	Proteinuria_unit		g/24h g/L Y/N mg/mmol creat		
11	RRT	Renal replacement therapy (RRT); Is the donor dependent on chronic renal replacement therapy? Yes/No/Unknown Fill in once, only when started in this follow-up period	String(1);[Y,N]		
12	RRT start date	Date of starting chronic renal replacement therapy	Date, format: DD/MM/YYYY		
13	Pregnancy	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		
Health issues (only new health issues since last follow-up)					

No	Item	Definition	Datatype (length); [validation]	Units	Mandatory/ Optional
14	Health issues	Menu(*Glossary)*: - Yes - No - Unknown	String(1);[Y,N,U]		
a	Abdominal surgery	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		
b	Abdominal surgery_specification	Menu: - Appendectomy =AP - Cholecystectomy=CH - Cesarean Section=CE - Bariatric Surgery=BA - Colon Surgery=CO - Hernia Surgery=HE - Other=O	String(3); [AP, CH, CE, BA, CO, HE, O]		
c	Malignancies	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		O, if Health issues=Y
d	Malignancies_specification	Menu: - Colon=CO - Lung=LU - Prostate=PR - Mamma=MA - Hematological=HE - Other=O	String(2); [CO, LU, PR, MA HE, O]		O, if Malignancies=Y
e	Hematological disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		O, if Health issues=Y

No	Item	Definition	Datatype (length); [validation]	Units	Mandatory/ Optional
f	Hematological disease_specification	Menu: - Monoclonal gammopathy of unknown significance=MS - Bleeding disorders=BL - Anemia = AN - Other=O	String(2); [MS,BL,AN,O]		O, if Hematological disease=Y
g	Neurological disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		O, if Health issues=Y
h	Neurological disease_specification	Menu: - Epilepsy=EPI - Peripheral nerve lesion=PNL - Non-malignant tumor=NMT - TIA=TIA - CVA=CVA - Other=O	String(3); [EPI, PNL, NMT, TIA, CVA, O]		O, if Neurological disease=Y
i	Cardiovascular disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		O, if Health issues=Y
j	Cardiovascular disease_specification	Menu: - Arrhythmia=AR - Ischemic heart disease=IS - Valvopathy=VA - Arterial hypertension=HY - Other=O	String(2); [AR, IS, VA, HY,O]		O, if Cardiovascular disease=Y
k	Respiratory disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		O, if Health issues=Y

No	Item	Definition	Datatype (length); [validation]	Units	Mandatory/ Optional
l	Respiratory disease_specification	Menu: - Chronic obstructive pulmonary disease (COPD)=CO - Lung infection =LI - Other infection=OI - Other=O	String(3); [CO,LI,OI,O]		O, if Respiratory disease=Y
m	Gastrointestinal disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		O, if Health issues=Y
n	Gastrointestinal disease_specification	Menu: - Peptic ulcer=PU - Inflammatory bowel disease=IBD - Gall bladder problems=GBP - Other=O	String(3); [PU, IBD, GBP, O]		O, if Gastrointestinal disease=Y
o	Psychiatric disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		O, if Health issues=Y
p	Psychiatric disease_specification	Menu: - Schizophrenia=SZ - Depression=DE - Addition=AD - Other=O	String(2); [SZ, DE, AD, O]		O, if Psychiatric disease=Y
q	Psychological disorder	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		O, if Health issues=Y
r	Psychological disorder_specification	Menu: - Anxiety syndrome=AS - Other=O	String(2); [AS, O]		O, if Psychological disorder=Y

No	Item	Definition	Datatype (length); [validation]	Units	Mandatory/ Optional
s	Renal / urinary tract disease	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		O, if Health issues=Y
t	Renal / urinary tract disease_specification	Menu: - Chronic urinary tract infection=CT - Nephrolithiasis=NL - Other=O	String(2); [CT, NL, O]		O, if Renal/urinary tract disease=Y
u	Diabetes mellitus	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		O, if Health issues=Y
v	Other health issues	Menu: - Yes - No - Unknown	String (1); [Y,N,U]		O, if Health issues=Y
15	previous activity level	Did the donor return to previous activity level? (This item should only be collected during the 12 month follow-up visit.)Menu (*Glossary*): - Yes - No - Unknown	String(1);[Y,N,U]		O
16	previous activity level months	After how many months did donor return to previous activity level?	Integer [99]	Months, no decimals	O, if return to previous activity level = Y

VIII.5. Glossary

Not every item needs specification in this Glossary of terms. Some items however need an extra explanation about the way the item should be measured or collected.

Item	Definition
Complications (until 3 months after donation)	Menu: - No complications - Blood loss: need for transfusion - Kidney damaged during retrieval: this means that the kidney that is procured from the donor (graft) is damaged - Kidney can be used for transplantation - Kidney is discarded for transplantation - Other organ damaged during surgery: this means another organ (not the procured organ) is (physically) damaged during the operation. - Switch from laparoscopic procedure to open technique - Cardiac arrest - Thrombo/embolic complications - Pneumothorax - Anaphylactic reaction - Need for re-operation - Infection (urinary, wound, other): therapeutic use of antibiotics - Acute(temporary) Renal Replacement Therapy; Note: acute, short term, RRT can be a complication after donor surgery; if chronic RRT is needed, this is filled in the follow-up record - Other severe complications
Did the donor return to previous activity level?	This item should only be collected during the 12 month follow-up visit. This will be based on the person's answer and is no objective measurement. Menu: - Yes, within …. months - No - Unknown
Donor lost to follow-up	A donor is lost to follow-up if he/she has regularly been invited to follow-up appointments, but did not show up during 10 years. Because the mandatory follow-up frequency is at discharge, 1 year after donation and then every 5 years, this means the donor did not show up during at least three visits. The lost to follow-up date is the day after the donor was last known to be alive, e.g. if there is no more information on the donor after the follow-up of 1 year, the date lost to follow-up is year 1 + 1 day
Health issues	Only new health issues since the last follow-up record should be registered here

Item	Definition
Identification	The national authorities in (almost) every MS give an unique identification code to each individual. This code could be used to identify a person without collecting their name. If a country decides not to use the unique identification code, another method should be used to prevent collecting data about the same person twice. For example a combination of initials and date of birth. MS is distracted from the country delivering the data
Relation type	Genetically related - 1st degree genetic relative: parent, sibling, offspring - 2nd degree genetic relative: e.g. grandparent, grandchild, aunt, uncle, niece, nephew, - Other than 1st or 2nd degree genetically related, for example cousin Non-genetically related - Emotionally related: Spouse (if not genetically related); in-laws; adopted child, friend Non-related - Not genetically, nor emotionally related. This means that the recipient does not know the donor (e.g. altruistic donor, anonymous donor, cross-over donor)

VIII.5.1 Screen 1 - Donor demographics and pre-donation information

Donor demographics
Identification (ID number)
Date of birth
Age
Gender
Blood group
Country of residence
Nationality
Nationality_2
Ethnicity

Pre-donation information
Relation type
Weight
Height
Antihypertensive medication
Creatinine
Proteinuria

Medical history
Any significant co-morbidity *(pop-up screen)*

Comorbidies

Abdominal surgery	->Abdominal surgery_specification
Malignancies	->Malignancies_specification
Hematological disease	->Hematological disease_specification
Neurological disease	->Neurological disease_specification
Cardiovascular disease	->Cardiovascular disease_specification
Respiratory disease	->Respiratory disease_specification
Gastrointestinal disease	->Gastrointestinal disease_specification
Psychiatric disease	->Psychiatric disease_specification
Psychological disorder	->Psychological disorder_specification
Renal / urinary tract disease	->Renal/urinary tract dis_specification
Diabetes Mellitus	->Diabetes Mellitus_specification
Other disease	

VIII.5.2 Screen 2 - peri and postoperative data

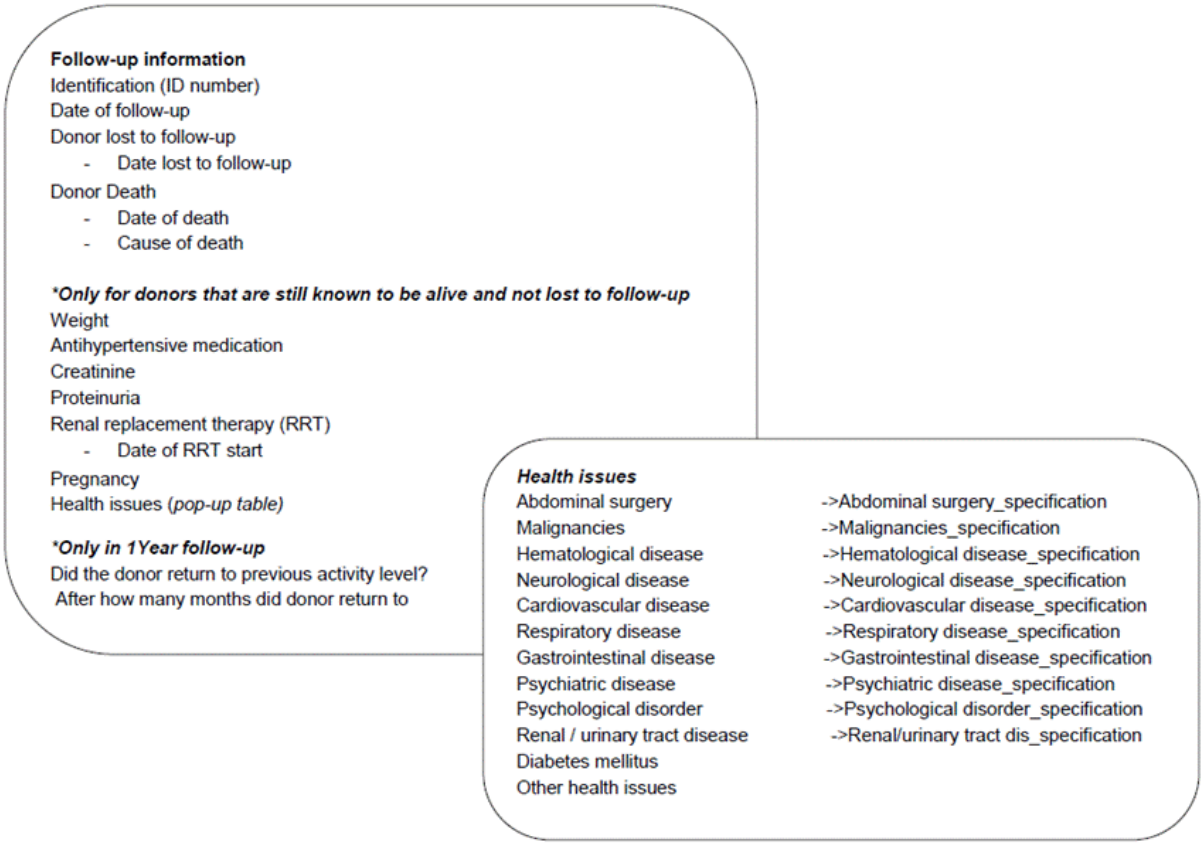
Peri-operative information
Identification (ID number)
Country of donor hospital
Date of donation
Left or right kidney
Operation technique
- Operation technique_other

Complications (until 3 months after donation (*pop-up screen*))

Length of hospital stay (LOS)
Number of days in ICU

Complications
Blood loss: need for transfusion
Kidney damaged during retrieval
Kidney damage
Other organ damaged during surgery
Switch from laparoscopic procedure to open technique
Cardiac arrest
Thrombo/embolic complications
Pneumothorax
Anaphylactic reaction
Need for re-operation
Infection (urinary, wound, other)
Acute (temporary) Renal Replacement Therapy
Other severe complications

VIII.5.3 Screen3 - Follow-up data



EKRR

IX. Description of the functional design and on technical needs, reporting requirements and IT (D6.3/.4/.5)

Responsible partner: ET
Document. WP6 Deliverable D3 D4 D5of 06.04.2020

IX.1. System description

Open platform

The EDITH deceased donation transplant registry is based on an open platform: openEHR. Open platforms are open in the sense that data can be are available is a standard format, based on open clinical models and can be wholly and freely accessed. Data and models in an openEHR based platform can be used with any vendors product that adhere to these standards. These qualities make an open platform very flexible. More on open platform in this excellent white paper by the Apperta Foundation: https://apperta.org/openplatforms/.

openEHR

'openEHR' is the name of a technology for e-health, consisting of open specifications, clinical models and software that can be used to create standards, and build information and interoperability solutions for healthcare. The various artefacts of openEHR are produced by the openEHR community and managed by the openEHR Foundation, an international non-profit organisation established in the year 2003 (https://www.openehr.org/about/what_is_openehr).

Flexibility

The openEHR platform gives the EDITH registry flexibility in setup. Besides gathering the data over a long period of time in a registry from existing registries, it is important to offer countries who do not have a registry a platform that they themselves can use for starting a registry.

The current setup is a single instance openEHR platform with a central database and a single instance front-end. However other setups are possible for instance we can keep the central database, but created a federated landscape of smaller openEHR based platforms and frontends that can deviate both on user interface, language and data collection from the central database as long as the EDITH dataset acrhetypes are incorporated in the country specific dataset. In this setup any country can create their own database based on their own specific needs and still be able to seamlessly deliver data to the central EDITH registry.

You can choose different vendors for the openEHR platform both “free” open source solutions (for instance http://ethercis.org/) or paid solutions. You can also choose to develop your own front-end, find an open source version (and extend it) or buy a solution from a vendor. We compared many solutions and came to the conclusion that an open source solution would require considerable effort to adapt to the needs of a registry, therefor it has a high initial cost, but perhaps lower running cost than a paid solution. However as the EDITH deceased donation transplant registry has limited funding and an unclear timeline after the project is concluded, we have opted for a paid solution.

The product we use is the Better Platform with Better Pathfinder Lite front-end application (www.better.care) it offers a lot of tools we use in our registry out of the Box. We run it ourselves in the AWS cloud in Frankfurt. At the moment Better has started to offer a SAAS solution (Azure cloud in France), which might be better fit in the future as no technical support for servers, netwerk is needed any more.

Functional Requirements

The solution is based on the requirement document EDITH design_v1_1.pdf (see Github repository).

Resources

Resources mentioned in this document can be find on our public github:
https://github.com/edith-project/deceased-registry

IX.2. Components

The registry uses several components to create, in this chapter we will describe them shortly and explain how the work together to provide the functionality as described in the requirements document.

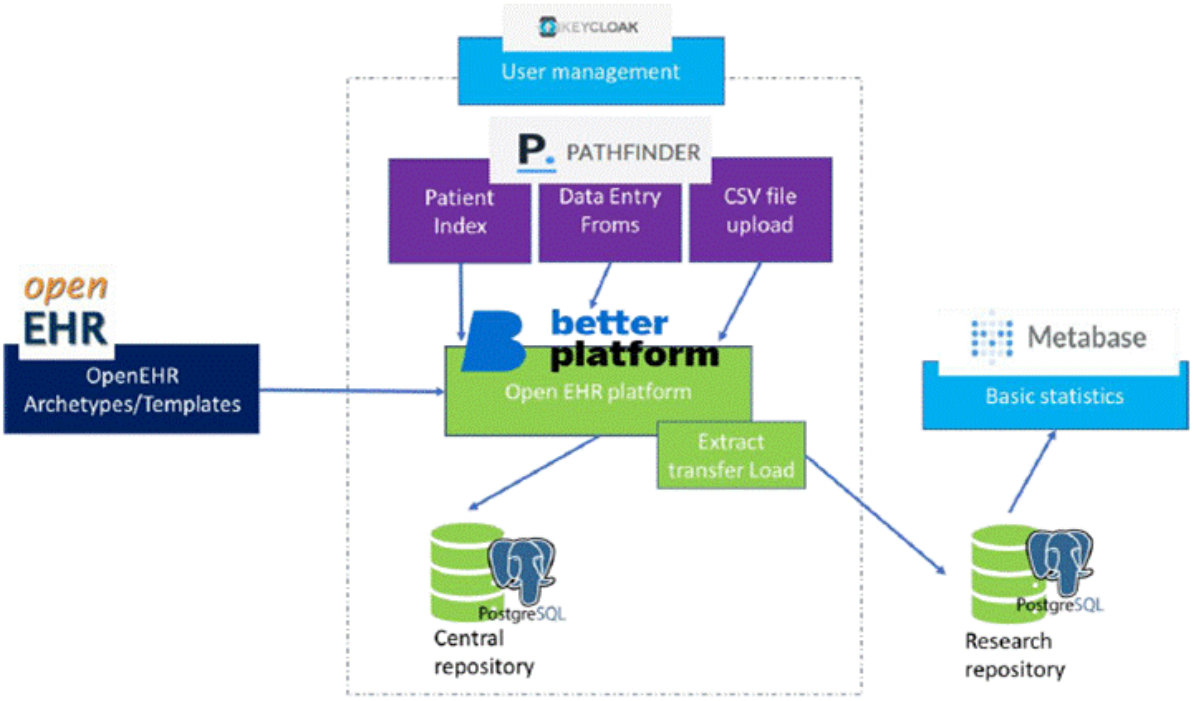


Figure 40: Schematic representation of components and how the interact

openEHR

archetypes and templates Archteypes are the small clinical building blocks holding concepts like blood group or weight, templates describe a clinical use case. These templates can be uploaded to the openEHR platform (Better platform) which will automatically generate everything that is needed to store and access data based on these templates through open EHR API's (documentation https://specifications.openehr.org/releases/ITS-REST/latest/index.html)

Keycloak

user management Keycloak is used to manage access to Pathfinder and Better Platform, user can use a single password to access these application. Metabase uses it own user access.

Pathfinder

Pathfinder is the front-end application that end-users (national competent authorities) will use to enter data in an initial and a follow-up data entry form. A csv file upload is available to upload data in bulk.

Better platform

The better platform provides a clinical data repository based on openEHR, specifications, in addition it provides a form builder, ETL (Extract transfer load), EHR explorer tool voor admins to quickly manage the platform.

Metabase

Metabase is a basic statics application, it can be used to quickly generate overviews on the data. The registry will provide data export possibilities for the National Competent Authorities (NCA).

Flow between components

Short summary of a typical workflow:

1. An engineer creates user accounts in keycloak
2. A Clinical modeler (or other employee at the EU registry) creates or updates openEHR template
3. Templates are uploaded to be better platform
4. Based on the template a Form is created or updated by the Clinical modeler
5. The form is tagged for pathfinder so it immediately becomes available in pathfinder
6. Data is collected by NCA's and entered in the forms or uploaded via the bulk upload.
7. The clinical modeler designs a data query (AQL) in EHR explorer to extract data needed for research.
8. ETL is configured to use the query to extract data and the extraction is scheduled.
9. The user of an NCA can extract the data from Metabase.

IX.3. AWS cloud configuration

In AWS the following components are used:

- AWS components used per environment (test, prod)

Think!EHR Explorer & Terminology adapter	EC2 Instance M5.Large
Think!EHR Platform	EC2 Instance T3.medium
Instance storage (estimate 20Gb per Instance)	EBS General Purpose SSD
PostgreSQL	Database
PostgreSQL (estimate 5Gb p/y)	DB Storage
PostgreSQL (estimate 5Gb p/y)	DB Backup Storage
PostgreSQL (estimate 10Gb p/y)	Data transfer

- Components shared between environments

Application Loadbalancer	
Route53 DNS	Hosted zone
VPC	VPN
Bckup Storage for Instance snaphots	S3

Figure 41 shows a schema of the implementation used for a single environment (in this case Test). The environment has its own VPC (Virtual Private Cloud) and a public and private subnet to secure the data in the private subnet. An application load balancer is used to balance client traffic, this will make the setup more flexibility as we could scale easily to extra instances of pathfinder or Better

platform (formerly known as Think!EHR platform). The Pathfinder and Metabase components run on the docker instances (easier to install) while the Better platform is not yet available on docker and needs a separate server.

Both the docker and platform servers use a Postgress database. Databases are back-upped daily and are retained for 3 days.

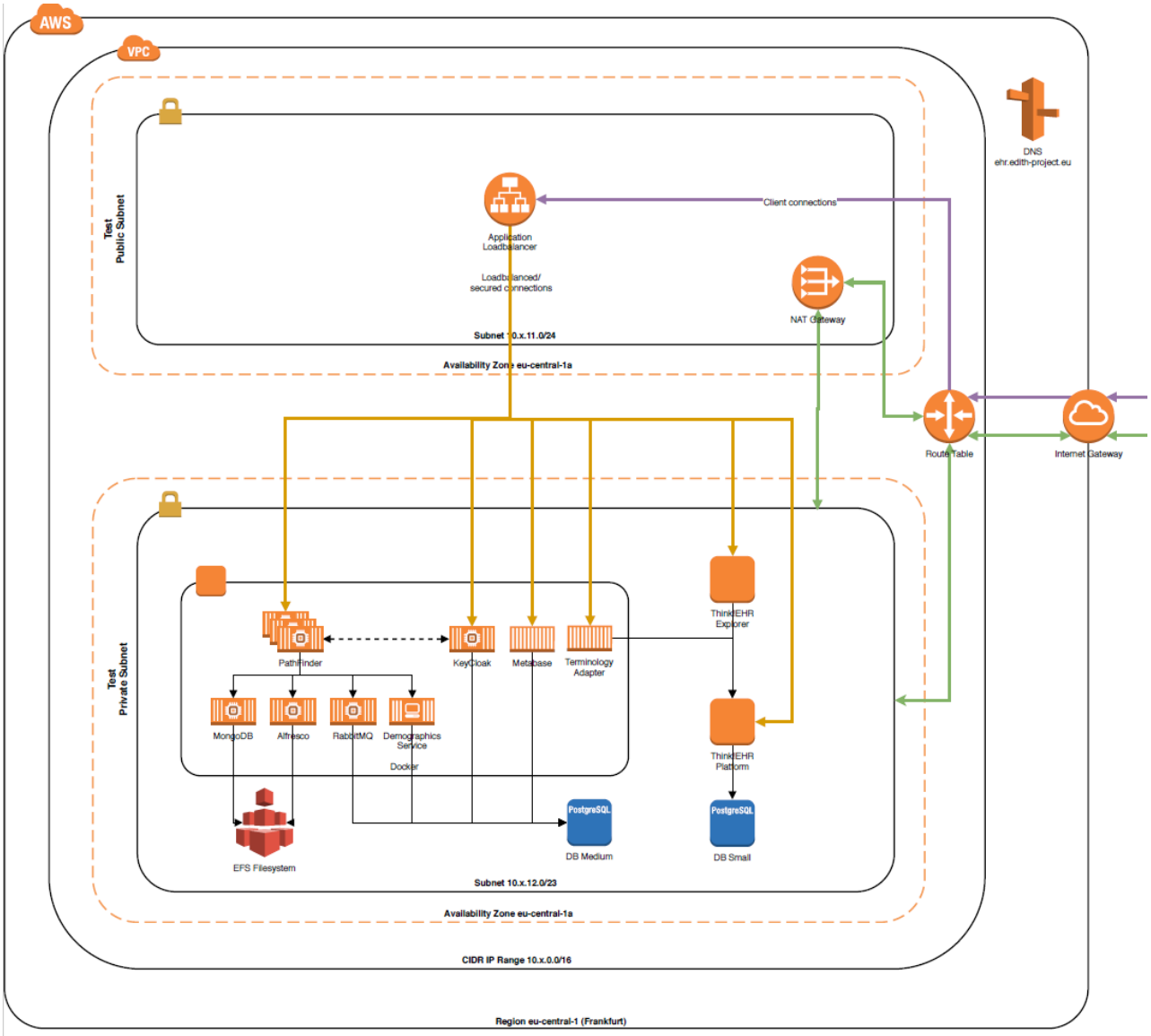


Figure 41: Implementation schema for a single environment (recipient FUR)

IX.4. openEHR archetypes and templates

Description

We use openEHR templates and arcehtypes to describe our dataset and create operational templates that can be used inside an openEHR platform.

Use

We have used Better's ADL-designer to create the openEHR archetypes and templates. Most archetypes are downloaded from the international open Clinical Knowledge Manager at openEHR.org (https://www.openehr.org/ckm/). You can download Archetype and Templates files used in the project from our public Github repository.

Configuration

We have created 2 templates which intern use archetypes (both local and CKM)

1. EDITH Initial, describes an initial follow-up record to be recorded as the first record after transplantations. Its fields contains information on donor, recipient and transplant for a kidney transplant (Figure 42)
2. EDITH Follow Up, describes information on the patients gathered by phycians on regular intervals. Also used to record death of a patient and failure of a transplanted graft (Figure 43).

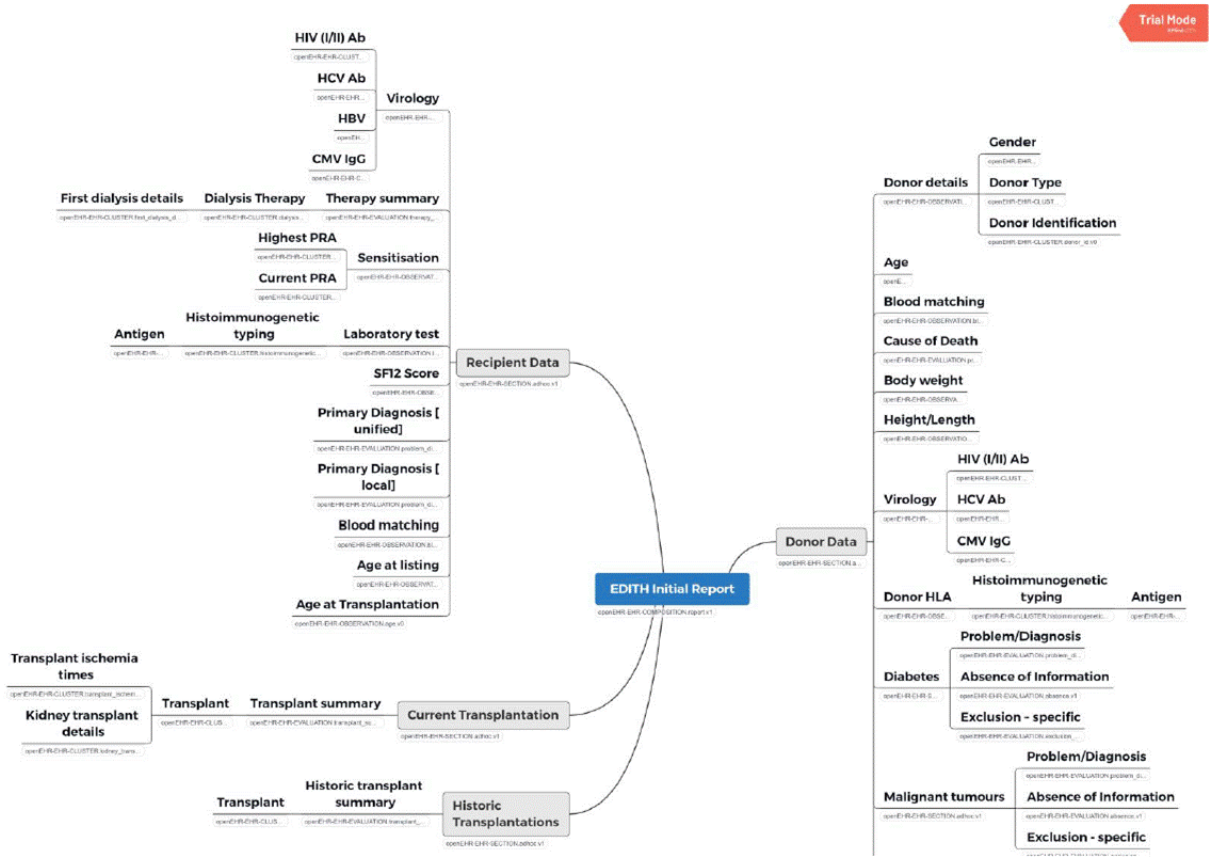


Figure 42: EDITH Initial archetypes mind map

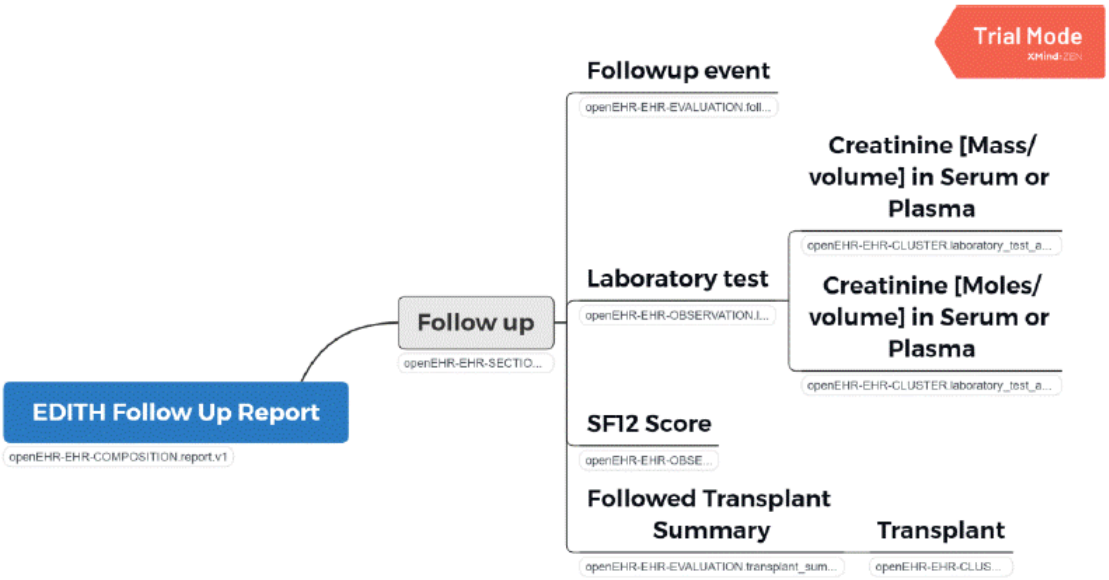


Figure 43: EDITH Follow-up archetypes mind map

IX.4.1 User management

Description

For user management KeyCloak is used for authorizing users to the Better and Pathfinder applications. For Metabase the internal .user management is used.

Use

KeyCloak is configured by the Technical admin of the platform

Configuration

We have three user levels:

1. NCA users (users that can enter and access data on country level), these users can access data including the local subject ID (patient ID that was defined by the NCA). NCA's can download statistics from metabase with patient ID for there own country, but without ID for all transplants.
2. Europe functional admins (can access patients for all countries)
3. Admins can configure and setup components described in this document.

IX.4.2 openEHR platform (Better)

Description

Within this project we are using Better platform (formerly known as Think!EHR) version 2.4.3. (Figure 44)

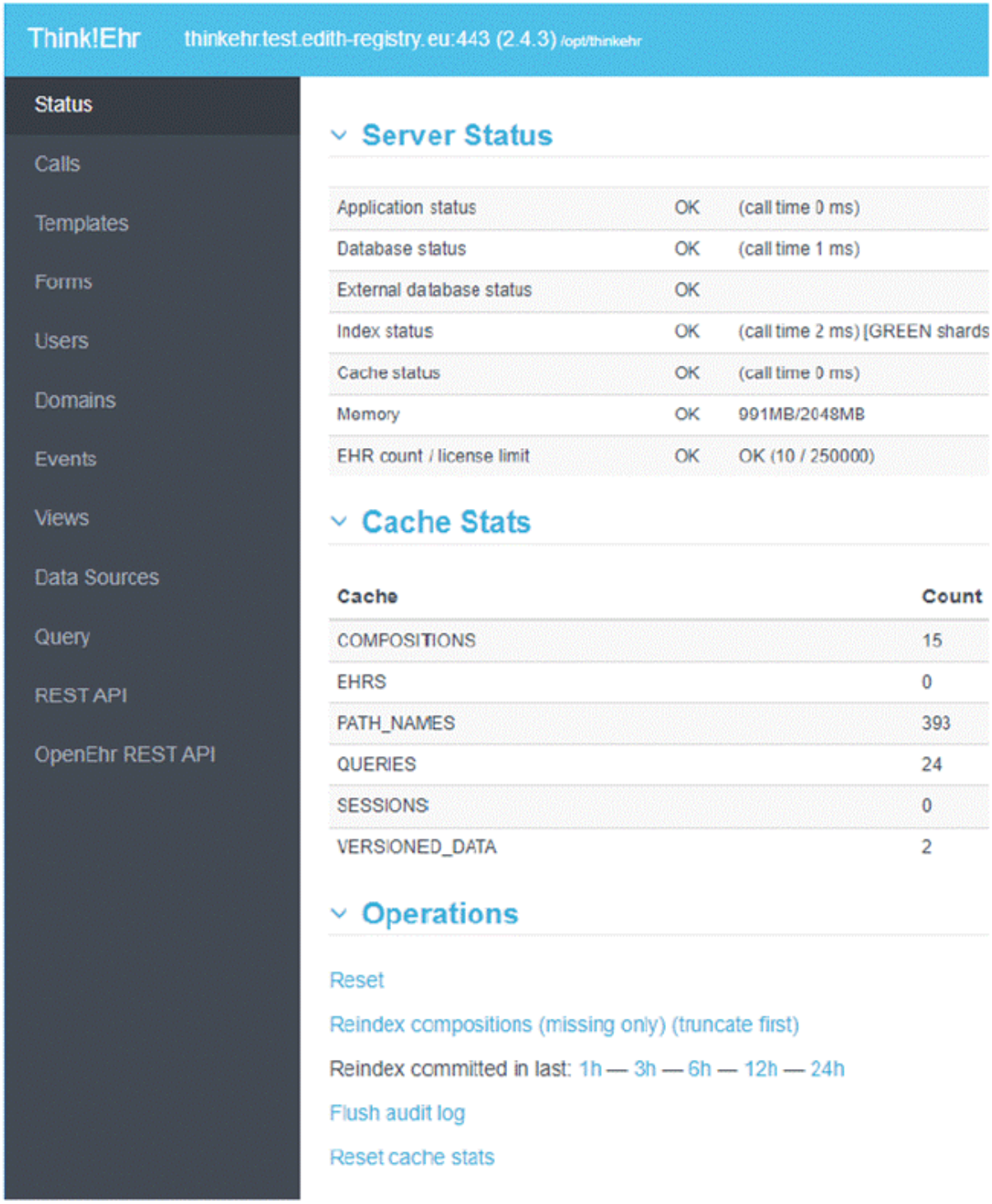


Figure 44: Admin console Better platform

Use

The platform can be configured by Admins. The following artefacts are uploaded to run the application:

- Templates (see openEHR archetypes and templates)
- Form builder
- Views; a view is created based on a AQL query (the openEHR query language) to create the patient list in the pathfinder application.

Configuration

The Better platform runs on a dedicated Linux server with a dedicated Postgress database.
It is a single node instance (but this platform can be clustered if needed).
It contains user account information for admins. Also a service account was created for the ETL user with only read access to the platform.

IX.4.3 ETL

Description

The Extract Transfer Load (ETL) tool from the Better platform is a tool to quickly access the data from a Better platform via an AQL query and transfer data to an relational database. As most statistics tools cannot access openEHR platforms directly it is an easy way to get data in to a database that the statistics application can use. ETL tool from Better version 1.1.6 is used.

Use

The platform can be configured by Admins. Connections are defined one to the openEHR instance and one connections to the Europe schema research database. And one for every country schema.

For each country a query is defined to retrieve country specific data from the openEHR, platform as well as European query (which excludes the Subject ID).

For every query a mapping is generated to a relational database schema.

The ETL processes are scheduled to run every hour, so the statistics database is maximum 1 hour behind on the openEHR database. It does a full refresh.

Configuration

The AQL queries can be found within the Github repository.

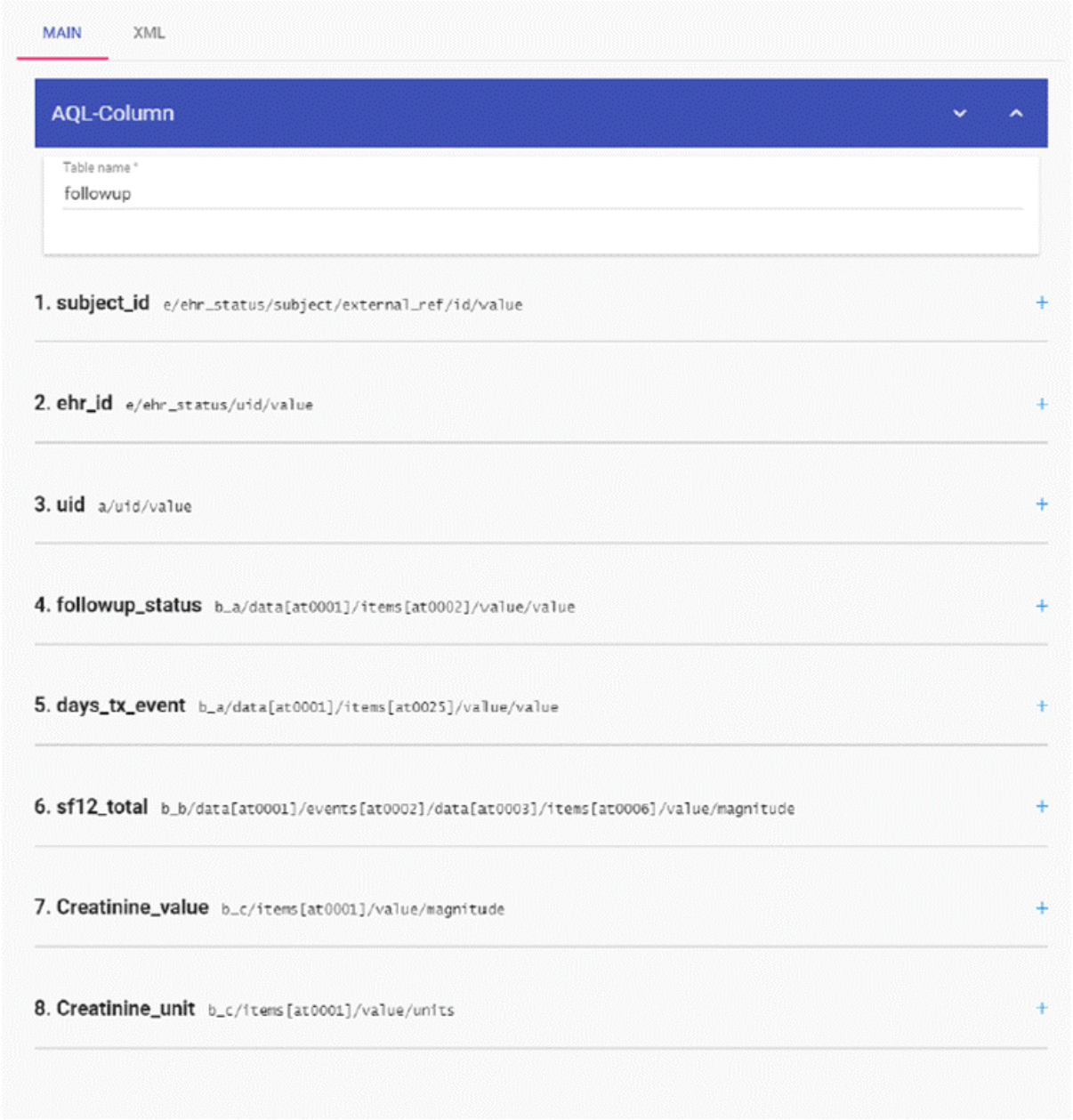


Figure 45: 7AQL to SQL mapping example

IX.4.4 Terminology adapter

Description

The terminology adapter contains all terminologies used within the archetypes. Examples are the HLA nomenclature, ICD-10 etc.

Use

The platform can be configured by Admins. Connections are defined one to the openEHR instance and one connections to the Europe schema research database. And one for every country schema .

A nomenclature is defined within a CSV file with at least the following columns:

- code, the code for a row within the Nomenclature
- descripition, a description that can be displayed for a specific codw
- parent, optional parent of the code if the code has a hierarchy

Configuration
The following terminology are defined (full csv files can be found in Github):

- Common translation
- CountriesEt
- ET_ABO
- ET_Rhesus
- ET-Virology_CMV_Code_2018
- ET_Virology_code_2018
- Formats
- Gender
- Grafts_V1
- HLA_nomenclature_2010
- ICD10
- ICD10_diabetes
- Languages
- ProcessDefinition
- terminologyDefinition

IX.4.5 Form builder

Description
Form builder is a drag and drop tool to create forms based on openEHR templates and the better platform

Use
Admin creates or updates a form based on a template. Tags it for use within pathfinder. Uploads the form into your OpenEHR platform. The form will automatically be used in Pathfinder.

Configuration
Form builder runs on tools.marand.si. Find the form description files in our Github. Two forms are created:

- Edith Initial to capture the initial form
- Edith Follow Up to capture the Follow Up form

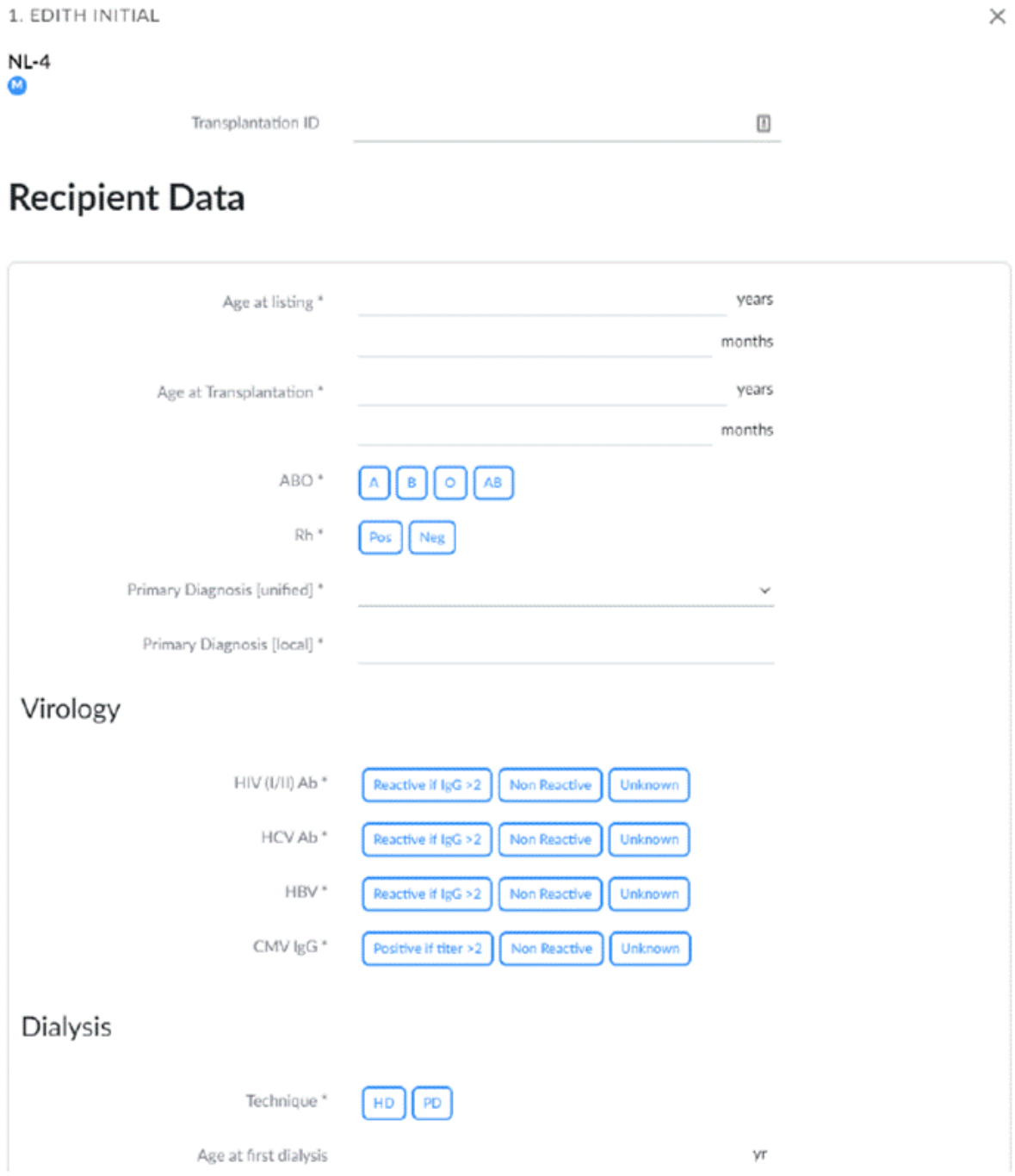


Figure 46: Part of the Edith Initial form

IX.4.6 Pathfinder

Description

Better Pathfinder is on openEHR front-end for quickly publishing forms based on openEHR so that endusers can use them. It is focused on data capturing and needs the Better openEHR platform to run on top off.

Use

Better Pathfinder is on openEHR front-end for quickly publishing forms based on openEHR so that endusers can use them. It is focused on data capturing and needs the Better openEHR platform to run on

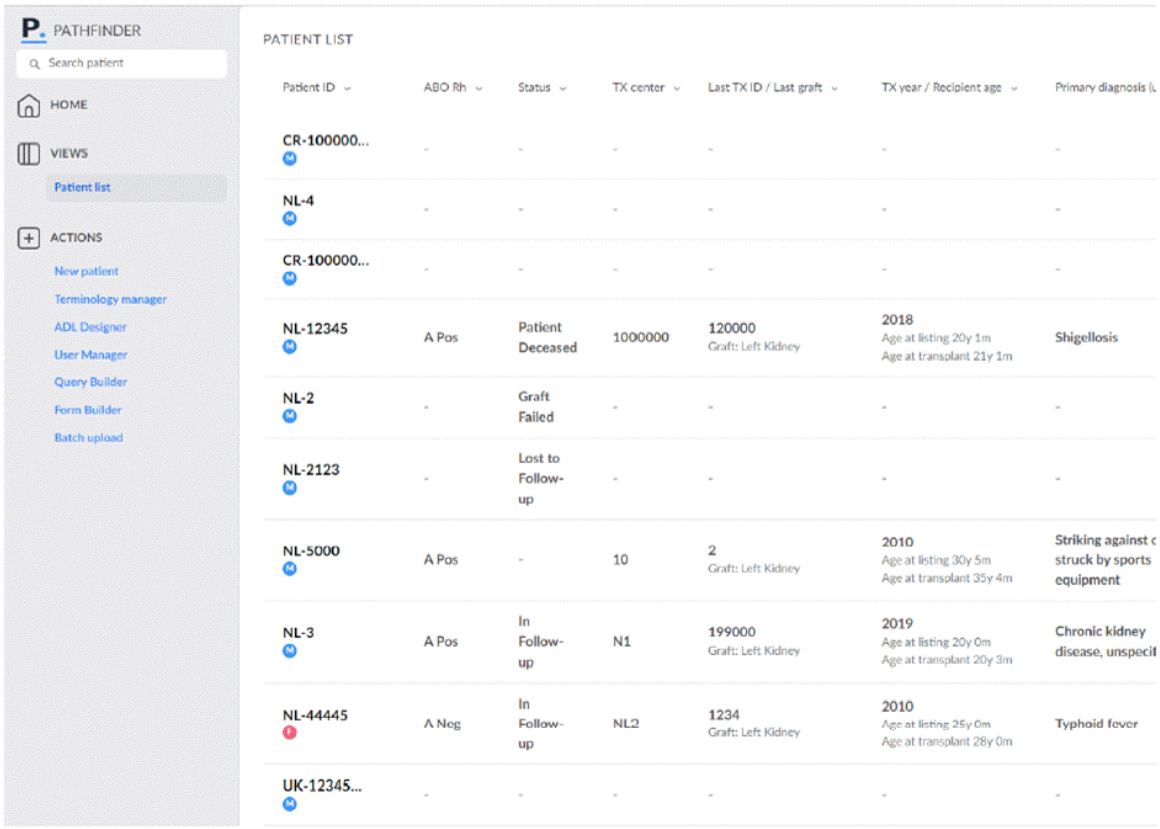


Figure 47: Pathfinder - Patient list

The following function can be used be End User within PathFinder.

- Patient list
  A list of all patients (visible for you user), you can select patients from here.
- Search patient
  Find a patient by patient ID.
- New Patient
  Register a new patient ID. Patient ID should start with countrycode and followed by a pseudonymised patient ID (Like NL-12345) generated by the NCA.

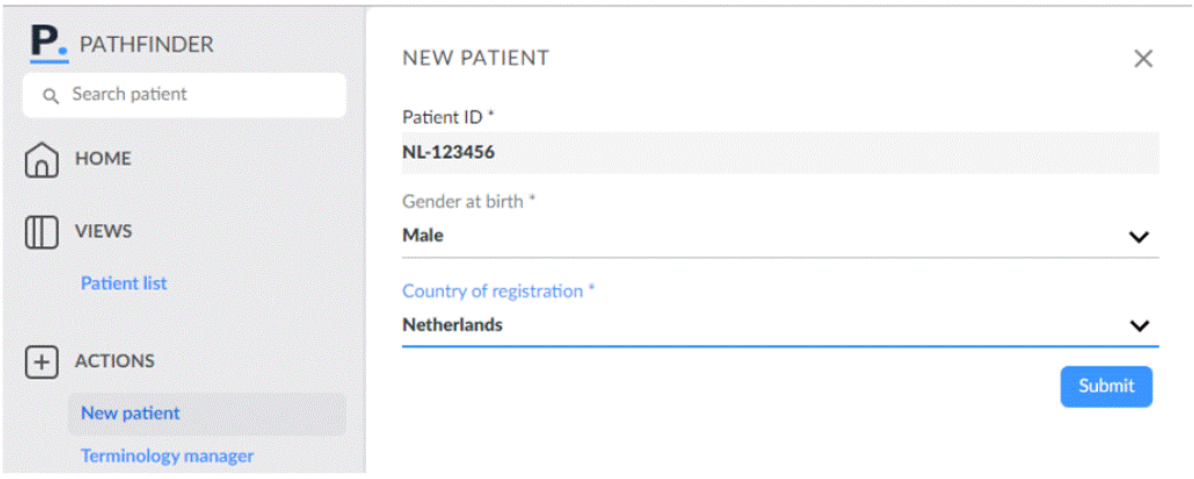


Figure 48:Register new patient

Batch Upload

Upload a csv file (format can be found on Github) containing multiple Initial or Follow Up records. Before uploading the csv file select the correct template from which the upload file was generated: “Edith Follow Up” or “Edit Initial”.

Patient view

Contains patient record, forms.

Patient record

The patient record contains a summary off the latest values for a patient. Also you can access all Initial and Follow-up form under the documents section. Within the documents session you can also edit the documents if they contain false information.

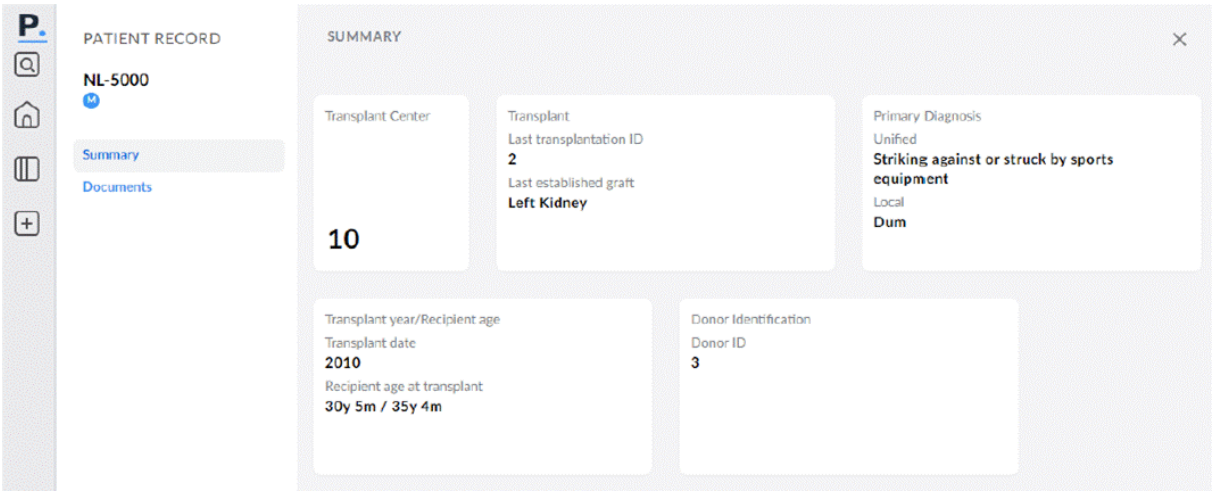


Figure 49:Patient record with summary

Forms

By opening one of the two follow-up forms: “Edith Initial” or “Edith Follow-up” you can enter the respective form for this patient.

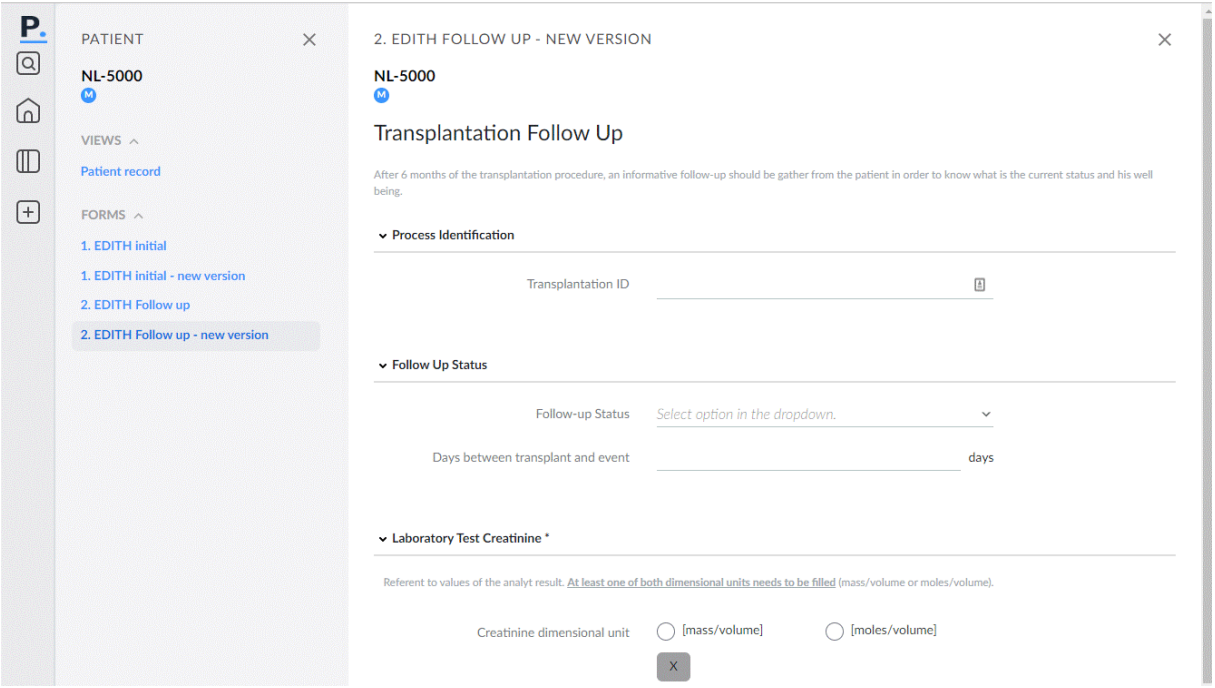


Figure 50: Follow-up form

Configuration

In the Github repository the forms and import formats can be found. A manual will be uploaded to the Github repository

IX.4.7 Statistics (Metabase)

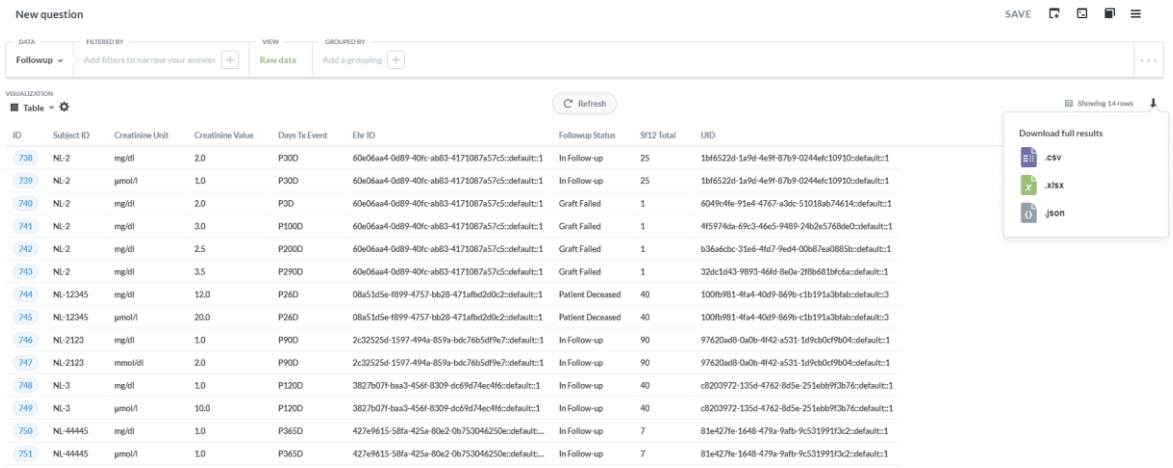
Description

Metabase is an opensource statistics program running on a docker instance in our configuration. It uses the postgress research database as its source database.

Use

All NCA's will get access to their own dataset as well as the full dataset anonymized. They can run some statistics on within metabase, but the main purpose is to be able to download the data in a flat and readable format.

Downloads are available in csv, xlsx and json format. Columns are configurable.



ID	Subject ID	Creatinine Unit	Creatinine Value	Days Tx Event	Ehr ID	Followup Status	SF12 Total	UID
738	NL-2	mg/dl	2.0	P30D	60e06aa4-0d89-40fc-ab83-4171087a57c5::default::1	In Follow-up	25	1bf6522d-1a9d-4e9f-87b9-0244efc10910::default::1
739	NL-2	µmol/l	1.0	P30D	60e06aa4-0d89-40fc-ab83-4171087a57c5::default::1	In Follow-up	25	1bf6522d-1a9d-4e9f-87b9-0244efc10910::default::1
740	NL-2	mg/dl	2.0	P3D	60e06aa4-0d89-40fc-ab83-4171087a57c5::default::1	Graft Failed	1	6049c4fe-91e4-4767-a3dc-51018ab74614::default::1
741	NL-2	mg/dl	3.0	P100D	60e06aa4-0d89-40fc-ab83-4171087a57c5::default::1	Graft Failed	1	4f5974da-69c3-46e5-9489-24b2e5768de0::default::1
742	NL-2	mg/dl	2.5	P200D	60e06aa4-0d89-40fc-ab83-4171087a57c5::default::1	Graft Failed	1	b36a6cbc-31e6-4fd7-9ed4-00b87ea0885b::default::1
743	NL-2	mg/dl	3.5	P290D	60e06aa4-0d89-40fc-ab83-4171087a57c5::default::1	Graft Failed	1	32dc1d43-9893-46fd-8e0a-2f8b681bfc6a::default::1
744	NL-12345	mg/dl	12.0	P26D	08a51d5e-f899-4757-bb28-471afbd2d0c2::default::1	Patient Deceased	40	100fb981-4fa4-40d9-869b-c1b191a3bfab::default::3
745	NL-12345	µmol/l	20.0	P26D	08a51d5e-f899-4757-bb28-471afbd2d0c2::default::1	Patient Deceased	40	100fb981-4fa4-40d9-869b-c1b191a3bfab::default::3
746	NL-2123	mg/dl	1.0	P90D	2c32525d-1597-494a-859a-bdc76b5df9e7::default::1	In Follow-up	90	97620ad8-0a0b-4f42-a531-1d9cb0cf9b04::default::1
747	NL-2123	mmol/dl	2.0	P90D	2c32525d-1597-494a-859a-bdc76b5df9e7::default::1	In Follow-up	90	97620ad8-0a0b-4f42-a531-1d9cb0cf9b04::default::1
748	NL-3	mg/dl	1.0	P120D	3827b07f-baa3-456f-8309-dc69d74ec4f6::default::1	In Follow-up	40	c8203972-135d-4762-8d5e-251ebb9f3b76::default::1
749	NL-3	µmol/l	10.0	P120D	3827b07f-baa3-456f-8309-dc69d74ec4f6::default::1	In Follow-up	40	c8203972-135d-4762-8d5e-251ebb9f3b76::default::1
750	NL-44445	mg/dl	1.0	P365D	427e9615-58fa-425a-80e2-0b753046250e::default:...	In Follow-up	7	81e427fe-1648-479a-9afb-9c531991f3c2::default::1
751	NL-44445	µmol/l	1.0	P365D	427e9615-58fa-425a-80e2-0b753046250e::default:...	In Follow-up	7	81e427fe-1648-479a-9afb-9c531991f3c2::default::1

Figure 51: Metabase download

X. EKRR Dataset (D6.3/.4/.5)

Responsible partner: ET
Document. EKRR data set from 29.01.2020

X.1. Donor variables

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
D1.1:ER	d_id	Donor ER ID	ER ID code, could be the same as used in the National or Regional registry in combination with a country code (ISO code) of the country that delivers the data or determined by Consortium	String	example NL-000001
D1.2	d_gender_birth	Donor Gender at birth	Donor's gender at birth	Coded list	- Male - Female - Unknown
D1.3	d_blood_group	Donor Blood Group	Donor's blood group	ET_ABO	- A - B - AB - 0
	d_rhesus Donor	Donor Rhesus	Donor Rhesus	terminology ET_RHESUS	- Positive - Negative
D1.4	d_height	Donor Height	Donor's body height	decimal (3.2)	
	d_height_unit	Donor Height unit		unit	- Cm - in_i (inch)
D1.5	d_weight	Donor Weight	Donor's body weight	weight decimal (3.2)	
	d_weight_unit	Donor Weight unit		unit	- kg - lb_av (pound)

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
D1.6	d_age	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.	Duration is 8601	- Years and months
		Donor Cause of Death - coded system used		not implemented as pilot is for KI	
D1.7		Donor Cause of Death	Two separate fields: one for coding system used and one for the respective death code	not implemented as pilot is for KI	
D1.8	d_cause_of_death_unified	Unified Cause of Death	For Kidney And Pancreas: ICD-10.	terminology ICD10	
D1.10	d_type	Donor Type	Type of donor	coded list	- DCD - DBD - Living
D1.11	d_malignant_tomour	Malignant tumours in the donor*	Evidence for malignant tumours	coded list	Evidence for malignant tumours
D1.11	d_malignant_tomour_absence		No information available about malignant tumors	coded list	No information available about malignant tumors
D1.11	d_malignant_tomour_exclusion		No evidence for malignant tumours	coded list	No evidence for malignant tumours
D1.12 (D3.24)	d_hla_code	Donor HLA - typing A-B-DR (1-2) antigen	One string only A1, A2, B1, B2, DR1, DR2 either or split is possible	Terminology HLA_nomenclature_2010	
	d_hla_locus	Donor HLA Locus	Locus e.g. HLA-A, HLA-B	Terminology HLA_nomenclature_2010	

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
New	d_medication_name, d_medication_ever_used	Donor Past history of hypertension	Was the donor treated with anti hypertension drugs	Medication name (string): Medication_ever_used (boolean):	Anti hypertension drugs - True - False
New	d_creat_mass_volume d_creat_moles_volume	Donor Creatinine at time of offer/retrieval	Donor Creatinine at time of offer/retrieval	decimal (3.2)	
	d_creat_mass_volume_unit d_creat_moles_volume_unit	Donor creatinine unit		unit	- Umol/l - mmol/dl - mg/dl
D.2.2	d_cmv_igg	Anti-CMV	IgG	Positive if there is a CMV IgG titer higher than 2 , Non-Reactive, Unknown	Reactive,, Non-Reactive, Unknown
D2.4	d_hiv_ab	HIV (I/II)	Antibodies against Human Immunodificiency virus subtype 1 or 2	Reactive (= if IgG>2), Non-Reactive, Unknown	Reactive,, Non-Reactive, Unknown
D2.8	d_hcv_ab	HCV Ab*	Antibodies against hepatitis C virus	Reactive (= if IgG>2), Non-Reactive, Unknown	Reactive,, Non-Reactive, Unknown
D3.33	d_diabetis_type	Diabetes	Was the the donor diabetic? And what type?	Terminolgy ICD_10_diabetis	
D3.33	d_diabetis_absence		No information available about diabetis	coded list	- No information available about malignant tumors
D3.33	d_diabetis_exclusion		Patient is not diabetic	coded list	- Patient is not diabetic

X.2. Recipient variables

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
NEW: ER	r_id	Recipient ER ID	ER ID code, could be the same as used in the National or Regional registry in combination with a country code (ISO code) that delivers the data or determined by Consortium	String	example NL-000001
R1.1	r_gender (from demographics)	Recipient Gender at birth	Patient's Gender at birth	Male, Female, Unknown	- Male - Female - Unknown
R1.2	r_blood_group	Recipient ABO Blood Group	Patient's Blood Group Type	Terminology ET_ABO	- A - B - AB - O
	r_rhesus	Donor Rhesus	Donor Rhesus	terminology ET_RHESUS	- Positive - Negative
R1.3	r_prim_diag_local	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.	string	
R1.4: ER	r_age_at_listing	Recipient age at listing in years	Number of years between date of listing and date of birth	Duration iso 8601	Years and months
R1.5	r_prim_diag_unified	Unified Primary Diagnosis	For kidney and pancreas: ICD-10	terminology ICD10	ICD10
R1.9:ER	r_dial_age_at_first r_dial_age_at_first_unit	Age in years at start of first dialysis	The age the recipient had reached being put on dialysis for the first time, before his first transplantation. For second and third transplantation, this variable is not entered.	decimal (3.1)	unit: yr

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
NEW	r_dial_time_from_first	Time from first dialysis to waitlisting	Number of days between date first dialysis and date of waitlisting	Duration iso 8601	days
T1.19 (T3.22)	r_hla_code	Recipient's HLA - typing A-B-DR (1-2) antigen	One string only A1, A2, B1, B2, DR1, DR2 either or split is possible	Terminology HLA_nomenclature_2010	
	r_hla_locus	Donor HLA Locus	Locus e.g. HLA-A, HLA-B	Terminology HLA_nomenclature_2010	
R2.1	r_hiv_ab	HIV (I/II) Ab*	Reactive (= if IgG>2), Non-Reactive, Unknown	coded list	- Reactive - Non reactive - Unknown
R2.5	r_hcv_ab	HCV Ab	Reactive (= if IgG>2), Non-Reactive, Unknown	coded list	- Reactive - Non reactive - Unknown
New	r_hbv	HBV	Reactive (= if IgG>2), Non-Reactive, Unknown	coded list	- Reactive - Non reactive - Unknown
New	r_cmv_igg	CMV	Reactive (= if IgG>2), Non-Reactive, Unknown	coded list	- Reactive - Non reactive - Unknown
New	r_dial_tech	Dialysis type	The type of last dialysis used - Hemodialysis (HD) - Peritoneal (PD)	coded list	- HD - PD
New	r_sensitised	Sensitisation before first transplantation		Boolean	- True - False
	r_current_pra_technique	Technique for determining antibodies on which PRA is based			- Luminex - Elisa - DTT - CDC - Other

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
	r_current_pra r_current_pra_unit	Current PRA (=last value known before transplantation)		Integer / unit	0-100%
	r_highest_pra_technique	Technique for determining antibodies on which PRA is based			- Luminex - Elisa - DTT - CDC - Other
	r_highest_pra r_highest_pra_unit	highest PRA(=last value known before transplantation)		Integer / unit	0-100%

X.3. Transplantation variables

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
T1.1:ER	tx_id	Transplant ER Number ID	ER ID code, could be the same as used in the National or Regional registry in combination with a country code (ISO code) that delivers the data or determined by Consortium	string	example NL-000001
NEW	d_gender_birth	Recipient ID	ER ID code, could be the same as used in the National or Regional registry in combination with a country code (ISO code) that delivers the data or determined by Consortium	string	example NL-000001

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
NEW	d_id	Donor ID	ER ID code, could be the same as used in the National or Regional registry in combination with a country code (ISO code) that delivers the data or determined by Consortium	string	example NL-000001
T1.2:ER	r_age_at_transplant	Age in years at transplant	the number of years and months between date of transplant and date of birth	Duration iso 8601	years and months
NEW	tx_time_dialysis_and_transplant	Time from first dialysis to transplant	the number of days between date of first dialissys and date of transplant	Duration iso 8601	days
New	tx_date	Year of transplant		Partial date (Year)	
T1.3	country (from demographics)	Country	Country where recipient is registered as recipient at time of transplant.	ISO-Code 3166	
New	tx_center_id	Centercode	Nationale ISOcode combined with National center code	string	example NL-001
New	tx_pre_emptive_transplant	Preemptive transplantation	Was the patient preemtively transplanted?	coded list	- Yes - No
New	tx_number_previous_kidney	Number of preceeding kidney transplants	How many kidney transplant did the patient have before this transplantation	integer	
T1.7	tx_cold_ischemia_time	Total Ischemic Time HOURS	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.	Duration iso 8601	hours and minutes

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
T2.11	tx_graft	Type of transplant	Multiple grafts can be added. So two rows for LKI plus RKI transplant or two or more for a multi organ transplant. Alternatively enter only kidney here and use the multi_organ_transplant checkbox to indicate multiple organs were used. LKi, Left Kidney RKi, Right Kidney BKi, Kidney en Bloc WLiv, Whole Liver LLSLiv, Left Lateral Segment ERLLiv, Extended Right Lobe RLLiv, Right Lobe LLLiv, Left Lobe LLiv, Left Split Liver RLiv, Right Split Liver He, Heart BLu, Both Lungs LLu, Left Lung RLu, Right Lung Pa, Pancreas In, Intestine Ut, Uterus Eso, Esophagus Sm, Stomach Col, Large intestine (Colon) VCA, Vascularized composite allograft	Terminology graft_v1	- LKi - RKi - BKi - WLiv - LLSLiv - ERLLiv - RLLiv - LLLiv - LLiv - RLiv - He - BLu - LLu - RLu - Pa - In - Ut - Eso - Sm - Col - VCA

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
New and Tier 2 or 3 datafields that would be advisable	tx_graft_id	Graft ID	Nationale ISOcode combined with National graft ID. Only applicable if grafts get their own ID.		
New	tx_multi_organ_transplant	Was the kidney transplanted part of a multi organ transplant	Multi organ, kidney(s) plus any other organ as defined in graft	Boolean	- True - False
	tx_sequence	Sequence of this transplant within the year of transplant (order)	Starting with 1 fro first transplant within the transplant year. Can be left empty if transplant_id is a sequential id.	Integer	
T1.4	htx_id	Historic: Transplant ID	Specification of previous transplant(s). For each of the previous transplants the specification will be required. Multiple historic transplants can be stored. Historic transplants are transplants not registered within the Edith database. ER ID code, could be the same as used in the National or Regional registry in combination with a country code (ISO code) that delivers the data or determined by Consortium	string	example NL-000001
	htx_multi_organ_transplant	Historic: Was the kidney transplanted part of a multi organ transplant	Multi organ, kidney(s) plus any other organ as defined in graft	Boolean	- True - False
	htx_center_id	Historic: Centercode	Nationale ISOcode combined with National center code	string	example NL-001

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
	htx_graft	Historic: Type of transplant	Multiple grafts can be added. So two rows for LKI plus RKI transplant or two or more for a multi organ transplant. Alternatively enter only kidney here and use the multi_organ_transplant checkbox to indicate multiple organs were used. LKi, Left Kidney RKi, Right Kidney BKi, Kidney en Bloc WLiv, Whole Liver LLSLiv, Left Lateral Segment ERLLiv, Extended Right Lobe RLLiv, Right Lobe LLLiv, Left Lobe LLiv, Left Split Liver RLiv, Right Split Liver He, Heart BLu, Both Lungs LLu, Left Lung RLu, Right Lung Pa, Pancreas In, Intestine Ut, Uterus Eso, Esophagus Sm, Stomach Col, Large intestine (Colon) VCA, Vascularized composite allograft	Terminology graft_v1	- LKi - RKi - BKi - WLiv - LLSLiv - ERLLiv - RLLiv - LLLiv - LLiv - RLiv - He - BLu - LLu - RLu - Pa - In - Ut - Eso - Sm - Col - VCA

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
	htx_graft_id	Historic: Graft ID	Nationale ISOcode combined with National graft ID. Only applicable if grafts get their own ID.		
	htx_sequence	Sequence of this transplant within the year of transplant (order)	Starting with 1 fro first transplant within the transplant year. Can be left empty if transplant_id is a sequential id.	integer	

X.4. Follow-up variables

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
F1.1: ER	r_id	Recipient ER ID	ER ID code, could be the same as used in the National or Regional registry in combination with a country code (ISO code) that delivers the data or determined by Consortium	Alphanumerical code	example NL-000001
	tx_id	Transplant ER Number ID	ER ID code, could be the same as used in the National or Regional registry in combination with a country code (ISO code) that delivers the data or determined by Consortium	string	example NL-000001

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
T2.11	fup_graft	Type of transplant	Multiple grafts can be added. So two rows for LKI plus RKI transplant or two or more for a multi organ transplant. Alternatively enter only kidney here and use the multi_organ_transplant checkbox to indicate multiple organs were used. LKi, Left Kidney RKi, Right Kidney BKi, Kidney en Bloc WLiv, Whole Liver LLSLiv, Left Lateral Segment ERLLiv, Extended Right Lobe RLLiv, Right Lobe LLLiv, Left Lobe LLiv, Left Split Liver RLiv, Right Split Liver He, Heart BLu, Both Lungs LLu, Left Lung RLu, Right Lung Pa, Pancreas In, Intestine Ut, Uterus Eso, Esophagus Sm, Stomach Col, Large intestine (Colon) VCA, Vascularized composite allograft	Terminology graft_v1	- LKi - RKi - BKi - WLiv - LLSLiv - ERLLiv - RLLiv - LLLiv - LLiv - RLiv - He - BLu - LLu - RLu - Pa - In - Ut - Eso - Sm - Col - VCA

NR referring to EFRETOS or New field	short_name	Variable name	Definition	Unit or coding	Allowed values
New and Tier 2 or 3 datafields that would be advisable	fup_graft_id	Graft ID	Nationale ISOcode combined with National graft ID. Only applicable if grafts get their own ID.	string	example NL-000001
	fup_status	Follow-up event for which the follow-up is entered	- Patient Deceased - In Follow-up (normal follow-up) - Lost to Follow-up - Graft Failed	coded list	- Patient deceased - In Follow-up - Lost to Follow-up - Graft Failed
F1.3, F1.6 and NEW	fup_days_since_transplant	Time (Number of days) between transplantation and follow-up event	Time (Number of days) between transplantation and the date that the recipient was last seen alive	Duration iso 8601	days
F1.4	fup_cause_of_graft_failure_local	Primary Cause of Graft failure		string	
	fup_cause_of_graft_failure_local	Unified Primary Cause of Graft failure	ICD-10	Terminology ICD10	ICD-10
F1.7	fup_cause_of_death_local	Cause of Death	All coding systems are allowed	Death cause code	
F1.8	fup_cause_of_death_unified	Unified Cause of Death	For Kidney and Pancreas: ICD-10	Terminology ICD10	ICD10
F1.9	fup_creat_mass_volume fup_creat_moles_volume	Serum creatinine at date last seen		decimal (3.2)	
	fup_creat_mass_volume_unit fup_creat_moles_volume_unit	Unit of Creatinine at data last seen		unit	- Umol/l - mmol/dl - mg/dl

Pilot of the EDITH registries

ELDR

XI. Report on support given during the course of the project to different national registries (D5.4)

Responsible partner: IDIBAPS/NTS
Document. D5.4 of 09.11.2020

XI.1. Introduction

This work package is supporting the establishment of registries to follow-up living kidney donors by EU Member States (MS) following the EU Directive 2010/53/EU on standards of Quality and Safety of human organs intended for transplantation where is written: “Member States shall ensure that a register or record of the living donors is kept and shall endeavour to carry out the follow-up of living donors”.

EU Member States will be responsible for building their own national registries and WP5 will support them through functional and technical advice, based on the structure of the ELDR which will support supranational data collection.

The ELDR was created as web-based application approachable by common internet surfing programmes (any HTML5 standard browser); the language used for the ELDR is English. ELDR supports direct data entry as well as file upload by countries/centres, and a data download functionality.

This EDITH deliverable describes the support offered to the interested Member States of the European Union to integrate their donor data into the ELDR.

XI.2. Methodology

In the first phase of the project a questionnaire was sent to all MS to collect information about the current activity in living donation, living donor follow-up registration and the plans and/or willingness to develop or adapt eventual existing national registries as well as to deliver information to the ELDR (see Deliverable 5.1).

After this first phase, the ELDR was designed with its specifications (dataset, functional and technical requirements, see Deliverable 5.2). Governance organization for the ELDR (and data request handling) was also established (see Deliverable 5.3) and in October 2019 the ELDR was ready to start its implementation. Once the ELDR was implemented on production the coordinators of WP5 (NTS and IDIBAPS) contacted all those Member States that were willing to participate in the registry. This task was divided between both partners of WP5. NTS contacted all centres that were willing and able to participate in the ELDR and IDIBAPS contacted all centres that needed help to realize a living donor registry or to participate in the ELDR. All contacted centres received several useful documents (see Deliverable 5.5) and were offered technical as well as logistical help with the data base.

In order to have as many donors as possible in the ELDR as part of a contingency plan IDIBAPS used contacts at centre level in those countries where the National Authorities could not comply with sharing data (Spain, Germany, Czech Republic; see Deliverable 5.5). IDIBAPS offered help also to the individual centres they contacted.

This deliverable will explain, on a country level, all the situations encountered, and describe the consultancy given.

XI.3. Results

From the questionnaire results analysis was concluded that 19/24 EU member States that have answered the questionnaire were willing to participate in an ELDR; 13 were willing and able, 6 were not able yet. All those countries were approached by email in where the official invitations were sent and/or help was offered. After first answers additional documents were required. Therefore, an agreement to define the rights and responsibilities of both delivering country and the ELDR consortium in terms of data handling was prepared. This is considered an important document and required for data exchange, especially due to national GDPR regulations. The cooperation agreement has been developed by the ELDR consortium with help of legal experts and has been forwarded to all 15 countries that received the original ELDR invitation as well as the 5 centres that were contacted by IDIBAPS (for more details please see XII Report of ELDR implementation (D5.5)). Additionally, Data Security ELDR policies have been prepared and sent to all the countries (document attached as Annex 2 to section XII Report of ELDR implementation (D5.5)). Also, few centres required specific agreements format as their internal protocols required.

In order to satisfy the needs presented by the MS, WP5 of the EDITH project put at each MS disposition the following channels of help:

- As feature of the ELDR registry the following staff functions are offered
    - daily support,
    - helpdesk,
    - database management,
    - (technical) development and improvements
- Email disponible for addressing queries
- Phone calls disponible for answering in real time
- Video conferences in where a “live demonstration” of data entering will be shown

The process of data entering started in December 2019. Lithuania has entered the first donor on 5/12/2019; Spain started 20/1/2020, Slovenia and Italy 24/2/20, the Netherlands, Germany and Czech Republic in March 2020, and France in May 2020. During the summer donors from Ireland were added, the UK delivered their data followed by Croatia and Portugal. In Table 39 below we will explain the difficulties faced by the centres and how we were able to solve these difficulties.

Table 39: Problems during

Country	Problems	Solution	Help provided
ALL	test conversion/upload	possibility to test the conversion and upload on test (UAT) before production	credentials on UAT, and after satisfactory test changed to productio
The Netherlands	upload errors	XLS upload did not work, but could be solved to save file as csv file	check file, test UAT and return csv + instruction for next time
	upload problem file size	split file to maximum of 5000 records	answer with solution by mail; larger file size desire noted for next ELDR version
Italy	error in the value formatted in the Blood Group	problem is that they tried to enter donors with blood group 0 (null), while the ELDR only accepts O; easiest way to resolve this was to replace the 0 with an O and upload the donors again	checked registered data, test UAT and reply by mail
	problem that it is not possible to delete all records uploaded, the operation is allowed only for the 10 records shown in each page	suggested just to upload a corrected file, it was not necessary to delete the old donors, but if that would be necessary (either on test or on production) for a complete set (in which the current deletion function would take too much time), we could ask the ELDR system manager for help	reply by mail
	errors for country codes	Code list for countries for file upload adapted in ELDR; for non existing codes advice to enter <NULL>	consulting and adaptation ELDR by technical manager and answer/instruction by mail
	upload problem file size	split file to maximum of 5000 records	answer with solution by mail; larger file size desire noted for next ELDR version
France	no specific questions for help other than GDPR compliance		
Ireland	questions regarding ELDR access and file format		clarifications and instructions were given through emails and phone calls
Latvia	questions on delivery of sensitive information like name and date of birth	answered that these items are not mandatory, but can be used to find the right donor and can be filled with any (dummy) information	answer by email
Croatia	problems encountered in evaluation phase (direct data entry)	several problems that could be resolved were resolved by IDIBAPS technical manager; others are noted as desires for next version	evaluation document, some points further tested on UAT, solution proposals and questions have been communicated by email
	questions on batch upload in the production phase: use of ID, possibility	* same external ID needs to be used to link the 4 ELDR files	questions answered by emails and phone calls

Country	Problems	Solution	Help provided
	to differentiate centres in case of national file upload, the creation of csv-files and the right date formats	* this is possible only in case of several user accounts for the different centres instead of 1 account on national level	
Lithuania	question on timeframe and funds	answered by email	questions answered by email
Czech Republic	coverage of the local registry is 95%, rest is in other centres	contacted the centre with 95% of the activities. They agreed to collaborate. No technical difficulties presented while filling the data	several mails were exchanged until final insertion of data was made.
Germany	cooperation is dependent on the realization of the National Registry, which is currently under development.	contacted single centre Charité Medical University Berlin Agreed to collaborate. No technical difficulties presented while filling the data	a centre-based agreement was prepared, signed by IDIBAPS and Charité for local ethical approval. Several mails with technical instructions were exchanged.
Slovenia	would need additional administrative support	were contacted different times and finally positive answer was given. Data entering ongoing	clarifications and instructions as per request were given through emails and phone calls.
Slovak Republic	differences in databases, although this can be solved in time		
Bulgaria	at the moment time is needed to collect the available data from hospitals and to establish a national program providing an organizational model and financing	required more time to discuss the project and our invitation.	After several attempts to contact the national institute in charge of Donation and transplantation, we were able to establish a communication and by October 2020, Bulgarian Executive Agency for Medical suppliers signed the agreement.
UK	several questions on the inclusion of donors and conversion of data to the required ELDR format and values		clarifications and instructions were given through emails
	upload problem file size	split file to maximum of 5000 records	answer with solution by mail; larger file size desire noted for next ELDR version
	upload errors	upload errors due to old version (previous version of UAT ELDR in cache)	check file, test UAT and return csv + instruction (clear cache or use incognito mode)
Portugal	questions on data compliance: whether uncompleted donors could be uploaded in the registry due to few missing information.	checking user manual	reply by mail to each query and suggested to use the batch upload methodology.

XI.4. Conclusions

We can conclude that there were different modalities of help/support which were provided to the participating countries. Since all the participants were facilitated to test in the UAT environment, less problems were encountered when they passed on to the production ELDR environment. Most of the issues were solved by email correspondence between registry users and NTS/IDIBAPS/technical manager. A few corrections and improvements in the registry were made during this time. Considerations for adding functionalities or improving the existing ones were summarized aiming to change them in the near future. To mention few of them:

- Donor self-reporting
- Adaptation to new advances in electronic and mobile technologies
- Adaptation to the new requirements, regulations and capacities in terms of donor data management
- Display more results in the dashboard tab

The few countries that had logistical issues and were not able to participate in the registry, were contacted several times in order to find any possible solution (eg Bulgaria; Latvia).

This experience showed that the ELDR is a user-friendly application and has the capacity to deal with a big amount of data. The technical manager (helpdesk) was able to fix the problems presented so far, which is reassuring for the future.

XII. Report of ELDR implementation (D5.5)

Responsible partner: IDIBAPS/NTS
Document. EDITH_D5.5 (excl appendix1-4).pfd of 09.11.2020

This report describes the European Living Donor Registry development and implementation as well as the EU Member States participation status including the reported data in the ELDR.

XII.1. ELDR development

EDITH WP5 was aimed at the realization of a European Living Donor Registry (ELDR) for living kidney donors, supporting lifelong follow-up data collection. An important rationale for this development is that EU Member States are both legally (EU Directive 2010/53/EU) and morally obliged to follow-up living donors in order to protect their safety. The ELDR consists of a database, a web-based application supporting both direct data entry and file upload, a data download facility, and a report facility complying with all legal requirements. The NTS ("Nederlandse Transplantatiestichting", which stands for Dutch Transplant Foundation) and IDIBAPS (Institut d'Investigacions Biomèdiques August Pi I Sunyer, located in Barcelona, Spain), together the "ELDR consortium", are responsible for the development and hosting of the ELDR. Parties participating in the ELDR will sign a cooperation agreement with the ELDR consortium concerning ELDR data handling (see section 3); all parties will comply to the General Data Protection Regulation (GDPR) 2016/670 regarding to the processing of personal data and have security measures in place. The use of the ELDR is described in the ELDR Manual (see section XIII ELDR User Manual (D5.2)).

XII.1.1 Web based application and database

The ELDR is a web based application, supporting both direct data entry (typically from local centres) and file upload (typically from National databases).

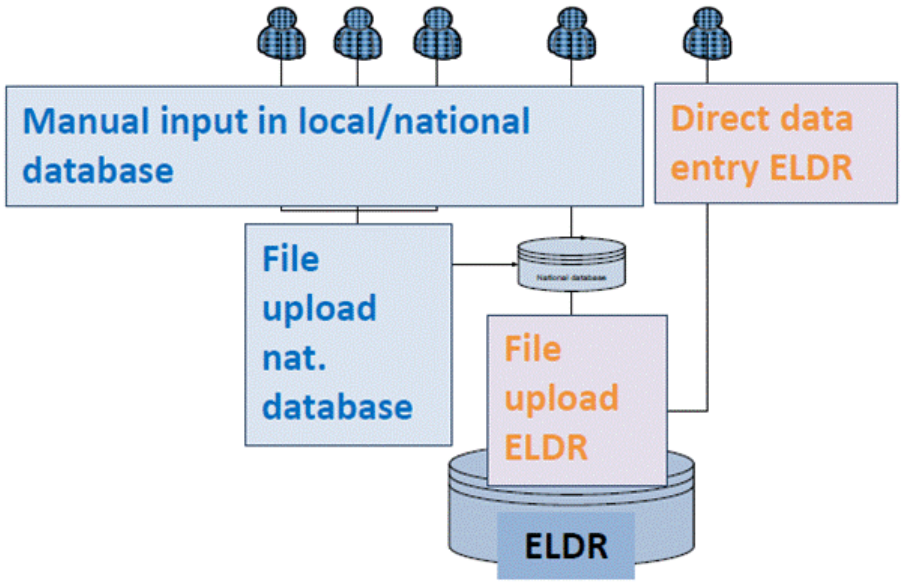


Figure 52: Structure of ELDR supporting direct data entry and file upload

The ELDR database is hosted by IDIBAPS, Barcelona.

The access link to the ELDR is: https://eldr.edith.eulivingdonor.eu

For testing purposes an User Acceptance and Test (UAT) environment is available at https://uat.edith.eulivingdonor.eu

The database is built according to the ELDR file specifications, which were part of Deliverable 5.2 (Appendix 2) (see section VII Report on the ELDR specifications (D5.2)).

All application features are described in the ELDR manual, which were also part of Deliverable 5.2 (Appendix 1) (see section VII Report on the ELDR specifications (D5.2)).

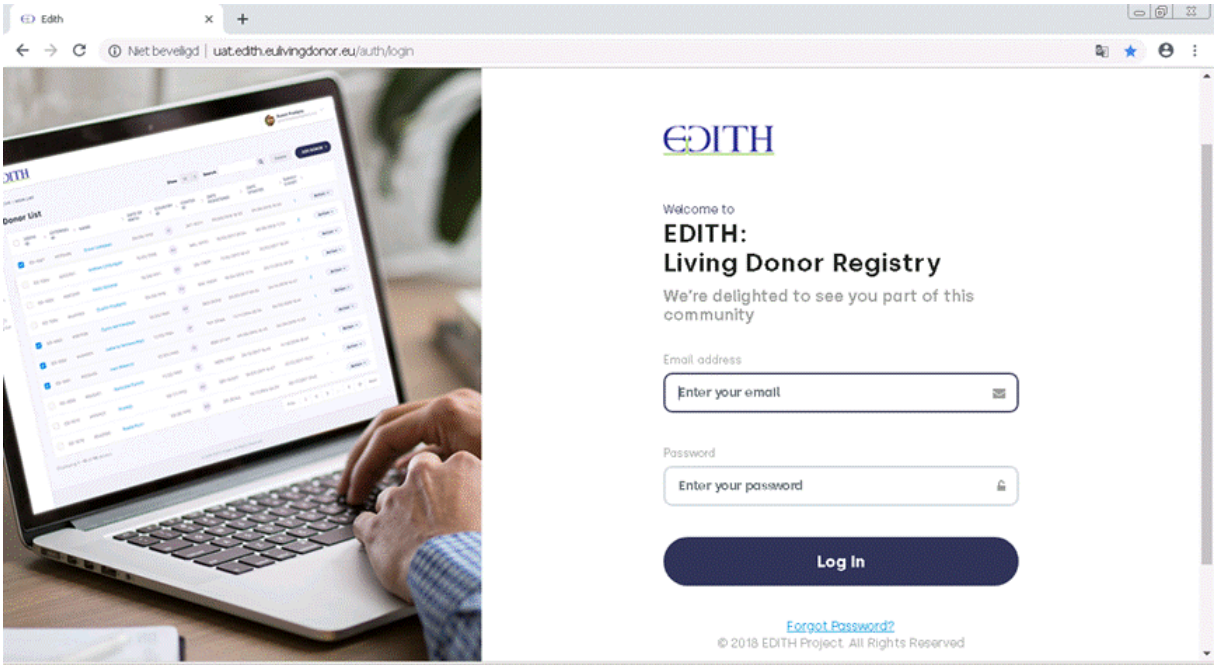


Figure 53: ELDR login screen

XII.1.2 Data entry

Data entry is possible for authorized users with the right authorization profile in the ELDR. Users log in to the ELDR using their email address and password. The transit of data is encrypted using an SSL certificate with an RSA public key of 2048 bits.

Direct data entry (also for living donors themselves)

The ELDR allows the users to enter donor information manually into the registry from the browser. The input of data is divided in the different entities also described in the file specifications: the living donor, pre-donation information, post-operation information and follow-up information. Data can be entered, viewed, updated and deleted and all actions are audited. Donor self-reporting, a feature mentioned in the project plan, is technically feasible, but not included in the implemented version of the ELDR.

Suggested ELDR adjustments to support donor self-reporting

In the application in the donor details section, a button can be added to send a follow-up survey via email to a donor; clicking the button will prompt for the email address to send the survey. This email address will not be saved in the database to avoid donor identification. The donor will receive an email with a link to complete a survey that will include a subset of the elements defined in the follow-up survey. This link will be active until the user sends the survey or until three months after it is sent. The survey will be rendered to be displayed on mobile screens or desktop automatically, and it will detect user local settings to show the text in the user's language. It will not be possible to send

a new follow-up by email while there is one pending to be answered. When the donor sends the survey, the data will be incorporated as a new follow-up to the existing data of the donor. Optionally, surveys may be sent to donors using WhatsApp. In that scenario the donor phone number will be prompted and the system will try to establish an automated chat asking all the questions on the follow-up.

XII.1.3 File upload

The ELDR allows users to upload data from batch files. The maximum number or records in one upload is 5000. More records will result in an upload error, so users need to split files to upload smaller files, if they should have files that exceed 5000 records. There is a separate upload possibility for each of the 4 files: donor, pre-donation, post-operation, and follow-up. The file templates (either comma (“,”) separated or semicolon (“;”) separated) can be viewed in the application. Uploaded files will be checked. After every upload the user is notified about the number of successfully imported records, the number of records that were declined and the number of records that were imported with warnings. To view the errors or warnings detected during the file uploading as well as all successfully uploaded records, a report with the upload results can be downloaded and analyzed.

XII.1.4 File download and report facility

The ELDR allows data extractions for manual reporting. Currently the dashboard of the ELDR only includes one report with the number of reported donors per country by sex (see section 7 for the current content of the ELDR). The dashboard doesn’t include pre-defined and automated reports yet, but the reports in section 7 of this Deliverable are a blueprint for the future reporting facility. In section 8 we have added the results of a questionnaire distributed among the ELDR users to check the relevance of the proposed reports as well as to make an inventory of additionally required reports. A few suggestions for ELDR dashboard reports:

- Number of donations performed per year (and per country/year)
- Donor age (at time of donation) and age-distribution
- Donor death within the first month, the first year
- Kaplan-Meier long-term donor survival, age-adjusted
- Kaplan-Meier long-term freedom from renal replacement therapy
- Donor kidney function over time (pre-donation and at different time points after donation)
- Percentage of donors with 5-year-function below 60 mL/min CKD-EPI

Access to the dashboard is configurable through the user settings. The dashboard is updated in real time (as new data is received, the visualizations will be automatically updated). In the future the dashboard will be elaborated with new reports.

XII.2. ELDR implementation

The ELDR was developed by IDIBAPS and extensively tested by NTS. This was done at the test environment (UAT) and the process of development and testing took approximately one year. In October 2019 the ELDR (version 1.0) was ready for production and after that this first implementation was tested by Croatia (WP3) as well as made available to all EU countries that were willing and able to participate in the ELDR (see sections 3 and 4 of this Deliverable). After ELDR implementation, the helpdesk support was established for the duration of the project by dedicated NTS and IDIBAPS staff personnel. Also an online platform was realized to manage the Helpdesk support service for users of the EDITH platform. The following tasks are carried out:

Active participant's follow-up activity

- Evaluation of the necessities of the countries without National Registry to offer them "tailored solutions"
- Direct contact with coordinators

XII.2.1 Production testing by Croatia and evaluation of the user-friendliness by ELDR users

ELDR evaluation Croatia

The Croatian Ministry of Health, Institute for transplantation and biomedicine, (Work Package 3 of the EDITH project: evaluation of EDITH) has conducted evaluation of the ELDR application. They have invited all Croatian kidney transplant centres (University Hospital Zagreb, University Hospital Rijeka, University Hospital Osijek and Clinical Hospital Merkur) to evaluate the ELDR application. All four centres have been assigned with access to the ELDR application test environment to perform validation of the application in line with suggested parameters: -

- User friendliness of the ELDR app
- Overall visibility of the web app
- Usefulness of the ELDR app for everyday work
- Overall/long term usefulness of the ELDR app
- Overall quality of the ELDR app

Additionally, they have been asked to point out advantages and disadvantages of the application and provide feedback by completing an evaluation questionnaire created for this purpose. Evaluation has also been conducted by the Ministry of Health Croatia (WP3) team.

Summary of all received answers send to WP5 on December 27th 2019 by the Ministry of Health Croatia (WP3) team:

Table 40: Answers received after Croation piloting

Based on your experience on ELDR app, please grade: (1-very bad / 2-bad/ 3-good / 4-very good / 5-excelent)
1. User-friendliness of the ELDR app
☐ 1 ☐ 2 ☐ 3 ☒ 4 ☐ 5
2. Overall visibility of web app
☐ 1 ☐ 2 ☐ 3 ☒ 4 ☐ 5
3. Usefulness of the ELDR app for (your) everyday work
☐ 1 ☐ 2 ☒ 3 ☐ 4 ☐ 5
4. Overall/long term usefulness of the ELDR app
☐ 1 ☐ 2 ☐ 3 ☒ 4 ☐ 5
5. Quality of the ELDR app
☐ 1 ☐ 2 ☐ 3 ☒ 4 ☐ 5

Most items were rated “very good” with the exception of the Usefulness of the ELDR for everyday work (which was rated 3, so “good”). Note: the ELDR is not meant for use in daily living donor care, but as a follow-up registration to be able to monitor and research long term implications of living kidney donation. Therefore, the fact that this topic was rated lower that the other items is not surprising. We conclude that the question was not well put, as we intended only to check whether the application was easy to work with on a daily basis.

A summary of all received answers has been prepared by the Croatian WP3 team and this has been sent to WP5 as part of the evaluation. This has resulted in a number of improvements by WP5 which have been implemented on production in 2020.

Evaluation by active ELDR users (October 2020)

At the end of the project, the ELDR staff has sent a questionnaire to all active ELDR users. As part of the questionnaire, to evaluate the ELDR experiences of the ELDR users, a grading of the user friendliness of the different parts, as well as the provided documentation has been requested.

Seven questionnaires have been returned to us, from six different countries. Overall the ELDR-users that returned the questionnaire were positive on the user friendliness of the ELDR application and documentation:

Table 41: Answers received after Croation piloting

Based on your experience with ELDR, please grade: (1-very bad / 2-bad/ 3-good / 4-very good / 5-excellent/ 6-not done)	Number of users per grade (total questionnaires returned, N=7)
1. User.friendliness of log-in procedure	Excellent =4 Very good = 2 Good =1
2. User-friendliness of the key-entry	Excellent =4 Very good = 2 Not done/answered =1
3. User-friendliness of the file-upload procedure	Excellent =4 Very good = 2 Bad = 1 Not done = 1
4. User-friendliness of extract procedure	Excellent = 2 Not done/answered = 5
5. Overall friendliness of the ELDR	Excellent =4 Very good = 3
6. Usefulness of the documentation	Excellent = 3 Very good = 3 Not answered = 1

XII.2.2 ELDR invitations to countries willing and able to use the ELDR

After the implementation of the ELDR on the production environment, invitations have been sent in two batches to the National Competent Authorities (NCA) of all countries that indicated that they were willing and able to participate in the ELDR from the ELDR questionnaire (Deliverable 5.1):

- The first invitations were sent on October 21st 2019 to the first four countries (either closely related to WP5/WP6 or volunteer to evaluate the first ELDR version):
    - the Netherlands
    - Spain
    - Croatia
    - UK
- The second mailing to eleven other countries willing and able to participate was sent in November 2019 to
    - France
    - Greece
    - Hungary
    - Italy
    - Latvia
    - Lithuania
    - Poland
    - Portugal

- Ireland
- Romania
- Malta

The original invitation consisted of an e-mail with 6 attachments:

- Invitation letter
- Access rights form
- ELDR Manual
- ELDR File specifications
- EDITH registries governance proposal
- EDITH registries temporary governance document

Besides official invitations from the project Dr. M. Manyalich from IDIBAPS has contacted several physicians from different countries to motivate them to participate in the ELDR.

XII.2.3 ELDR Cooperation agreement, ELDR policy document, and DPIA

Based on the first responses on the ELDR invitation several Member States requested an agreement to define the rights and responsibilities of both delivering country and the ELDR consortium in terms of data handling. This is considered an important document and required for data exchange, especially due to national GDPR regulations. The cooperation agreement has been developed by the ELDR consortium with help of legal experts, and has been forwarded to all 15 countries that received the original ELDR invitation as well as the 5 countries that were contacted by IDIBAPS to offer help to start a living donor registry. This cooperation agreement is included in this document as Annex 1. Until now this cooperation agreement has only been returned by four countries. Most participating countries have probably viewed this document as a statement from the side of the ELDR staff how to handle and protect the data. Countries that delivered their data to the ELDR obviously were satisfied with the regulations and safeguards put in place on side of the ELDR. However, to continue the ELDR after finalization of the EDITH project, it is important to collect a signed data delivery agreement from all participating countries. This is one of the recommendations in the Data Protection Impact Assessment (DPIA) which has been conducted on the ELDR and the European Kidney Recipient Registry by WP5 and WP6. In the data delivery agreement also the obligations (like the data protection safeguards) of the participating countries have to be described and agreed upon. The current cooperation agreement might need to be transformed to a data delivery agreement after finalization of the project.

Data security is only briefly mentioned in the Cooperation agreement and has further been described in the enclosed ELDR policies document (Annex 2).

XII.2.4 ELDR Participants – status report September 2020

In the following table an overview is provided on the participation of countries that received the invitation mail, were contacted to offer help or for other reasons.

Country	Access ELDR	Participation	Agreement and/or status comments
The Netherlands	PROD – 1 user	NATIONAL – FILE UPLOAD 3/8 centres uploaded Donors, pre-donation, post-operation and follow-up surveys	Information forwarded by national registry based on NCA/centre agreements; some centres have not yet formally signed that document as this takes more time due to local GDPR regulations; this was further delayed due to COVID-19 crisis
Spain	PROD – 4 users	LOCAL – FILE UPLOAD Hospital Universitario 12 de Octubre Hospital Universitario Marques de Valdecilla Hospital Clinic de Barcelona Hospital Universitari de Bellvitge 4 centres uploaded Donors, pre-donation, post-operation and follow-up surveys	Agreement not signed at national level yet. Only local participation at the moment (with local agreements IDIBAPS/centre); ONT is positive about national participation after project phase. Once the ELDR is definitely established, the governance of the registry is definite and the means to make the registry sustainable are clear, ONT will be pleased to consider their participation.
Croatia	PROD-2 users	NATIONAL Donors and pre-donation information uploaded	Status October 12th: All 3 Croatian centers with living donors were invited to send living donor data to the Croatian NCA (in line with EDITH/ELDR requirements); the Croatian NCA takes care of the ELDR data upload
United Kingdom	PROD-2 user	NATIONAL - FILE UPLOAD Donors, pre-donation, post-operation and follow-up surveys uploaded	
France	PROD -2 users	NATIONAL – FILE UPLOAD Donors, pre-donation, post-operation and follow-up surveys uploaded	
Greece			No response yet
Hungary			Hungary is not participating in the ELDR yet both because of the absence of a translated ELDR agreement, and because of the current organisation of the living donor data collection in Hungary.
Italy	PROD-3 users	NATIONAL(CNT) - FILE UPLOAD Donors, pre-donation, post-operation and follow-up surveys uploaded	Information forwarded by CNT. Italy has entered in February all data that they had in their registry from 2001 up till then.
Latvia			In 2019 the transplant centre was reorganized and processes/functions were divided by separate hospital structures, which needed to be solved. In 2020 IDIBAPS received several positive answers by email, but there has not been activity in the ELDR yet.
Lithuania	PROD-2 users	LOCAL – DIRECT DATA ENTRY Vilnius University Hospital Santaros Klinikos 1 centre registered 1 donor	Reminder 9/3 in which NTS has asked to inform us when Lithuania expects to be able to send further data (note: until now only one Lithuanian-donor has been registered). Reply 10.3 that this will be checked, but no further information received after that; *possibly some delay in this process due to COVID-19 crisis. Last reminder sent 12/10/20.*
Poland			No response yet to several contact intents

Country	Access ELDR	Participation	Agreement and/or status comments
Portugal	PROD – 1 user	NATIONAL – DIRECT DATA ENTRY Instituto Portugues de Sangue e da Transplantacao Donors, pre-donation, post-operation and follow-up surveys registered	The agreement is signed and Portugal has entered the data in the ELDR.
Ireland	PROD – 1 user	NATIONAL – FILE UPLOAD donor information has been uploaded, no additional information has been uploaded yet	Agreement signed. In July donor information was uploaded. After restart of the transplant program there has been a change of responsible persons with The National Kidney Transplant Service in Beaumont Hospital. The new contact person has not yet uploaded the other files (pre-donation, post-operation and follow-up information).
Romania			The new executive director of NTA has been contacted and expressed willingness to participate in the ELDR.
Malta	PROD – 1 user		Malta mentioned in March to be ready to send data. Status April 4th: necessary access rights have been granted and on the question how to input data the ELDR manual has been sent again.
Slovenia	PROD -2 users	LOCAL/NATIONAL – FILE UPLOAD Zavod RS za presaditve organov in tlkv Slovenija-transplant (2) Lubljana (0) Donors, pre-donation, post-operation and follow-up surveys uploaded	Slovenia will upload more information when they have received the data from the other centres.
Czech Republic	PROD-1 user	LOCAL – DIRECT DATA ENTRY Institute for clinical and experimental medicine Prague, Czech Rep Donors, pre-donation, post-operation and follow-up surveys entered	Agreement signed. The centre with 95% of all living donor activity (with local registry) has been contacted and is participating in the ELDR.
Germany	PROD-1 user	LOCAL – FILE UPLOAD Charité Universitätsmedizin Berlin Donors, pre-donation, post-operation and follow-up surveys uploaded	Although the German National Registry still is under development, a single center (Charité Medical University Berlin) agreed to collaborate in the ELDR. Agreement signed between the center and IDIBAPS.
Bulgaria			Status October 6th: The Executive Agency Medical Supervision stated their willingness to collaborate with the ELDR and has signed the cooperation agreement. The Bulgarian contact persons for the ELDR have been approached for ELDR data delivery.

XII.3. ELDR Content

In the beginning of November 2020 12 countries have delivered data to the ELDR: For Italy, the Netherlands, the UK, France, Ireland, Croatia and Portugal the national registries have delivered the data. As they can only forward information for the centres that have agreed to this, the ELDR numbers might still not be representative of all country donors. For Spain, Germany and Czech Republic individual centres participate in the ELDR, and therefore also the ELDR numbers are not representative to the country as a whole. Also Slovenia and Lithuania are participating and have entered their first donor(s) in the registry.

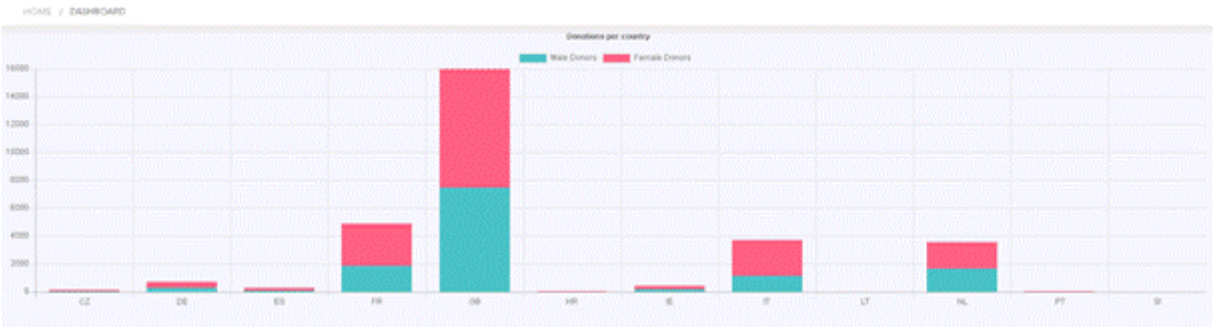


Figure 54: ELDR content status (dashboard report) November 2020

The total number of records in the ELDR by the beginning of November are:

Table 42: Total number of records in the ELDR (November 2020)

Donor	29809
Pre-donation	29091
Post-operation	28785
Follow-up	67072

Four countries have more than 1000 donors in the ELDR: the UK (approximately 50% of all donors in the ELDR), France, Italy and the Netherlands. All of them have delivered their data by file upload.

Four countries have more than 100 donors in the ELDR: Germany, Spain, Czech Republic and Ireland. Only Czech Republic has used direct date entry to deliver their information; the other 3 countries used file upload.

Two countries have entered more than 10 donors in the ELDR: Croatia and Portugal; Croatia used file upload, Portugal used direct data entry.

Two countries have entered less than 10 donors in the ELDR: Slovenia and Lithuania; these records were entered by direct data entry.

XII.3.1 ELDR number of records per file (donor, pre-donation, post-operation, and follow-up) per country

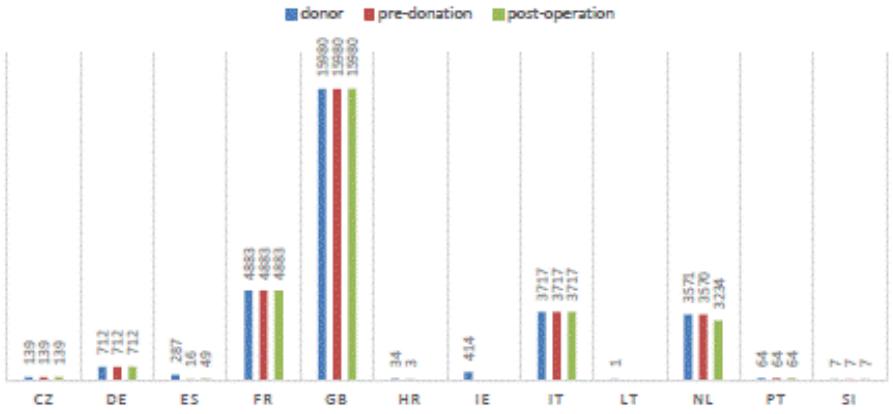


Figure 55: Number of donor, pre-donation and post-operation records per country

Seven countries have entered pre-donation and post-operation information on all their donors. For the Netherlands the number of post-operation records is slightly lower; Spain has not entered as much pre-donation and post-operation records as donors, Croatia has just entered their first pre-donation records, and Ireland and Lithuania have only entered donor information in the ELDR so far.

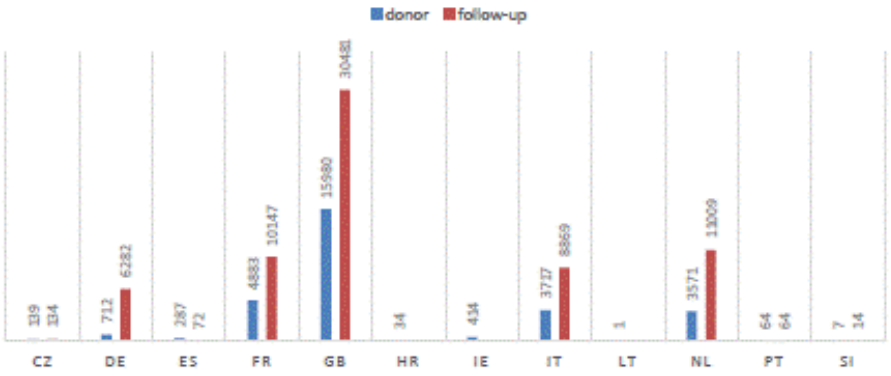


Figure 56: Number of donor and follow-up records per country

The average number of follow-up entered in the ELDR per donor is 2.3. Germany has entered most follow-ups per donor (approximately 9).

Table 43: average number of follow-up records per donor and country

Country	average number of follow-up records per donor
CZ	1.0
DE	8.8
ES	0.3
FR	2.1
GB	1.9
HR	0.0
IE	0.0
IT	2.4
LT	1.0
NL	3.1
PT	0.0
SI	2.0
total	**2.3**

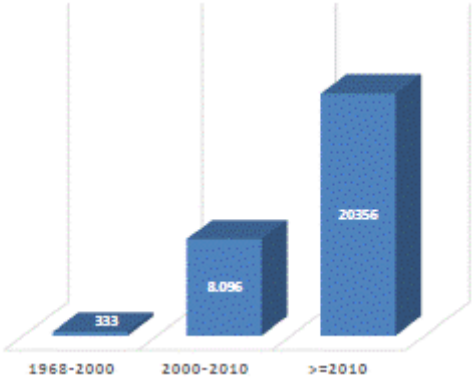
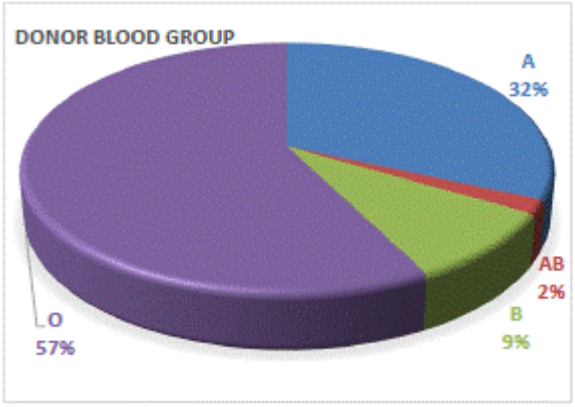


Figure 57: Period of donation

note year of donation is only known for donors with post-operation information delivered

Most information is available on living donation procedures from the last decade, but also approximately 8000 donors from the period 2000-2010 and 330 donors from the period before 2000 have been reported to the ELDR. This is important to get more insight in the longer term consequences of living donation. Note: for the donors from whom no post-operation information has been received, the donation period is unknown.

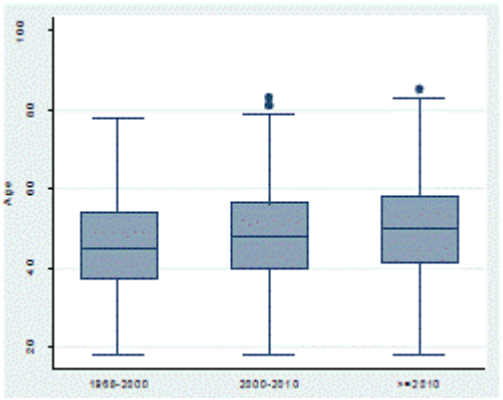
XII.3.2 Reported donor, pre-donation and operation information



Number of donors per blood group	
A	9313
AB	513
B	2649
O	16862
	29337

Figure 58: Donor blood group

Fifty-seven percent of the living donors are blood group 0 donors. Donors with blood group 0 are considered “universal donors” since they can donate to recipients of all blood groups, while A donors can only donate to A/AB recipients, B to B/AB recipients and AB to AB recipients only.



Period	N	mean	median
1968-2000	333	45.2	45
2000-2010	8096	47.4	48
>=2010	20356	49.5	50
Total	28785	48.9	49

Figure 59: Donor-age distribution over time

This figure - donor-age distribution in time - shows that the reported donors are getting older in time.

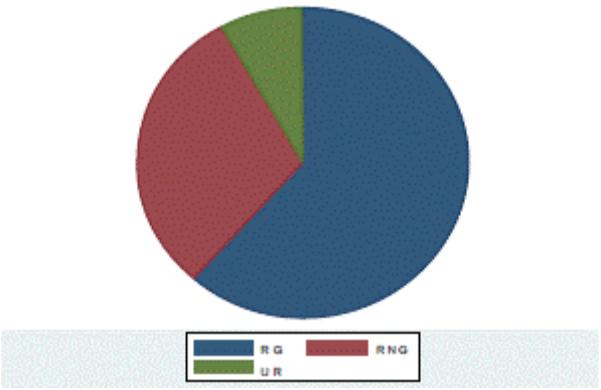


Figure 60: Donors per donor relation

This graph shows that the majority of reported donors are genetically related to the recipient. This is followed by the group of non-genetically related donors (like spouses and friends) and the smallest group is the group of unrelated donors.

When we differentiate donor relation in time, we see that in the last decades there is a shift towards more non-genetically related and to more unrelated donors:

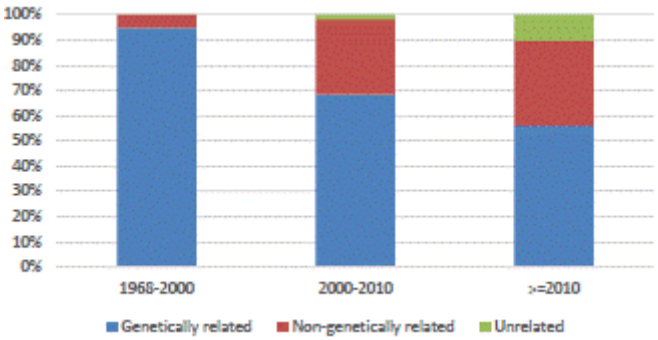


Figure 61: Donor relation

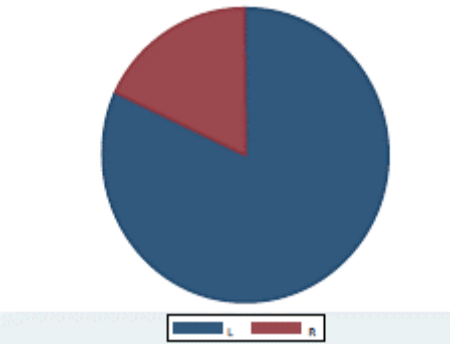


Figure 62: Donor kidney L/R

In the majority of the reported donors the left kidney is donated; this is usually preferred because of the longer vein length. Only in approximately 20% of the reported donors the right kidney has been donated.

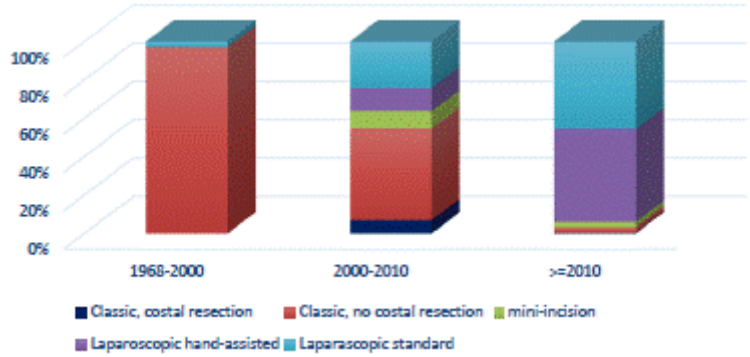


Figure 63: Living donor operation techniques in time

There has been in change in the operation technique used. Before 2000 the classic technique has mainly been used in the reported donors. In the period 2000-2010 a mix of different techniques has been used and since 2010 the laparoscopic technique (either standard or hand-assisted) is the most common technique.

XII.3.3 Reported follow-up information

In the following section we present all information that has been received in the ELDR until the end of October. As noted before, this information is incomplete. The donors are not representative of all country donors. Furthermore the follow-up information in the ELDR is incomplete; some countries have not delivered follow-up information, other countries haven't delivered follow-up information on all donors, so the results presented in this section must be interpreted with caution, as they might be biased. However they give us some insight in living kidney donation in Europe and the potential value of a sound European living donor registry. In this section we present several figures on survival and clinical results; in all these figures the numbers on the x-axis present the number of donors at risk until that time.

Table 44: Follow-up information

Total records with follow-up	95088
duration of follow-up (years)	3.7(4.3)SD
Median duration of follow-up (years)	2.1
Range (years)	0-49.6
Total years of follow-up	233490

The overall living donor survival up to 25 years post donation is approximately 90% for the reported donors in the ELDR.

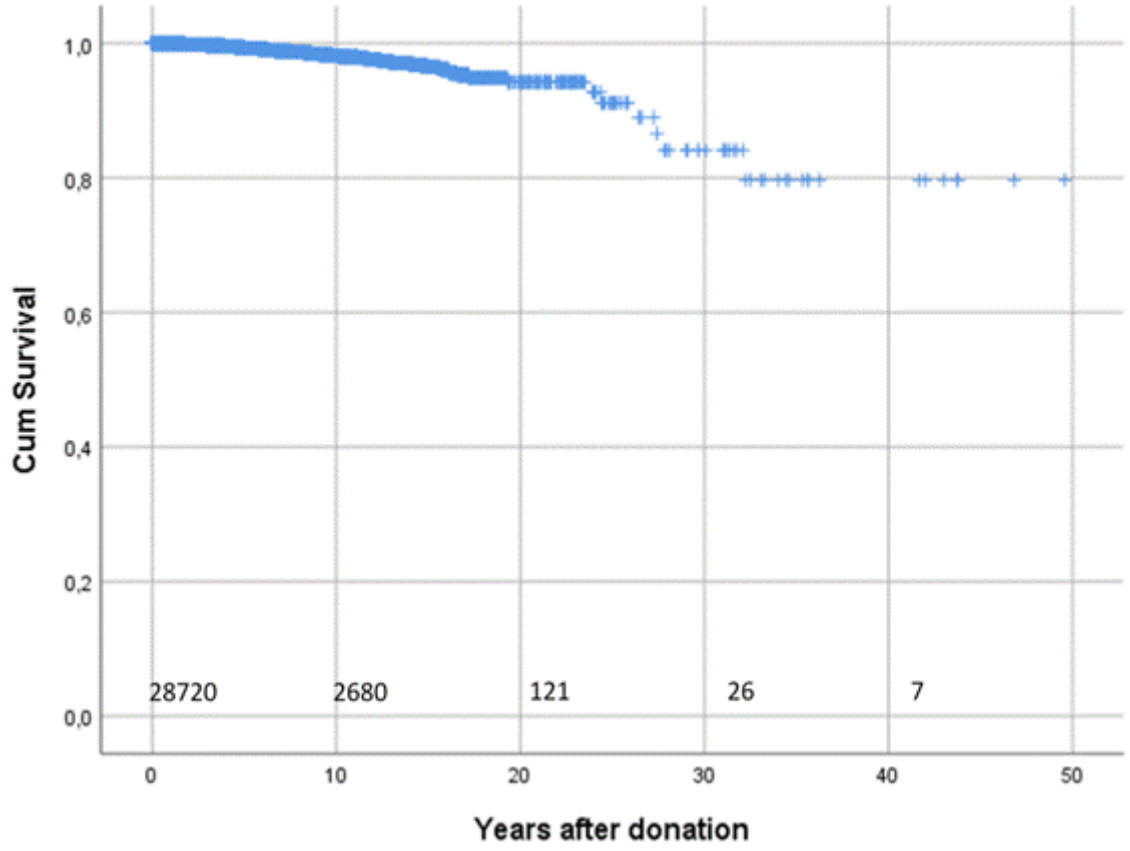


Figure 64: Donor survival

This is slightly better for females compared to males:

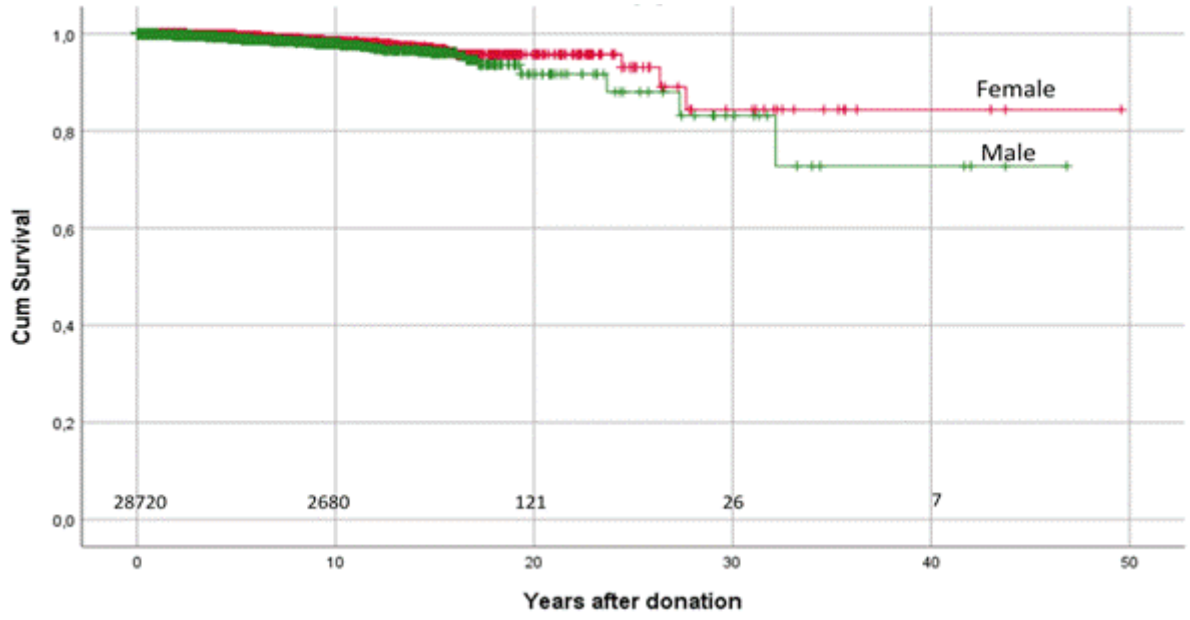


Figure 65: Donor survival by gender

And of course this is highly correlated with age at donation:

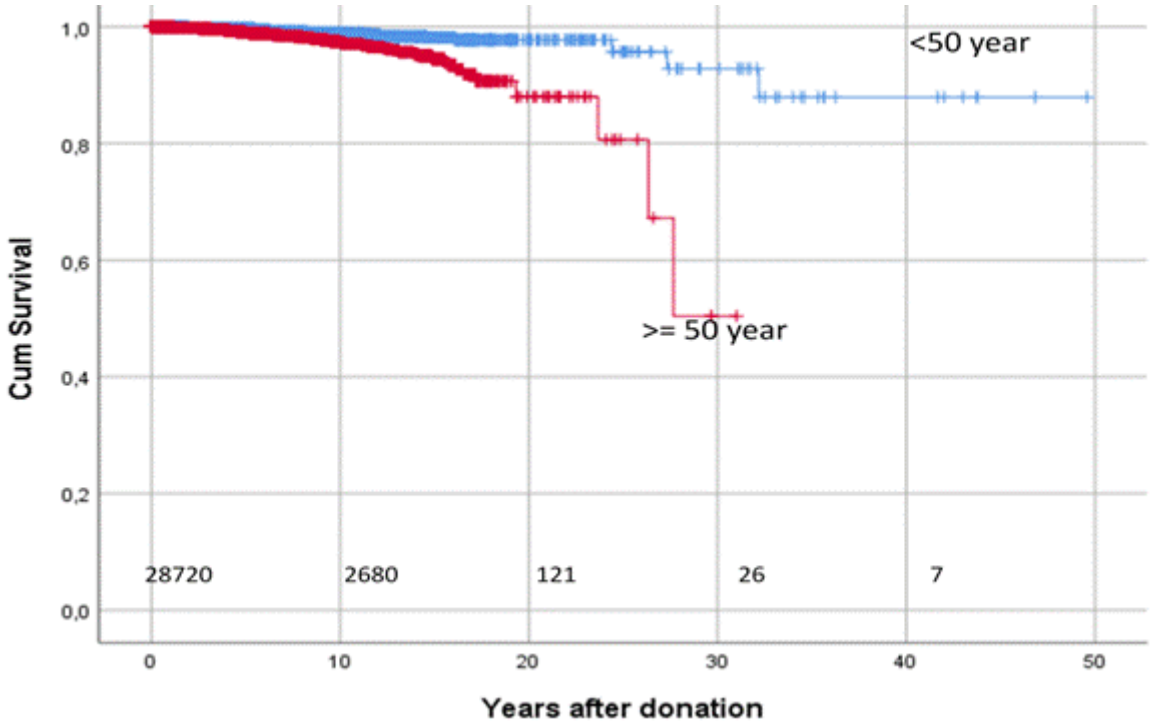


Figure 66: Donor survival by age (at donation)

Table 45: Events after donation

Number of donors	28723
Number of donors with ESRD	5 (0.02%)
Number of deceased donors	186 (0.6%)
Cause of death	
Neoplasm	25
Circulatory	7
Nervous system	2
Respiratory system	1
Mental disorders	1
Other	19
Unknown	131

After donation there is an immediate rise in serum creatinine (as expected) in the reported donors, but up to 40 years later there is no further rise in serum creatinine:

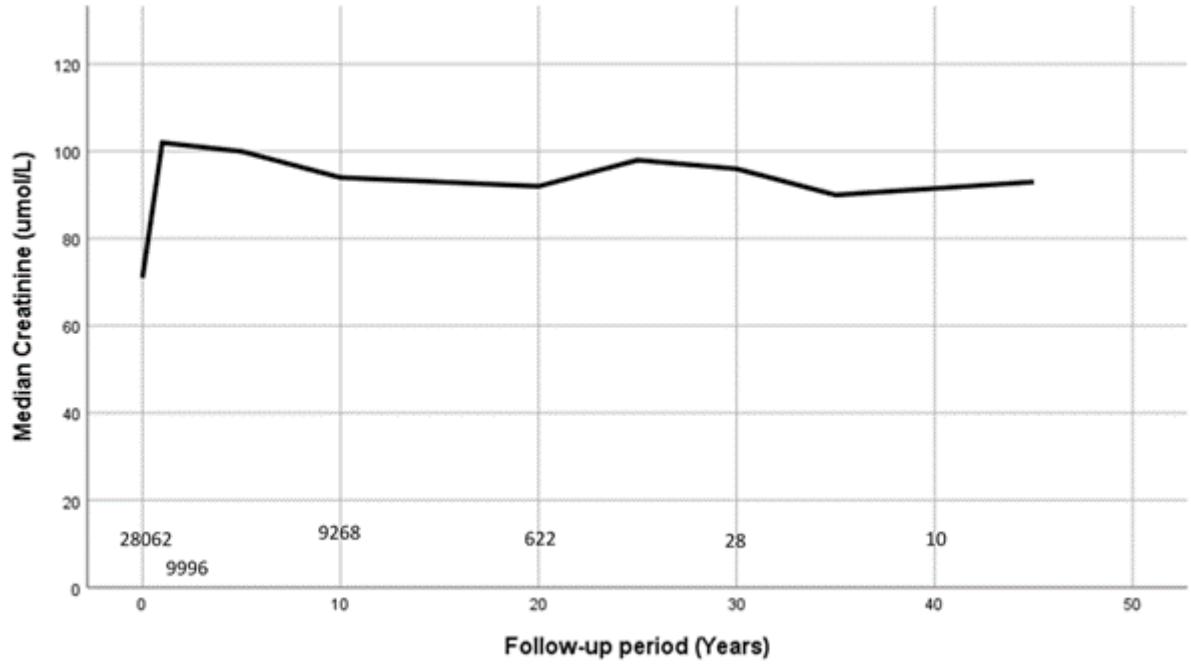


Figure 67: Median of creatinine (umol/L) by follow-up period (years)

Looking at the reported creatinine values by living donor age, we see that there is a rise in creatinine values in time. The creatinine values are slightly higher than what is usually seen in the normal population. The slope of the line, however, is similar to the slope in the normal population.

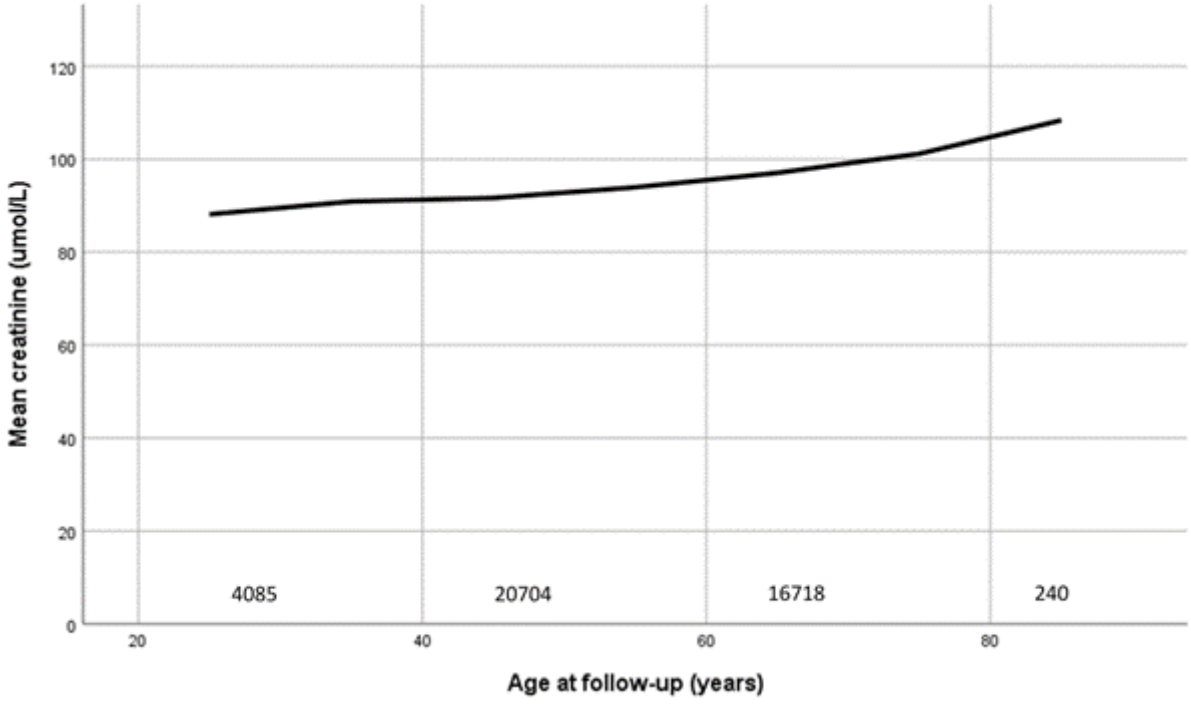


Figure 68: creatinine values by living donor age

After donation there is a rise in the mean proteinuria in the reported donors, but even in the 40 years of follow-up it remained very low (<0.2 g/L):

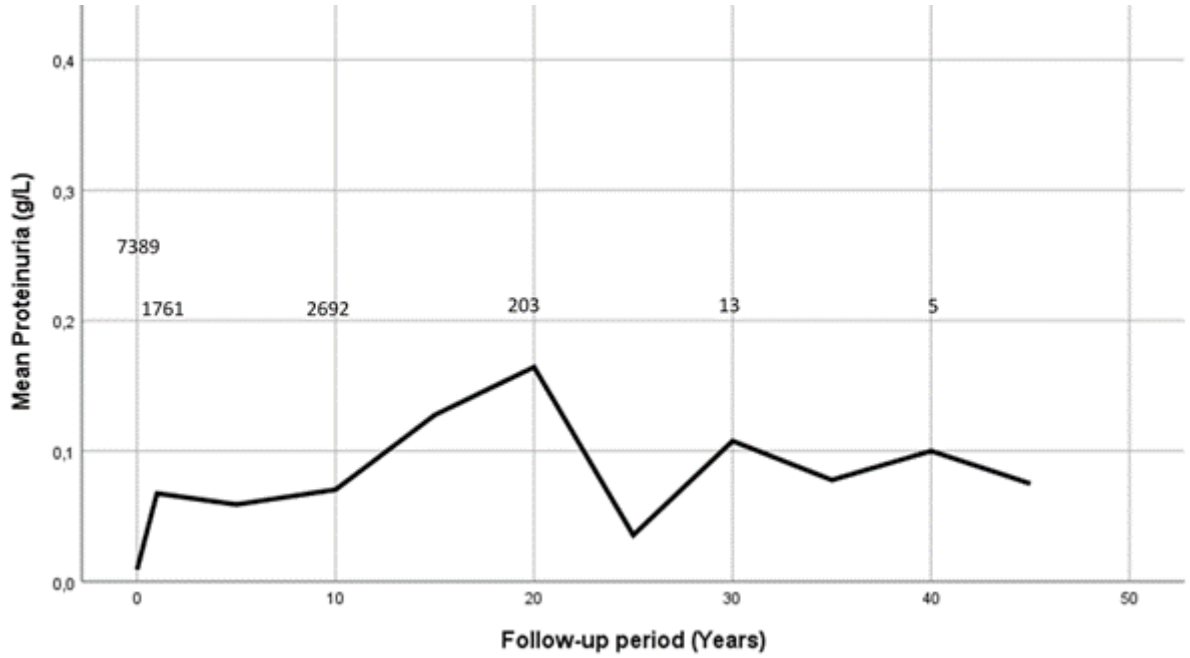


Figure 69: Mean of proteinuria by follow-up period (years)

If we look at the percentage of donors with proteinuria after donation (either reported as proteinuria "positive" or a value of >0 g/L we see that the percentage of donors rises up to 40%-50% directly after donation. However, the number of patients with proteinuria is not getting higher with more time after donation.

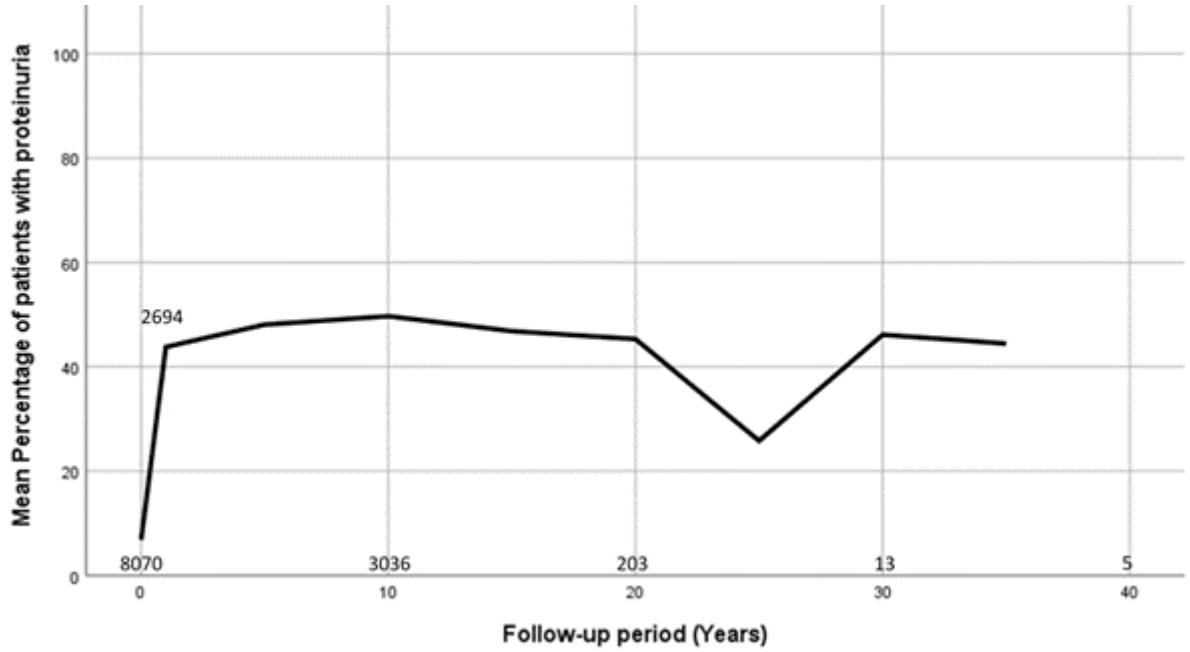


Figure 70: mean of percentage of patients with proteinuria by follow-up period (years)

There is a rise in the percentage of donors who need antihypertensive medication (up to more than 60%). This phenomenon is also present in the normal population:

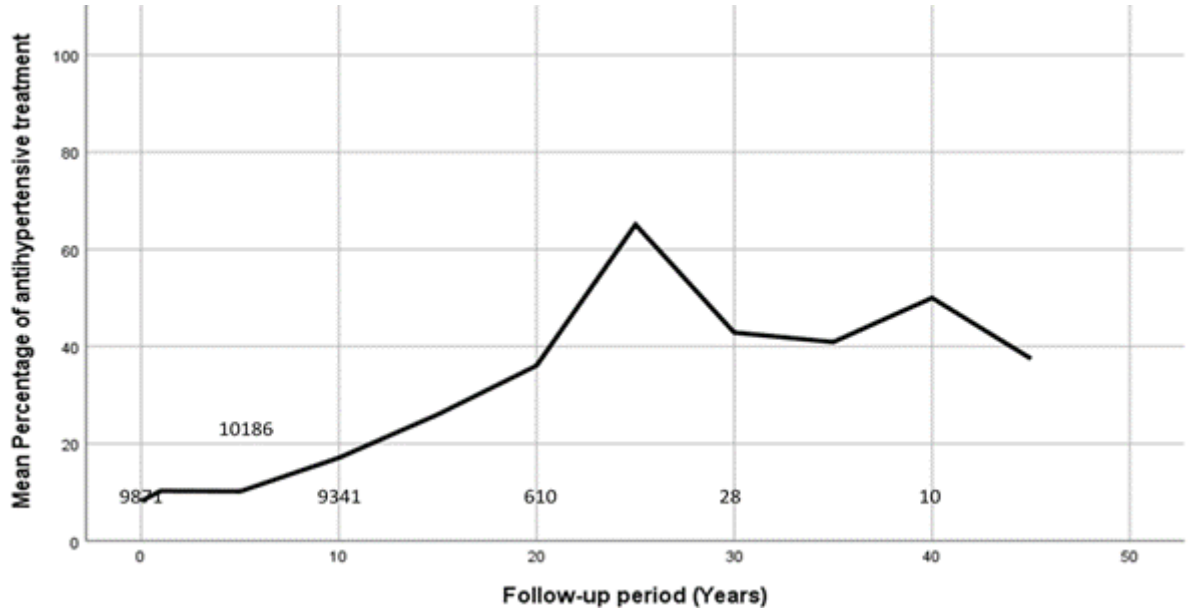


Figure 71: Mean of percentage of antihypertensive treatment by follow-up period (years)

XII.4. ELDR desired reports

After taking the ELDR into production, the last goal of the EDITH Work Package 5 was to ask for the experience with the ELDR and check which reports are wanted by the participants. Therefore we have directed a questionnaire to all "active " ELDR users in September 2020. 7 questionnaires have been returned to us, from 6 different countries.

We checked which reports are interesting for the ELDR users in two categories: 1= living donors general, pre-donation and post operation information and 2= follow-up. In each category we have provided a few exemplary reports based on ELDR data extracts from July 2020, and asked whether these are important, nice to have or not relevant, and whether these reports are relevant for information on the whole database, the whole database differentiated by country, and/or for the own country of the user. Also we have asked to indicate which other reports would be desired.

XII.4.1 Desired reports on living donors in general, pre-donation and post-operation information

For the living donor general, pre-donation and post operation 5 example reports have been prepared: number of donors per sex, donor blood group distribution, donor age distribution, donor relation and donor kidney (left/right). One respondent rated all example reports as nice to have; the other respondents rated all, or most, as important. Six respondents rated the report on number of donors per sex and age distribution as important; five respondents rated the blood group distribution and donor relations as important. Least important seems the report on donor kidney (L/R); 3 rated this as important, 2 as nice to have and 1 as not relevant. The answers differed for desired levels (whole database, the whole database differentiated by country, and own country of the user): some wanted 2 or 3 levels, others thought that some reports were only relevant for one of the 3 levels. One respondent added that it is desired to be able to compare the centre or country specific numbers with the ELDR total numbers.

Additional desired reports that were mentioned are:

- information on hypertension, CKD, diabetes, CVD, obesity and psychological issues
- complications during and after donation

- health issues specified
- lab results
- comorbidities
- complications post donation
- type and percentage of complications after donation

XII.4.2 Desired reports on living donors follow-up (outcome information)

For the follow-up 6 exemplary reports have been prepared: long term living donor survival, long term living donor survival differentiated by gender, long term living donor survival differentiated by agegroup, median creatinine after donation, median proteinuria after donation, use of antihypertensive drugs after donation. Almost all of these reports were rated as important by all 7 respondents, only the use of antihypertensive treatment were rated as nice to have by 2 respondents and the median proteinuria was rated nice to have by 1 respondent. Also here the levels varied, but due to the nature of those reports these were more often considered useful on ELDR total level.

Additional desired reports that were mentioned are:

- number of donors with renal replacement therapy (3x)
- renal failure time
- distribution of health issues (3x), possibly in relation to time after donation
- number of deceased donors
- causes of death for the donor who died (4x)
- total number of death and RRT initiations, median time to death and RRT (KM)
- total number of diabetes, median time to diabetes (KM)
- cardiovascular comorbidities, median time to CV comorbidities (KM)

XII.5. Conclusion

The ELDR information has the potential to be used to monitor the long term consequences of living kidney donation, especially with regard to the different acceptance criteria (both in time and per country). Up to now, however, the numbers of reported donors from the participating countries are far from complete, and therefore the results may be biased. The example reports show what information is gathered. To be able to draw conclusions on the long term safety and to identify risk factors for living kidney donation more information is needed in the ELDR and scientific research, taking account of confounding factors, should be performed.

Hopefully the ELDR will be further completed in the coming year(s) to fully use its potential!

XII.6. Annex

Annex 1: Cooperation Agreement

Version 1.0, January 2020

Between ELDR-consortium (NTS, IDIBAPS) and [……..] (the National Competent Authority / regional organisation / local hospital of the EU Member State:

…….

Concerning data handling of the ELDR

The Parties hereby agree to cooperate as follows:

Article 1. Purpose of the Agreement

1.1 This Cooperation Agreement (hereafter 'the Agreement') is to enhance cooperation between ELDR staff at NTS and IDIBAPS (the European EDITH consortium) and the Competent Authority/regional organisation or local hospital to start with data entry for the European Living Donor Registry (ELDR).

1.2 The Agreement builds on the principles embodied in the temporary ELDR GOVERNANCE ORGANISATION which applies during the EDITH PROJECT PHASE (2019/2020). The Agreement will be replaced by a new ELDR Cooperation Agreement with the future ELDR hosting organisation(s).

Article 2. Definitions

2.1 For the purpose of this Agreement, the following definitions shall apply:

EDITH: the Effect of Differing Kidney Disease Treatment Modalities and Organ Donation and Transplantation Practices on Health Expenditure and Patient Outcomes (EU project).

ELDR: European Living Donor Registry.

IDIBAPS: Institut d'Investigacions Biomèdiques August Pi i Sunyer in Barcelona.

MS: Member State of the EU that participates in the EDITH project.

NCA: National Competent Authority.

NTS: stands for "Nederlandse Transplantatie Stichting", which is the Dutch Transplant Foundation.

Article 3. The Parties

3.1 The ELDR consortium consists of employees of NTS and IDIBAPS. NTS is responsible for the functional management of the ELDR and IDIBAPS is responsible for the technical management and the hosting of the ELDR data.

3.2 Every EU Member State can join the ELDR. Either the NCA or one or more regional or local centers can participate.

Article 4. Duration

4.1 This Agreement enters into force when signed by the parties.

4.2 The duration of this Agreement is until 1 January 2021. Between 1 July 2020 (the end of the EDITH project) and 1/1/2021 there is a transition period in which the final Governance and ELDR organisation will be established.

Article 5. EDITH Project

5.1 The development of the ELDR is part of the EDITH project which received funding from the European Commission (EC).

5.2 EDITH Work Package 5 of this project is aimed at the realization of a European Living Donor Registry (ELDR) for living kidney donors, supporting lifelong follow-up data collection. An important rationale for this development is that EU Member States are both legally (EU Directive 2010/53/EU) and morally obliged to follow-up living donors in order to protect their safety.

5.3 There are no cost to participate in the ELDR during the EDITH project phase nor is there any financial compensation.

5.4 The intention set out in this Agreement should govern practice. Cooperation must comply with the applicable regulatory framework and recognized standards/guidelines 5.5 After the EDITH project parties will agree upon a new agreement, which will be built on the DRAFT Edith Governance of the ELDR.

Article 6. Start Data entry and Data access

6.1 The purpose of the registration is to monitor follow-up of living donors and in this way contribute to organ donation transparency which can help to increase the safety of living kidney donation. Aggregated reports will be available to all ELDR participants and the EDITH project organization.

6.2 Parties can only have entry to their own donor data and have no access to donor data of other Parties. Aggregated reports will be available to all Parties.

6.3 The Member States ensure the validity and accuracy of the data collected in the ELDR. The Member States are responsible for the quality of the data and for the completeness.

Article 7. Compliance

7.1 The Parties agree that compliance with this agreement is a joint responsibility. The parties will inform each other and recommend and make active efforts to ensure that all Parties comply with the agreement.

7.2 Parties will comply to the General Data Protection Regulation (GDPR) 2016/679 regarding to the processing of personal data and have security measures in place.

Article 8. Other

8.1 All other matters not covered trough this agreement must be agreed in writing.

8.2 Parties can terminate this Agreement by giving notice in writing and with taking in account a cancellation period of 1 month. The data already in ELDR will be deleted by IDIBAPS.

Signatures

Annex 2: ELDR Policies

Edited: January 27, 2020 Effective: February 21, 2020 Date Last Revised: February 20, 2020

A. ELDR Privacy Statement

1. Overview

The development of the ELDR is part of the EDITH project which received funding from the European Commission (EC).

EDITH Work Package 5 of this project is aimed at the realization of a European Living Donor Registry (ELDR) for living kidney donors, supporting lifelong follow-up data collection.

This privacy statement explains how we collect, handle and ensure protection of all personal data provided, how that information is used and what rights you may exercise in relation to your data. All data processing is done in compliance with the EU General Data Protection Regulation (2016/679) and the relevant updates.

2. What type of information do we collect?

For the purposes of the indicated project, ELDR will collect, process and store various categories of data as outlined below:

Registration of users:
Once the user has been pre-selected, a basic data related to name, email and occupation is collected for the creation and follow-up of the user account. Users may supply any additional information on a voluntary basis. The personal data of users is collected directly from the data subjects or from the delegated actors.

Donors information:
We collect donor information for registry purposes. The donor data is specified in the User Manual and introduced by the responsible user. The registry always complies with the GDPR . The data in this group has been marked as pseudonymized, this means that there is no easy way for the site to identify the individual person this data was collected from.

3. What is the aim of the data collection?

The purpose of the data collection is to monitor follow-up of living donors and in this way contribute to organ donation transparency which can help to increase the safety of living kidney donation. An important rationale for this development is that EU Member States are both legally (EU Directive 2010/53/EU) and morally obliged to follow-up living donors in order to protect their safety.

Countries are responsible for the collection of the follow-up data of their living donors, either in a national or an international registry. Data integrity as well as data completeness influence the reliability of the database and therefore the usefulness and any scientific results from data analysis rely on the accuracy of the data that is entered into the registry.

4. Who will use the data?

Ownership:
Different people living in different countries and working in different institutes in different types of functions will be working with the ELDR. Some users will be entering data, while others will be extracting data from the registry. Different user-profiles will be identified. Depending on the function and tasks, a certain profile will be assigned to a person. The profile determines which authority is granted, for example the right to enter data, the right to change data, the right to extract data on a centre level, the right to extract data on a national level, the right to view general information or the right to see detailed information. On a national level, the national application owners will be responsible for applying the authorisation policies. Information concerning the function and associated tasks will determine the profile and corresponding rights.

Data requests:
The donor centres are the primary owners of the data. Therefore, requests for an extract of their ‘own’ data by a donor centre should be granted without restriction. The competent authorities in those MS with an existing national follow-up database can be granted permission to receive an extract of their ‘own’ national data as well.

Access is only granted if the user’s profile allows this access. The possibility to change or delete data is only reserved for a limited number of users, also depending on their user’s profile. The application will log every data-action (add/update/view/delete) on donor-level, including time of the modification and the name of the moderator (the user that was logged-in).

5. Do we disclose any information to outside parties?

We do not sell, trade, or otherwise transfer to outside parties personally identifiable information.

Non-personally identifiable information may be provided to other parties for reporting and statistical purposes.

B. ELDR Breach Policy

1. Introduction

It is vital that we can identify, evaluate and act on eventual data breaches whenever they occur.

Consistent governance and control arrangements are also a regulatory requirement.

Identifying data breaches quickly and effectively to limit any impact is critical. Equally we need to understand where there are areas of weakness within the registry and continuously improve the registry to reduce the risk of significant control failures leading to data breaches.

2. Aims and objectives

This policy sets out:

- Policy statement on data breaches
- Definitions
- Reporting responsibilities

This policy aims to ensure that adequate controls are in place so that:

- Data breaches are identified, and action is taken quickly. Actions should be proportionate, consistent and transparent
- An assessment is completed to ensure that any major data breaches are reported to the Steering Committee.
- All data breaches and near misses are recorded and regularly reported
- Lessons are learnt to ensure similar mistakes are not repeated and appropriate control mechanisms are put in place.

3. Policy Statement

This policy is in place to raise awareness of data breach cases. To ensure that all staff can identify a case and understand the steps required for dealing with them.

This policy identifies inherent risk of a data breach and/or near-miss, which will ensure that the Steering Committee will be informed, able to manage actions relating to any real or potential serious data breach and be in a position to report to the stakeholders and affected individuals as appropriate.

4. Definitions

What is a data breach?
A data breach is “a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, data transmitted, stored or otherwise processed”. A data breach may mean that someone gets unauthorized access to sensitive data.

A data security breach can happen for many reasons:

- Loss or theft of data or equipment on which data is stored

- Inappropriate access controls allowing unauthorised use
- Equipment failure
- Human error
- Unforeseen circumstances such as a fire or flood
- Hacking attack
- 'Blagging' offences where information is obtained by deceiving the organization who holds it.

Human error is the most common cause of data breaches. These can happen for many reasons:

- Theft or loss of paperwork
- Data posted to incorrect recipient
- Data sent by email to incorrect recipient
- Failure to redact personal/sensitive data.

What is a near miss?
A near miss is an event that does not result in a data breach, but which had the potential to do so. Examples of such events might include data that was misplaced but found quickly internally or data that was sent out but was identified and returned.

5. Training

Mandatory training will be provided to all staff on data protection regulations

Training will be provided to all new employees including temporary and contracted staff. All employees will undertake refresher training annually

6. Identification

Data breaches or near misses may be identified as part of everyday business. They may be identified by staff or by a third party making us aware.

Where a data breach is identified the Steering Committee must be informed immediately. The staff member will investigate the occurrence and complete a risk assessment (see the Risk Matrix) to determine the notification requirements. The controls in place must be reviewed. Where no controls are in place, consideration must be given to introducing them. Was this an exceptional case that could not have reasonably been avoided, or does action need to be taken to avoid a recurrence?

7. Risk Assessments

When a data breach is identified a risk assessment should be completed using the Risk Matrix.

Depending on the risk assessment score the data breach will be reported to, owned and investigated (see the Risk Matrix).

The Data Breach Workflow should be used to work through the following stages.

8. Containment and recovery

Containment and recovery involve limiting the scope and impact of the data breach, and stemming it as quickly as possible.

The data breach owner must quickly take appropriate steps to ascertain full details of the breach, determine whether the breach is still occurring, recover any losses and limit the damage. Steps might include:

- Attempting to recover any lost equipment or personal information

- Shutting down an IT system
- Contacting the Admin Office and other key departments
- If an inappropriate enquiry is received staff should attempt to obtain the enquirer's name/contact details
- The use of back-ups to restore lost, damaged or stolen information
- If the data breach includes any entry codes or passwords then these codes must be changed immediately, and the relevant organisations and members of staff informed.

9. Investigation

If a data breach is identified then a formal investigation should be commenced by the designated member of staff (data breach owner) who should determine the seriousness of the breach and the risks arising from it. Specifically, the data breach owner should identify:

- Whose information was involved in the breach
- What went wrong
- The potential effect on the data subject(s)
- What immediate steps are required to remedy the situation
- What lessons have been learnt to avoid a repeat incident.

In order to support this process the data breach owner should complete the Data Breach Report form.

The investigation should consider:

- The type of information
- Its sensitivity
- How many individuals are affected by the breach?
- What protections are in place (e.g. encryption)?
- What happened to the information?
- Whether the information could be put to any illegal or inappropriate use
- What could the information tell a third party about the individual?
- How many people are affected?

The initial investigation should be completed urgently and wherever possible within 72 hours of the breach being discovered. A further review of the causes of the breach and recommendations for future improvements can be done once the matter has been resolved

However, some level of investigation might be required to carry out the Risk Assessment and determine the most appropriate route of escalation. In certain cases, when risk of a data breach is identified and contained, the timeframes for official escalation/notification can be extended to allow for a more thorough investigation. Extensions must be agreed at each stage and noted in the report.

10. Informing affected individuals

The registry should inform those affected where there is a significant breach of sensitive data and the risk of harm to those individuals is high.

Only the data breach owner and the Steering Committee can decide whether to advise affected individuals of a data breach and therefore the reasons for deciding to do this should be clearly set out in the investigation report and discussed with the data breach owner and other involved parties before affected parties are informed.

11. Learning lessons

The Lessons Learnt Action Plan for data breaches and near misses should be completed and will form part of the investigation process.

The action plan should clearly outline the lessons learnt. The controls agreed to reduce the risk of a further reoccurrence, a lead member of staff and a completion date.

The case will not be considered closed until all actions agreed have been completed.

12. Performance monitoring and responsibilities

90% of investigations should be completed within 10 working days of the data breach being identified.

13. Data breach Log

All data breaches, including near misses, will be recorded on the data breach Log. All issues identified by the application of this policy will be recorded in the data breach log and categorized according to whether it is a data breach or near miss.

This information will be reviewed and analysed at least every three months to identify patterns and monitor the implementation of agreed service improvements.

C. Security policies

1. Introduction

ELDR complies with requirements for privacy and security established by the General Data Protection Regulation (GDPR). This page outlines our privacy and security policy to protect personal data against loss or any unlawful processing.

2. Data safety and security

The registry is protected against any spyware or viral software which can lead to the damage or loss of data. Also, technical defects or power failure may have no influence on the collected data. Regular back-ups (daily) are made to facilitate data safety and security. The server should be well maintained, preventing physical damage to be the cause of destroying or losing data.

The human factor in data safety and security can be managed by defining proper authorisation policies (see section B.4). For all data in the database (from every country involved) only the co-workers of the ELDR have such an access possibility. For each country that has delivered data, credentials are provided to give access to identifiable data of their own country. In case individual centres have entered their data directly in the ELDR, these centres should also have one key to have access to the identifiable data of their own centre.

3. Users activities

When you browse through any website, certain information about your visit can be collected. ELDR collect your log in information automatically and continuously. We use this information to measure the number of users and for technical purposes such as improving navigation through the registry. This information is only available to ELDR website managers and other designated staff who require this information to perform their duties. Important to mention is that only pseudonymized living donor information is collected in any case.

4. Risk assessment

Risk assessment is the act of determining the probability that a risk will occur and the impact that event would have if it does occur. This analyzes the cause and effect of each possible event. Once risks have been identified and documented, risk analysis must be performed. During the risk analysis process, each potential risk event will be evaluated for the following:

- The probability that the risk will occur
- The impact of the risk if it occurs

These two factors of assessing the risk involving probability and impact shall be measured for probability using a scale of Low, Medium, and High. For each identified risk, a response must be identified. The probability and impact of the risk will be the basis of recommending which actions should be taken to mitigate the risk. Strategies and plans will be developed to minimize the effects of the risk to a point where the risk can be controlled and managed.

Contacting us

If there are any questions regarding the ELDR Policies you may contact us via edith@eulivingdonor.eu

XIII. ELDR User Manual (D5.2)

Responsible partner: IDIBAPS
Document. D5.2_APPENDIX 2_ ELDR_Manual of 09.11.2020 (shortened)

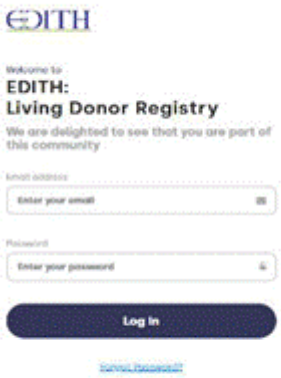
XIII.1. How to access the ELDR registry

This manual describes the use of the ELDR. If you need to use the ELDR, but you have no access (username) yet, please contact the administrators of the ELDR by mail: edith@eulivingdonor.eu.

The access link to the ELDR is: https://eldr.edith.eulivingdonor.eu

The website is accesible by an HTML5 compatible browser as: Mozila Firefox, Edge and Google Chrome.

Enter your email and password to log in into your registry account.



Once you entered your credentials, your will be redirected to the main page. This is the Donor List, with information on the donors that you have access to: At the top of the screen you see for which user and centre you are logged in:

Note: if you move the cursor to your account, you have the possibility to view your account details or to change your password

On the left you see the menu options you have access rights for, e.g.:

Main	access to Donor List, from where you can access all donor, pre-donation, post-operation and follow-up forms and enter/correct/delete information by direct data entry
Dashboard	access to basic statistical panel, currently only filled with 1 report (numbers of donors per country)
Data	Import (upload) /export (extract) donor batch files

Users	[: List of registry users]; this option is only available for administrators
Centers	[: List of participating centers]; this option is only available for administrators
Log Out	Log out icon.

Note: The registry will automatically logout after 15 minutes of user inactivity.

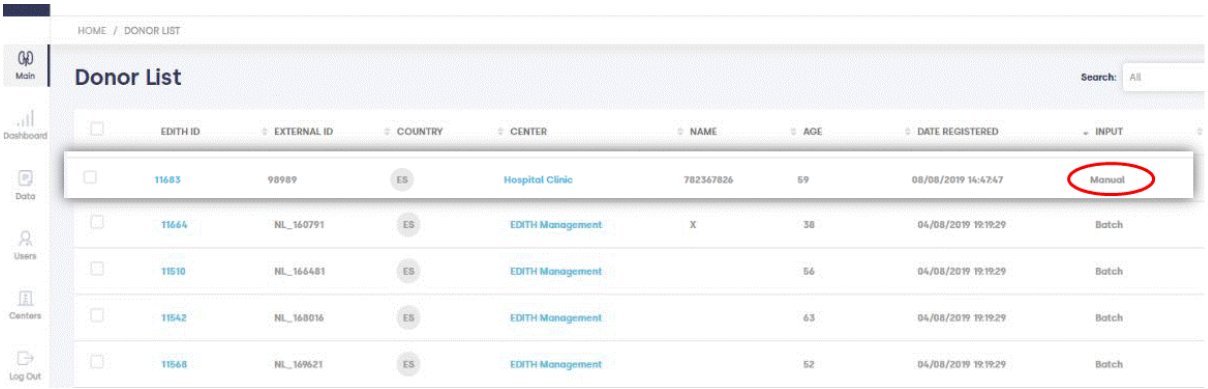
XIII.2. Direct Data entry

The ELDR allows the users to enter donor information manually into the registry from the browser.

XIII.2.1 Adding information

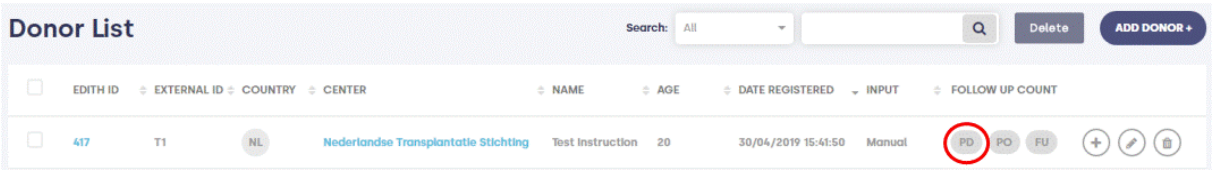
Adding a New Donor

- To add a donor, select the icon “Add Donor+” at the top right side of the main page
- Add all the necessary information to complete the donor profile.
- Mandatory values are marked with a blue asterisk, the other items are optional:
    - * Full Name (text field, both numbers and letters are accepted; this can be used to search for donors)
    - * External ID (idem; this number is required in the pre-donation, post-operation and follow-up records to link them to the right donor; therefore here the local hospital number could be used as the external ID. In order to have unique numbers only, please choose a country and centre prefix combined with the local hospital number in order to prevent duplicates)
    - * Gender: Male/Female
    - * Blood Group: A, B, AB, 0
    - * Age at donation (whole number) Date of birth (date); input possible by calender or manually, in format: DD/MM/YYYY
    - * Country of residence (List of Values (LOV)); NOTE: first entry is country of user Ethnicity (LOV)
    - * Nationality 1 (LOV); NOTE: first entry is country of user Nationality 2
- Once the information is completed click on “CREATE” icon at the bottom right of the browser page.
- If a mandatory value is missing or any entered value is invalid, one or more **alerts** will appear under the box/boxes.
- If all information is correct, you will receive a success message
- The new donor profile survey will appear on the “main page” list. The data will be categorized as a “Manual” in the Input column.

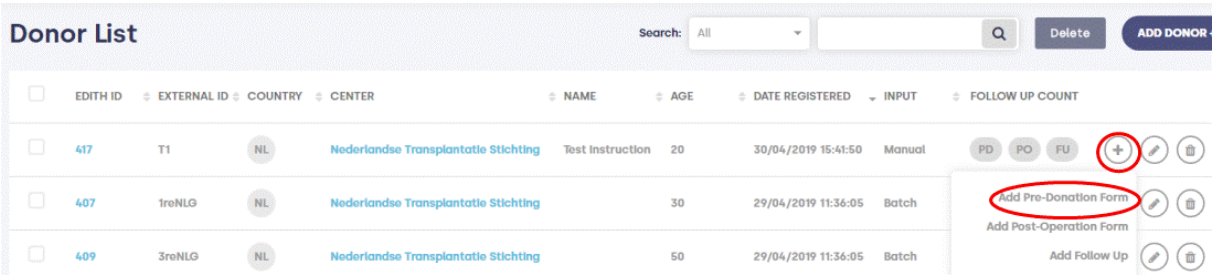


Adding a New Pre-donation (PD) Form

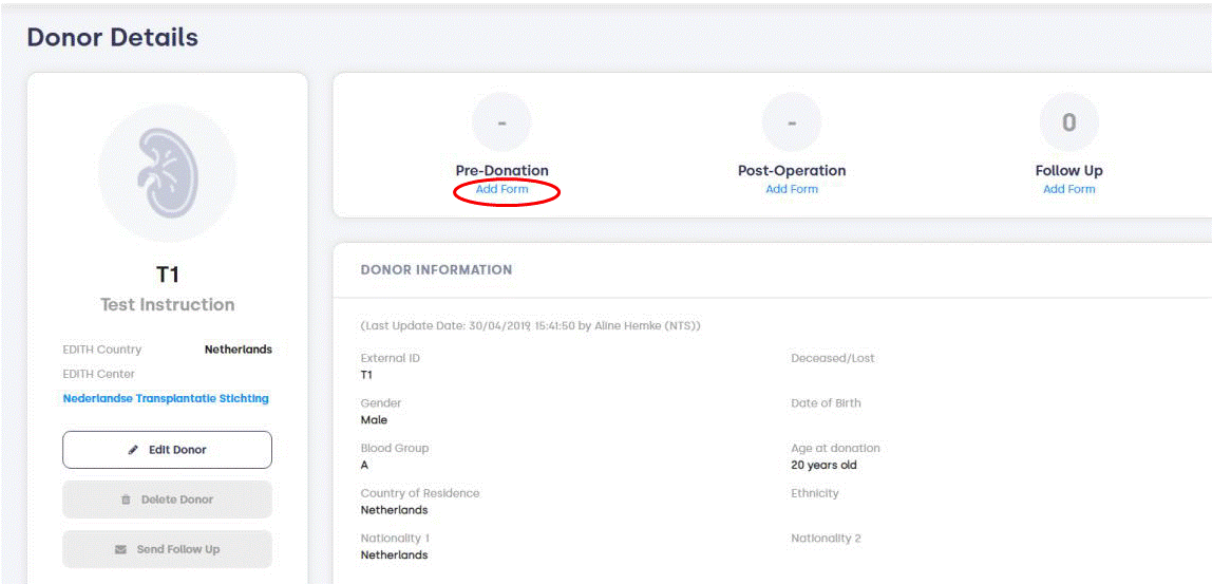
- To add a pre-donation (PD) form, there are several possibilities:
    - press on “PD” for the donor in the donor list. After this the donor is shown and you can add a Pre-donation form:



    - Go to “+” and then choose **Add pre-donation form** at row of selected donor in donor list



    - after selection of the donor, choose “Add Form” underneath the Pre-Donation tab



- Add all the necessary information to complete the pre-donation form.
- **Mandatory** values are marked with a **blue asterisk**, the other items are optional:
    - Relation type: Genetically related, Non-genetically related, Unrelated
    - Antihypertensive medication: Yes, No
    - Weight + unit: whole number, NOTE kg is default unit (this can be changed in lb)
    - Height + unit: whole number, NOTE cm is default unit (this can be changed in ft)
    - Creatinine + unit: number (1 decimal allowed), NOTE umol/L is default unit (this can be changed in mg/dl)
    - Proteinuria + unit: number (1 decimal allowed), NOTE 24 hour urine collection is default unit (this can be changed in Spot urine per gram per liter, Dipstick or CR (protein/creatinine ratio); NOTE2, if Dipstick then only values Positive/Negative are possible)

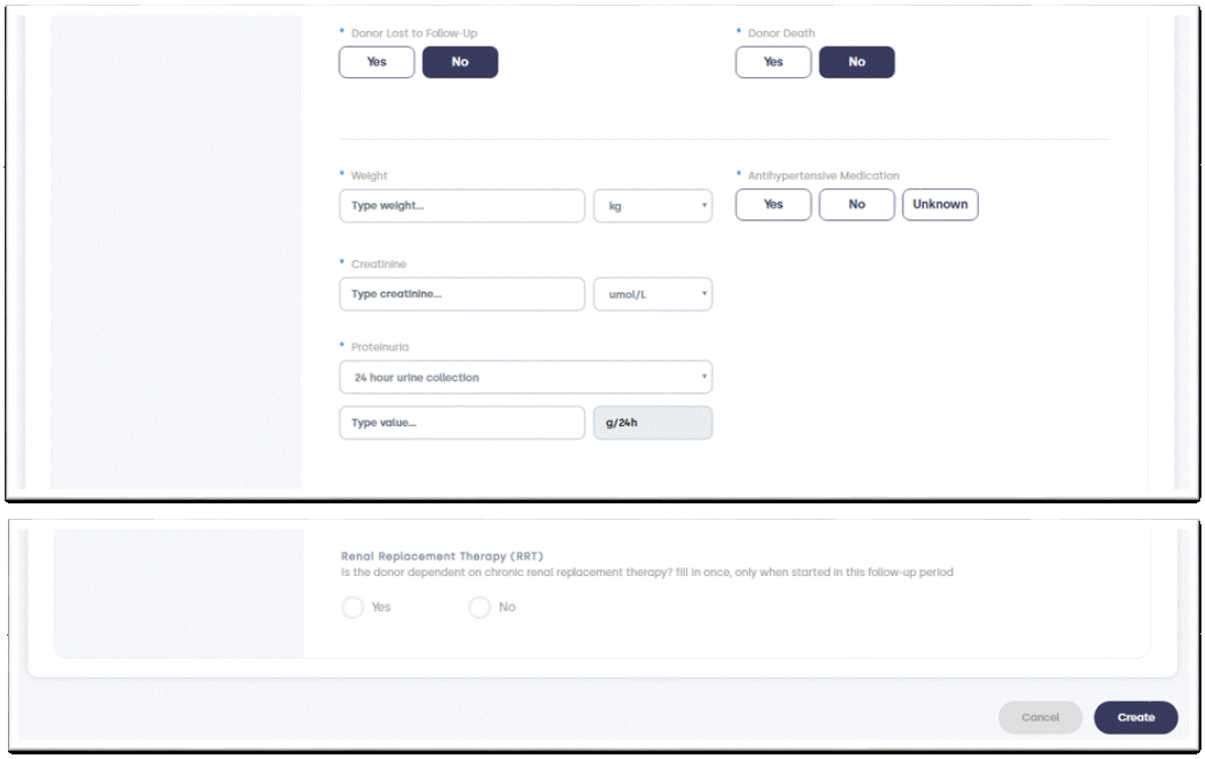
    - Any significant Co-morbidity: Yes/No/Unknown
      If you choose Yes for a co-morbidity, a specification field is opened and you can choose the specific co-morbidity from a list of values, for example for abdominal surgery
- Once the information is completed click on "CREATE" icon at the bottom right of the browser page.
- If a mandatory value is missing or any entered value is invalid, one or more **alerts** will appear under the box/boxes, also indicating on which tab the errors still exist.
  NOTE: If you have indicated that there are comorbidities but you didn't specify this on the comorbidity details tab, this results in a warning. You can save the record without completing the specific comorbidities. Since this is not recommended, please select "**No**" on the question whether you wish to continue and complete the comorbidity tab before saving the pre-donation record!)
- If all information is correct, you will receive a success message.
  The indicator of the Pre-donation form will be visible on the "main page" list by the blue PD box.

Adding a New Post-operation (PO) Form

- To add a Post-operation (PO) form, there are several possibilities:
    - Press on "PO" for the donor in the donor list.
      After this the donor is shown and you can add a Post Operation form
    - or go to "+" and choose ""Add Post-operation form"
    - after selection of the donor, choose "Add Form" underneath Post-Operation Form
- Add all the necessary information to complete the post-operation form.
- **Mandatory** values are marked with a **blue asterisk**, the other items are optional:
    - Country of Donor Hospital: LOV; NOTE: first entry is country of user
    - Date of Donation: date (default is today)
    - Left or right kidney: Left/Right
    - Operation technique: LOV
    - Length of Hospital stay (LOS): whole number
    - Number of days in ICU: whole number (smaller than or equal to LOS)
    - Complications during/after operation?: Yes/No
      If Complications= Yes, please enter this information on the complication details tab (scroll up till you can see this tab in left corner)
      If you choose Yes for Kidney damaged during retrieval, a specification field is opened. In case of other organ damaged, the possible values can directly be chosen. In all other cases the complications are only indicated by Yes/No/Unknown options
- Once the information is completed click on "CREATE" icon at the bottom right of the browser page.
- If a mandatory value is missing or any entered value is invalid, one or more **alerts** will appear under the box/boxes, also indicating on which tab the errors still exist.
  NOTE: If you have entered that there are complications but you didn't indicate this on the specific tab, this results in a warning. You can save the record without completing the specific complications. Since this is not recommended, please select "No" on the question whether you want to continue and complete the complication details tab before saving the post-operation form!)
- If all information is correct, you will receive a success message. The indicator of the Pre-donation Form will be visible on the "main page" list by the blue PO box.

Adding a New Follow-up (FU) Form

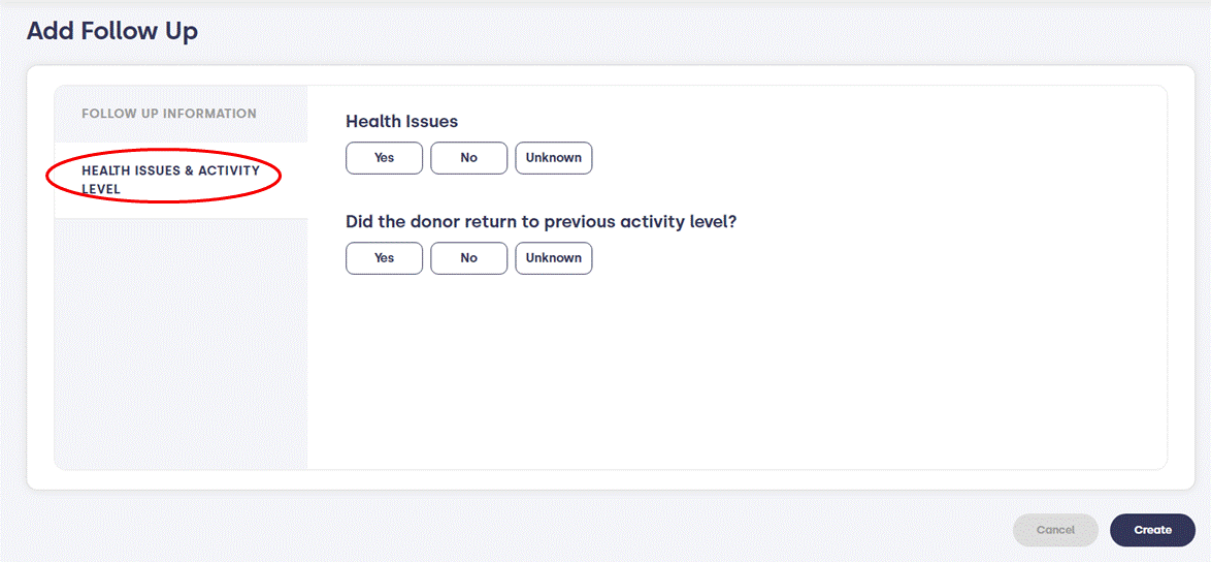
- To add a Follow-up (FU) form, there are several possibilities:
  - Choose FU for donor in donor list. After this the donor is shown and you can add can add a Follow-up form
  - Or go to ”+” and choose “Add follow-up”
  - after selection of the donor, choose “Add Form” underneath Follow-up
- In case a donor is lost to follow-up, or in case a donor has died, only the first part of the screen has to be entered (only with a date and in case of death also the cause of death); in that case the date of follow-up should be the same as the date of death/lost to follow-up. When both are No, this is a regular follow-up and the following items on the screen are shown:



In case of a female donor, also Pregnancy is added to the follow-up form

- Add all the necessary information to complete the Follow-up form.
- **Mandatory** values are marked with a **blue asterisk**, the other items are optional:
  - Date of follow-up: date (default is today)
  - Donor lost to follow-up: Yes/No * Donor Death: Yes/No
  - Weight + unit: whole number, NOTE kg is default unit (this can be changed in lb)
  - Antihypertensive medication: Yes/No/Unknown
  - Creatinine + unit: number (1 decimal allowed), NOTE umol/L is default unit (this can be changed in mg/dl)
  - Proteinuria + unit: number (1 decimal allowed), NOTE 24 hour urine collection is default unit (this can be changed in Spot urine per gram per liter, Dipstick or CR (protein/creatinine ratio); NOTE2, if Dipstick then only values Positive/Negative are possible)
  - Renal Replacement Therapy (RRT): Yes/No; if Yes also
  - Date of RRT (required if RRT = Yes)
  - Pregnancy: Yes/No/Unknown (only in case of a femal donor)

- On the health issues & Activity level tab the rest of the items can be filled out:
  - Health issues: Yes/No/Unknown
    The health issues & activity level tab can be found by scrolling up in the left corner (underneath the tab follow-up information). Don't forget to complete this tab
    If health issues = Yes, specifics can be entered. You can choose the specific health issue from a list of values, for example malignancies.



  - Did the donor return to previous activity level?: Yes/No/Unknown, if yes:
  - After how many months did the donor return to previous activity level?

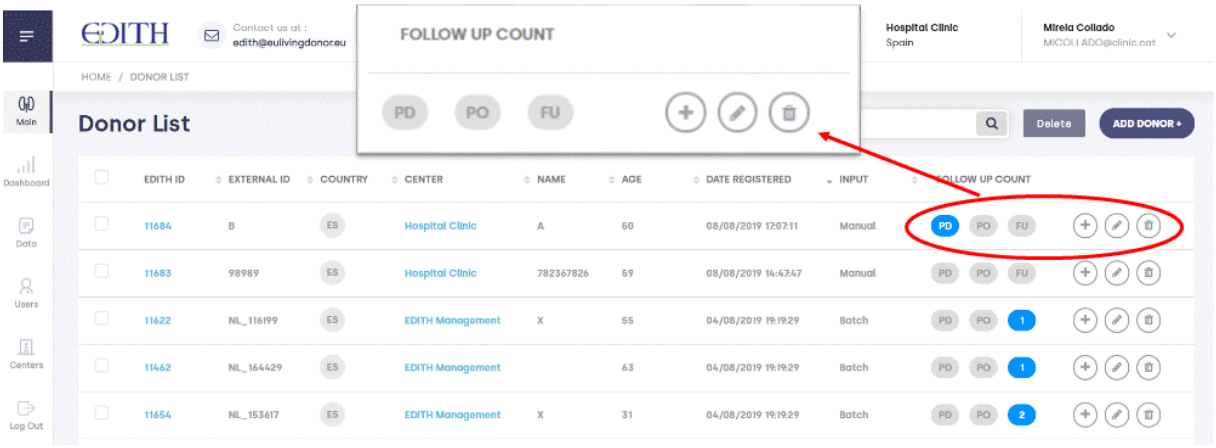
- Once the information is completed click on "CREATE" icon at the bottom right of the browser page.
- If a mandatory value is missing or any entered value is invalid, one or more **alerts** will appear under the box/boxes, also indicating on which tab the errors still exist.
  NOTE: If you have entered that there are health issues but you didn't indicate the specifics, this results in a warning. Note: you can save the record without completing the specific health issues, but this is not recommended so then please select "No" and complete the health issue details before saving the follow-up record!)
- If all information is correct, you will receive a success message. The indicator of the Follow-up Form will be visible on the "main page" list by the blue numbered box (here 1) underneath the follow-up count (right side of PO).

XIII.2.2 Viewing, editing or deleting information

- In the donor list you can **VIEW** all donors that you have access to with the following information:
  - EDITH ID
  - EXTERNAL ID
  - COUNTRY
  - CENTER
  - NAME
  - AGE
  - DATE REGISTERED (date and time of donor registration)
  - INPUT (either manual/batch = file upload)

- FOLLOW-UP COUNT; in blue the available records: Pre-donation (PD), Post donation (PO) and how many Follow-up (FU) records

After adding information, the user can always view, edit or delete the information. These actions are possible through the icons on the right side of each donor row:



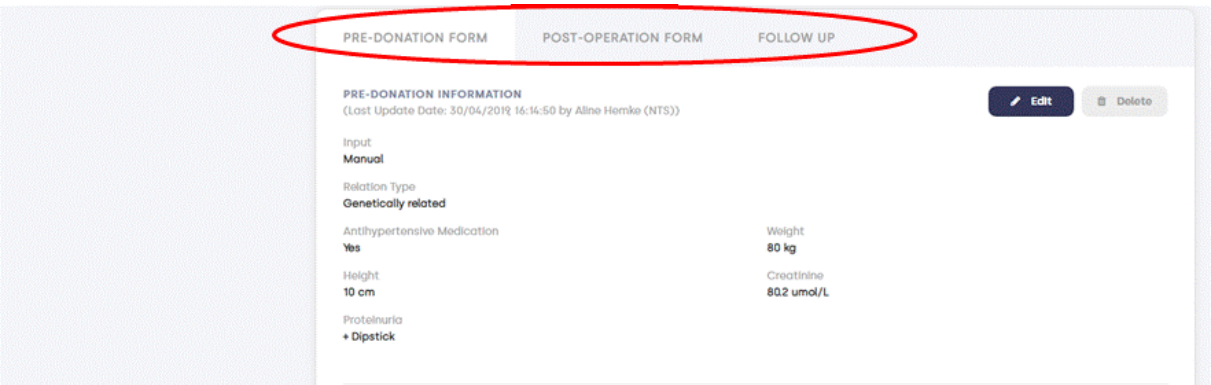
- To **Edit** any information, go to the pen-icon. The system will ask you to select which Form should be modified.
- To **Delete** all information of a donor press the icon with the bin. The system will ask you to provide the reason for the deletion (this is saved and can be viewed by authorized users in de audit information). Note: if a donor is deleted all linked PD, PO and FU forms will be deleted as well.

Search information

You can view the registered information by selecting the EDITH ID from the Donor List. If you want to view PD, PO, or FU information, you can do this by selecting the specific PD, or PO directly from the donor list. If you choose for the follow-up when there are several follow-ups available, you will have to choose the specific follow-up in the next menu.

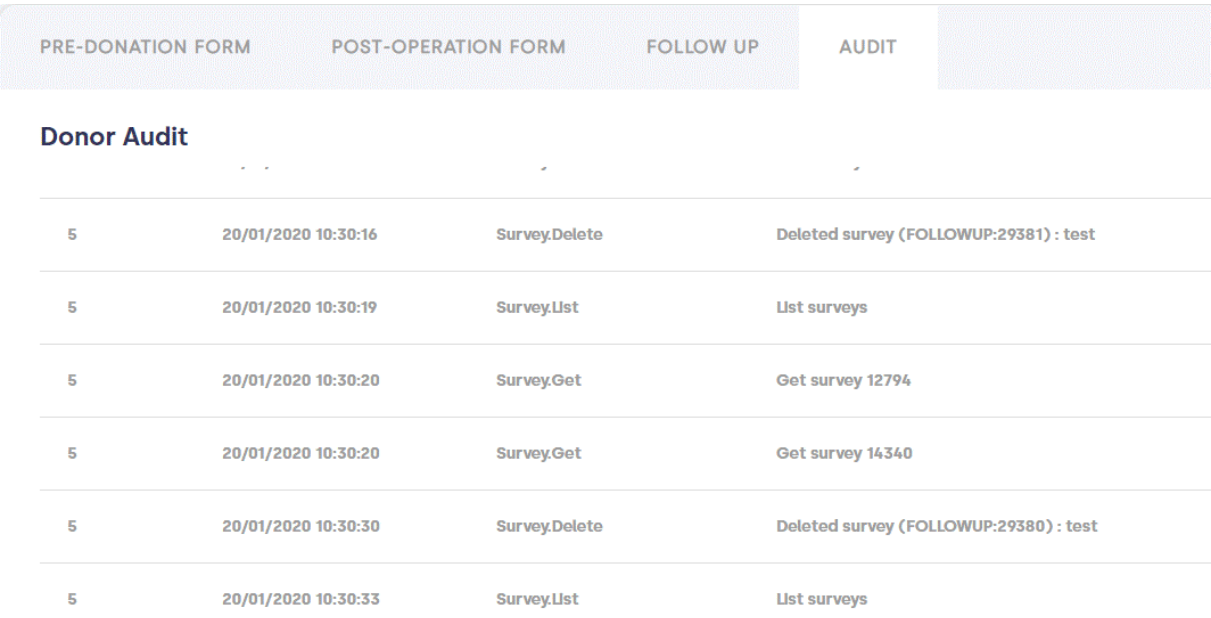
If the donor isn't immediately visible in the list, you can either scroll through all donors or search for a donor. By using the search button, this filters all donors from the Donor list who fulfill the search criteria. You can specify in which field the search must be done. When you choose "All" the search is done in all fields. You can also scroll through donors in donor list, and use the sort buttons in each item to sort (either ascending or descending).

To view donor, pre-donation, post-operation and follow-up information of one particular donor, select the blue EDITH ID, and scroll through the screen (and press the different tabs; normally only the PD is shown as this is the first tab)). Or you can go directly to the PD/PO/FU information in the donor list.



View audit information

Audit information gives insight in who has when entered, updated and/or viewed donor information. This is a separate tab after the pre-donation, post-operation and follow up tab. Here an example of the audit view for a donor with 2 follow-up records that are deleted, where for reason "test" was entered:



Correcting information

- When you are in the Donor List, you can go to the edit-button on the right side and then select the form that you would like to edit
    - donor from
    - pre-donation and post-operation from
    - Follow up

Deleting information

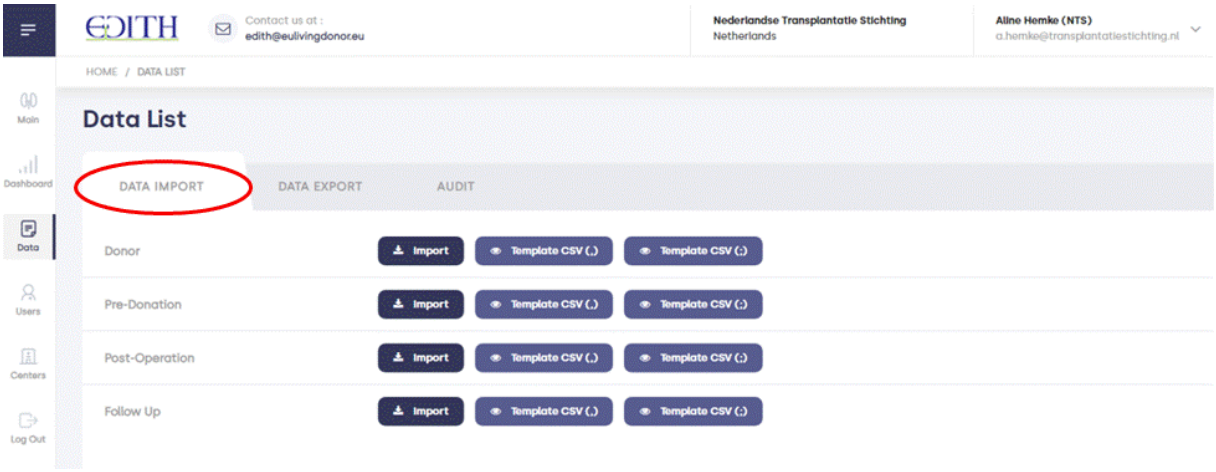
- Delet donor:
  Select the delete-button in donor list on the right side. It is also possible to delete more than one donor at the same time
- Delete donor forms
  Select the delete-button in donor menu.

- If you delete information, you always have to add a reason: this is recorded in the database and visible in the audit information. If you enter a reason, the deletion is confirmed with a notification

XIII.3. BATCH upload

The ELDR allows the users to **import** and **export** donor information from batch files through the section “Data”.

For each of the 4 files: donor, pre-donation, post-donation, and follow-up there is an upload possibility. The file templates - either comma (“,”) separated or semicolon (“;”) separated - can be viewed in DATA IMPORT.



To **download** a batch template, click on “Template CSV” in the “Data Import” section. Each Form (donor, pre-donation, post-operation, and follow-up) has its own Comma (or Semicolon) Separated Value (CSV) template

To **upload** your batch file, click on “Import” in the correct row (donor, pre-donation, post-operation, and follow-up). You are directed to your own computer and select the correct map where the .CVS file containing the information is located. Note: the number of records that can be uploaded in one time may not exceed 5000. More records will result in an upload error. If you have files that exceed 5000 records, you should split these and upload the smaller files separately.

When an error is detected during the file uploading, a file will be generated specifying the records that have not been added. In this case it is important to revise the CSV file and import the correct version. If the file upload is processed correctly, a “success” message will be displayed.

After every upload you get a notification of the upload, with or without errors and warnings. If there are errors/warnings you can view these by a report that is only available immediately after the upload by selecting the Download Results button! The resulting file is shown in the left under corner of your screen and can then be opened in Excel. It shows possible errors (or missing values) to correct or add.

Comments on file upload:

- It is essential that the header is exactly the same as in the template; therefore it is recommended to copy the original headers in your upload file, to avoid mistakes (resulting in upload errors).

- The date format that should be used is DD/MM/YYYY (with slashes).
- Mandatory items cannot be skipped in the ELDR forms. However, in DATA IMPORT mandatory missing values are accepted. If mandatory fields are empty in the uploaded file the upload report will give a warning that fields are missing, but the record will nevertheless be accepted (as opposed to an error: in that case a record is not accepted). The eventual unit field connected to this missing item also should be left blank in the uploaded file, because of the dependencies between fields.
- For mandatory fields, like Blood Group, Complications, and RRT, the unknown value ("U") is not accepted. If it is unknown in the local database, this should be left blank in the Upload file. Unknown values ("U") are only accepted for optional fields.
- If Comorbidity (Pre-donation), Complication (Post-operation) or Health issues (Follow-up) is either No ("N") or Unknown ("U") all subsequent specification fields should be left blank. If Comorbidity (Pre-donation), Complication (Post-operation) or Health issues (Follow-up) is Yes ("Y") at least one of the subsequent specificities should be Y (for the others Y, N, U or blanks are accepted).
- A pre-donation, post-operation or follow-up is only accepted if a donor with the same ID is present in the database.
- In case a donor has died, the date of death and cause of death should be filled, as well as the follow-up date (this should be filled with date of death); all other fields should be left blank.
- In case a donor is lost to follow-up, the date lost to follow-up should be filled, as well as the follow-up date (this should be filled with date of lost to follow-up); all other fields should be left blank.

XIII.3.1 Batch File Layout: Donor Template

File naming convention	Donor_XXX.CSV
Where XXX can be any identifier such as: - Sequence number (e.g.: Donor_001.CSV) - Timestamps (e.g.: Donor_20181210.CSV) - Interval reference (e.g.: Donor_CA_112.CSV)	

For file description and specifications, please see sections VII Report on the ELDR specifications (D5.2) and VIII ELDR Dataset (D5.2)

Validation rules

- 1 entry per line
- 10 fields per line
- Warning: if mandatory fields (except ExternalID; this will lead to an error) are empty
- Error: if any values are out of expected range
- Error: if dependencies are not valid

XIII.3.2 Batch File Layout: Pre-donation survey

File naming convention	PRE_XXX.CSV
Where XXX can be any identifier such as: - Sequence number (e.g.: PRE_001.CSV) - Timestamps (e.g.: PRE_20181210.CSV) - Interval reference (e.g.: PRE_CA_112.CSV)	

For file description and specifications, please see sections VII Report on the ELDR specifications (D5.2) and VIII ELDR Dataset (D5.2)

Validation rules

- 1 survey per line
- 35 fields per line
- Warning: if mandatory fields (except ExternalID, this will result in an error) are empty
- Error: if external ID does not exist for the center where the logged user belongs
- Error: if any values out of expected range
- Error: if dependency violation

XIII.3.3 Batch File Layout: Post-operation survey

File naming convention	POST_XXX.CSV
Where XXX can be any identifier such as: - Sequence number (e.g.: POST_001.CSV) - Timestamps (e.g.: POST_20181210.CSV) - Interval reference (e.g.: POST_CA_112.CSV)	

For file description and specifications, please see section VII Report on the ELDR specifications (D5.2) and VIII ELDR Dataset (D5.2)

Validation rules

- 1 survey per line
- 21 fields per line
- Warning: if mandatory fields (except ExternalID, this will result in an error) are empty
- Error: if external ID does not exist for the center where the logged user belongs
- Error: if any values out of expected range.
- Error: if dependency violation

XIII.3.4 Batch File Layout: Follow-up survey

File naming convention	FU_XXX.CSV
Where XXX can be any identifier such as: - Sequence number (e.g.: FU_001.CSV) - Timestamps (e.g.: FU_20181210.CSV) - Interval reference (e.g.: FU_CA_112.CSV)	

For file description and specifications, please see section VII Report on the ELDR specifications (D5.2) and VIII ELDR Dataset (D5.2)

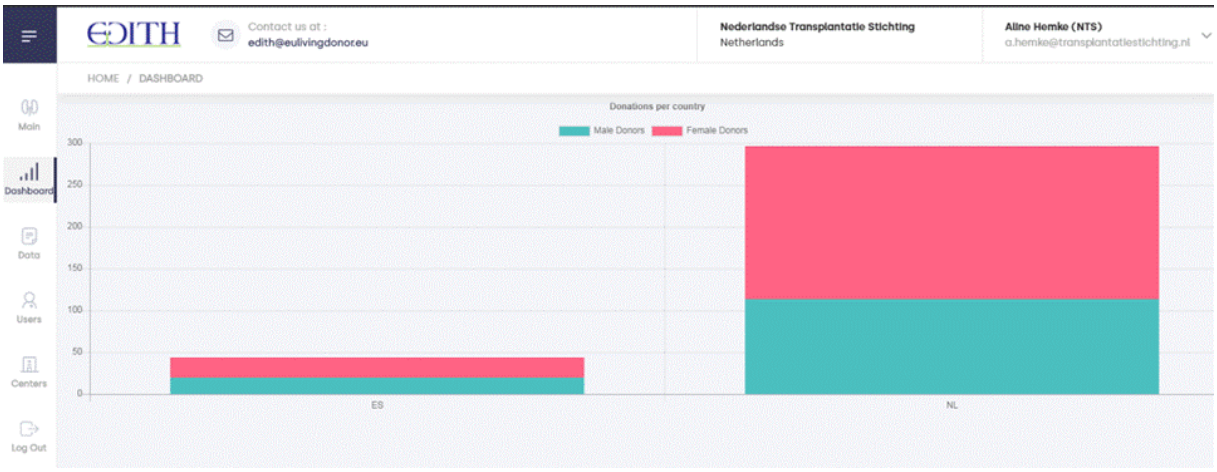
- 1 survey per line
- 42 fields per line
- Warning: if mandatory fields (except ExternalID, which would return an error) are empty
- Error: if external ID does not exist for the center where the logged user belongs to
- Error: if any values out of expected range.
- Error: if dependency violation

XIII.4. Data extracts and reports in the dashboard

Optionally, the user can **download** the data available in the registry through the "**Data export**" section. All available donor, pre-donation, post-operation and follow up information can be exported to a CSV file, that can be saved and/or opened in for instance Excel, to make own reports/analyses.

Furthermore, authorized users can view data available in the registry through reports that have been made available in the "Dashboard"

At the moment the dashboard only contains 1 report (the number of male and female donors per country); this will later be elaborated with additional standard reports.



XIII.5. FAQ

- What is a .CVS file?
  The batch template is a .CSV file (also known as comma-separated values). CSV is a simple file format used to store tabular data, such as a spreadsheet or database. Files in the CSV format can be imported to and exported from spreadsheet programs such as Microsoft Excel or OpenOffice Calc.The file begins with a header line containing all the field names.
- How to fill the batch file with the donor information?
  - Download the template provided in the section “Data”. There are two templates available, be sure which one is compatible with your spreadsheet program, (,) or (;).
  - Open the file with a spreadsheet program (f.i. Microsoft Excel)
  - Read carefully the header line.
  - Introduce the data according to the codes shown in section “fields description” in the batch file layout and following the order set out in the header line.
  - Optional values could be left empty
  - Each row represents 1 survey. The user can add as many rows as required, but with a maximum of 5000 records per upload. If you have more records, please split the file in two or more separate files that should be uploaded separately.
  - Remember to name the file as specified in the batch file layout, section “file naming convention”.
  - **Example 1: Donor Form**
    ExternalID,Name,DOB,Age,Gender,BloodGroup,CountryOfResidence,Nationality,Nationality_2,Ethnicity
    A1,,12/09/1958,60,F,O,ES,ES,ES,W
- Delimiter options: Comma (,) or semicolon (;), witch file should I chose?
  The system would use comma or semicolon as a default delimiter depending on the spreadsheet language (and the way decimals are displayed). Depending on the delimiter option, the program will display the file
- What are dependencies?
  The term “Dependencies” is referring to linked values. As an example: “malignancies” and “type of malignancies” are dependent values. When Malignancies = “no malignancies” and “type of malignances” is filled with a value, an error message will be displayed. Another example are weight and weight unit.

EKRR

XIV. Example Kidney Transplantation Activity Report (D6.1/.2/.7)

Responsible partner: ET, NHSBT
Document. WP& Deliverable 1 2 7 FINAL (002) PB_Update Can Meek no table of 26.11.2020

REPORT FOR 2019 (1 JANUARY – 31 DECEMBER 2019)

XIV.1. Kidney transplants, 1 January – 31 December 2019

Figure 1.1 shows the total number of deceased kidney only transplants performed in the last year, by type of donor and country. The UK performed the highest number of transplants from donors after circulatory death (DCD). The number of transplants from donors after brain death (DBD) was the highest in Italy.

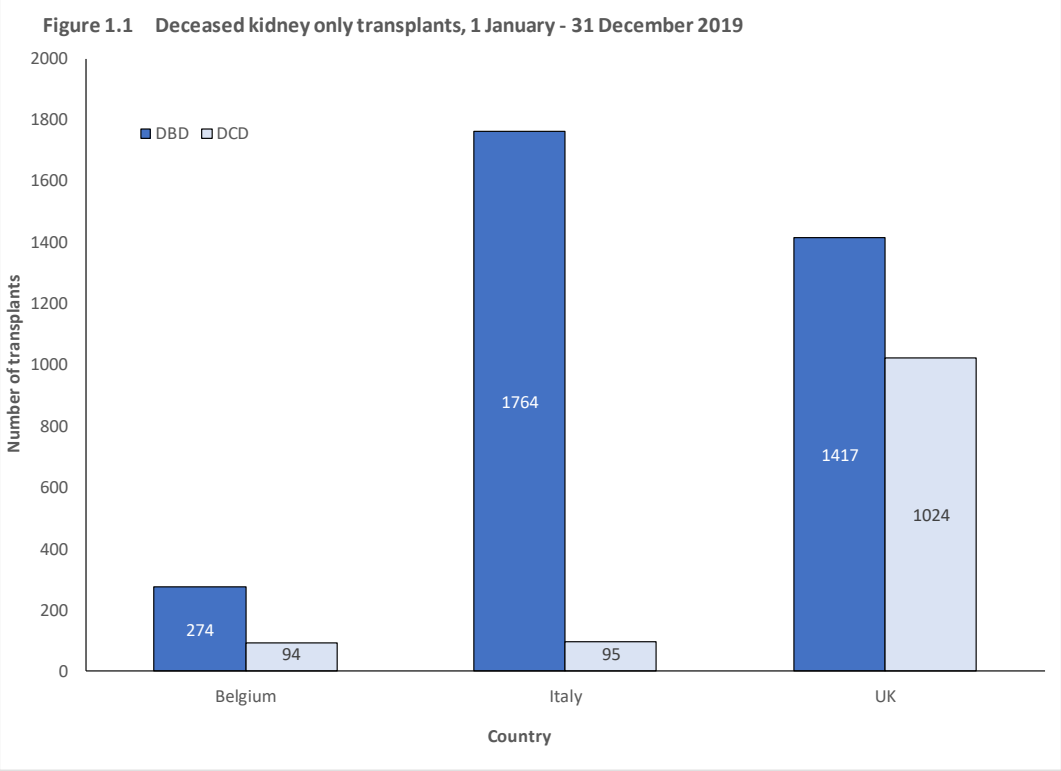
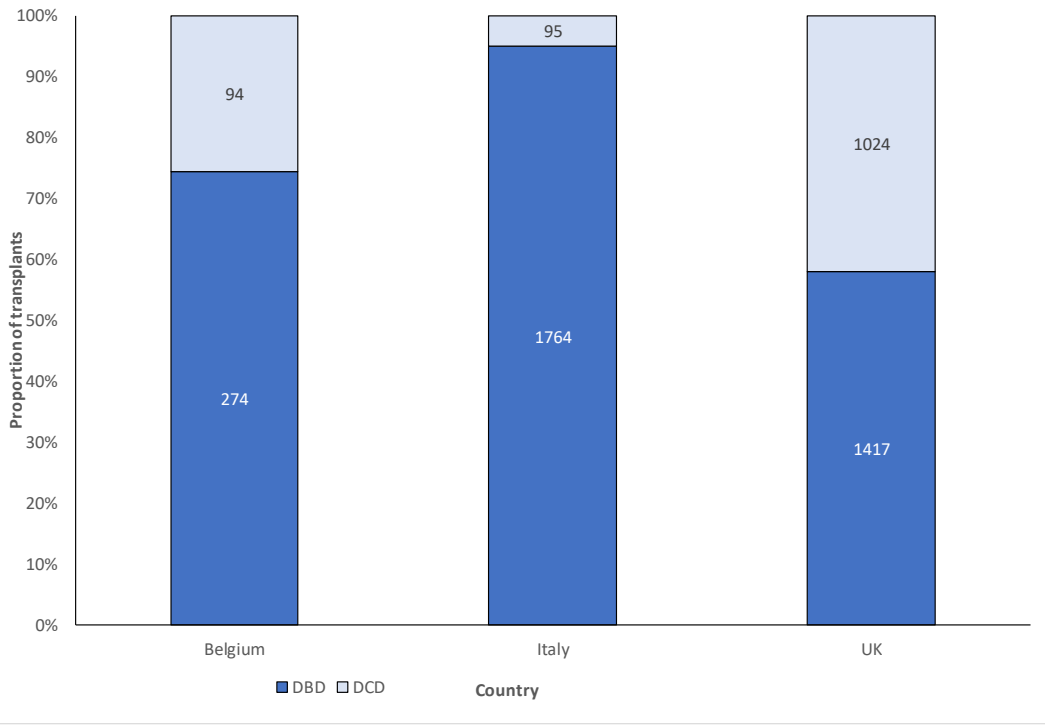


Figure 1.2 shows the proportion of DBD and DCD donor transplants performed by country.

Figure 1.2 Deceased kidney only transplants, 1 January - 31 December 2019



XIV.2. Demographic characteristics of recipients, 1 January - 31 December 2019

The blood group, sensitisation and age group of patients who received a kidney only transplant are shown by country in Figure 1.3, 1.4 and 1.5, respectively. Note that all percentages quoted are based only on data where relevant information was available.

Figure 1.3 Deceased kidney only transplants, 1 January - 31 December 2019, by blood group

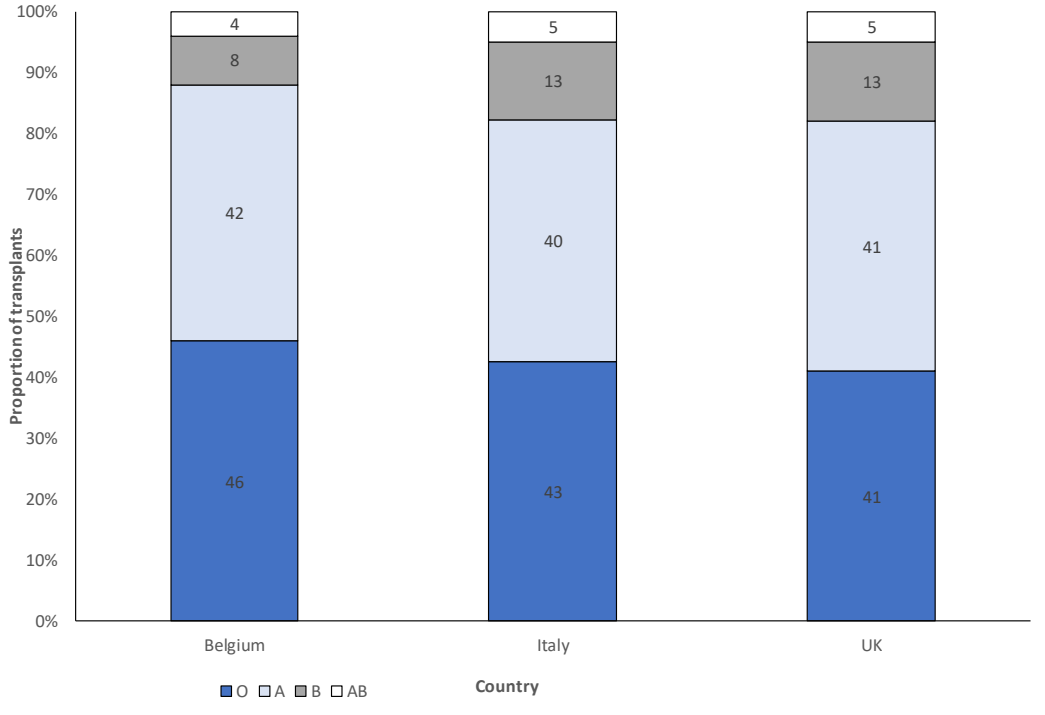


Figure 1.4 Deceased kidney only transplants, 1 January - 31 December 2019, HSP

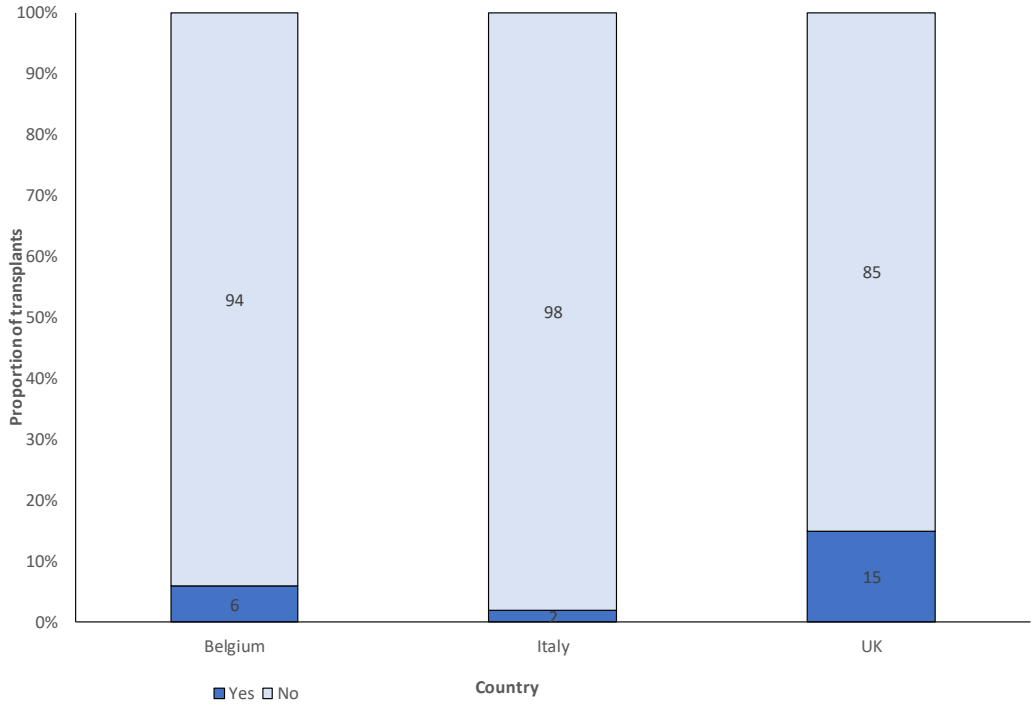
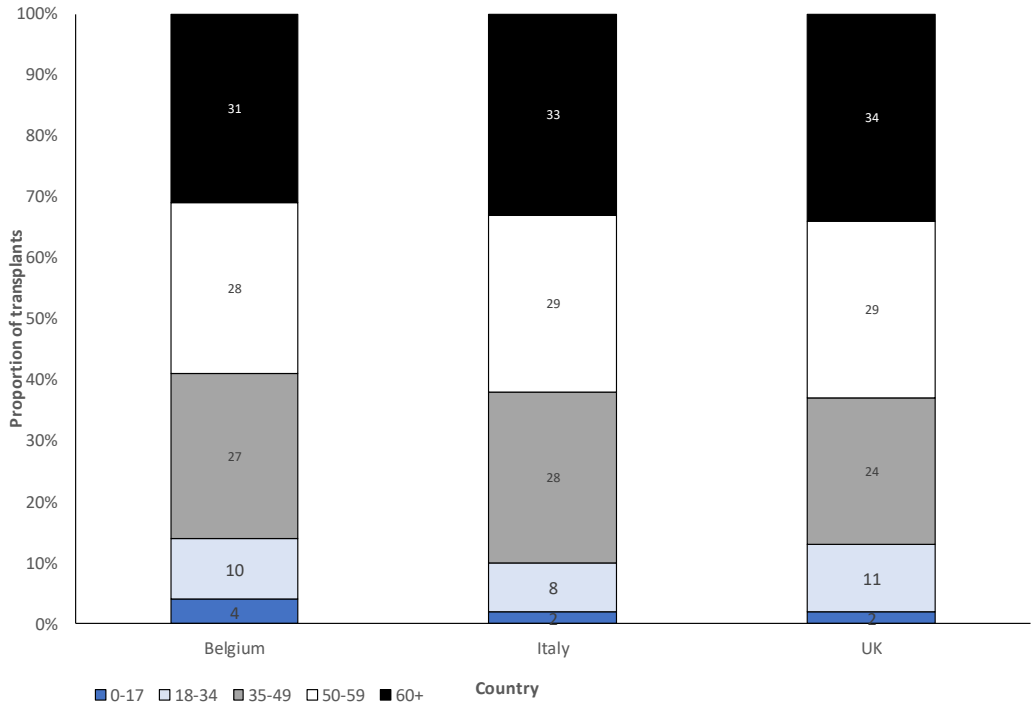


Figure 1.5 Deceased kidney only transplants, 1 January - 31 December 2019, by age group



XIV.3. Cold ischaemia time, 1 January – 31 December 2019

The length of time that elapses between a kidney being removed from the donor to its transplantation into the recipient is called the Cold Ischaemia Time (CIT). Generally, the shorter this time, the more likely the kidney is to work immediately and the better the long-term outcome. Evidence indicates that transplant outcome is only adversely affected when CIT is longer than 20 hours, although many deceased donor kidney transplants with a CIT of more than 20 hours have been very successful.

The factors which determine CIT include a) transportation of the kidney from the retrieval hospital to the hospital where the transplant is performed, b) the need to tissue type the donor and cross-match the donor and potential recipients, c) the occasional necessity of moving the kidney to another hospital if a transplant cannot go ahead, d) contacting and preparing the recipient for the transplant and e) access to the operating theatre.

Median CITs are shown in addition to inter-quartile ranges. Fifty percent of the transplants have a CIT within the inter-quartile range. Figure 1.6 shows the median total cold ischaemia time in DBD donor kidney only transplants by country.

Figure 1.6 Median cold ischaemia time of DBD donor kidney only transplants, 1 January - 31 December 2019

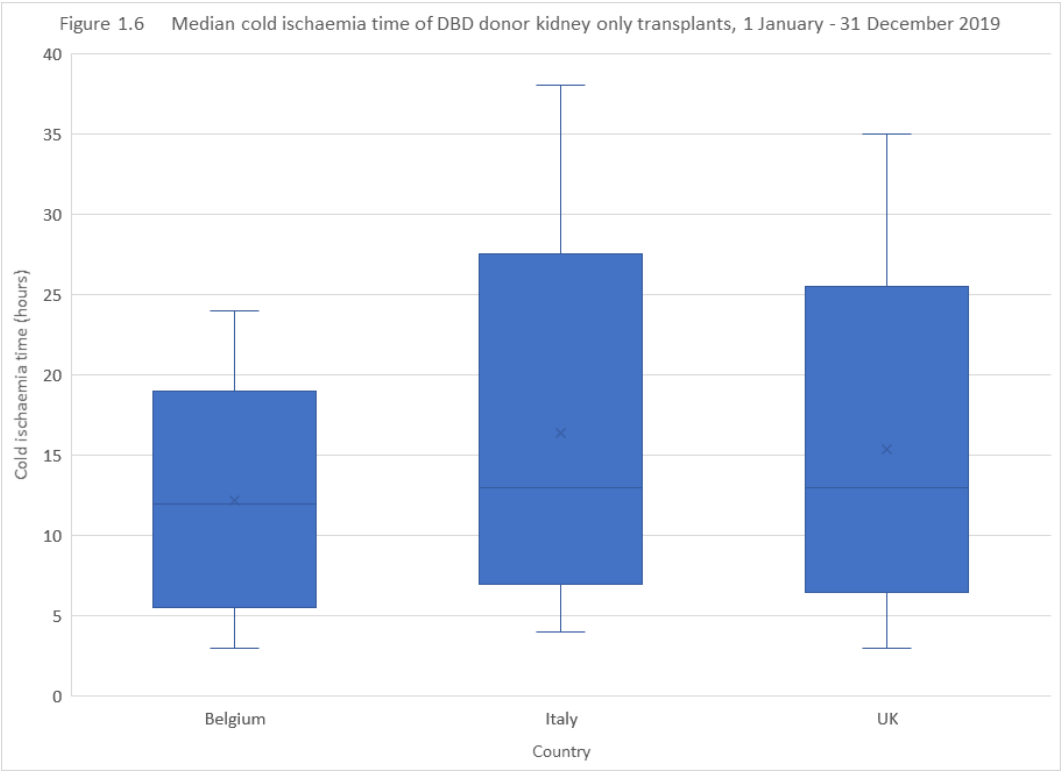
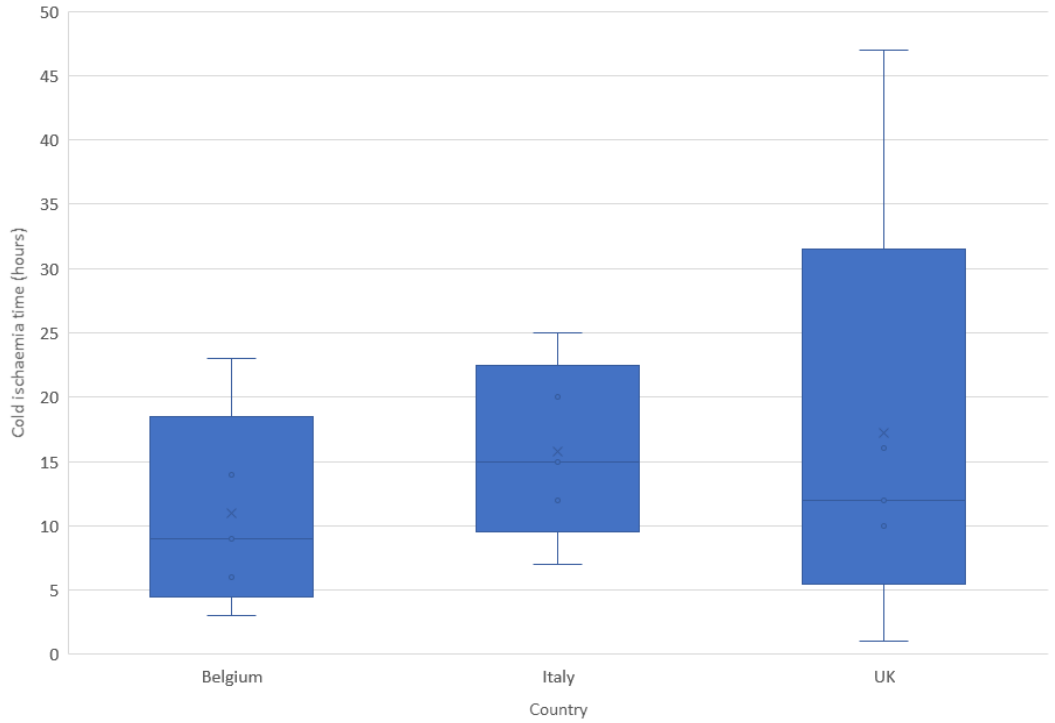


Figure 1.7 shows the median total cold ischaemia time in DCD donor kidney only transplants by country.

Figure 1.7 Median cold ischaemia time of DCD donor kidney only transplants, 1 January - 31 December 2019



XIV.4. Deceased donor graft and patient survival

Will be available in future versions of the Activity Reports.

Governance and sustainability of the EDITH registries

XV. EDITH Governance (D5.3/D6.6)

Responsible partner: EDITH partners
Document. EDITH governance from 29.02.20202

This section addresses the governance and administration of the future European Living Donor Registry (ELDR) and European Kidney Recipient follow-up Registry (EKRR), in the following referred to as European Transplant Registries (ETRs). It builds on the recommendations from the previous EU projects EFRETOS and ACCORD. Despite the fact that the ETRs are now focused on kidney donation and transplantation only, this governance scheme could also apply if the European Transplant Registries should be elaborated in the future to include other organs.

The aim of this EDITH governance proposal is to provide a concept for managing the new European Transplant Registries in such a way

- that all partners adhere to the agreed upon rules and regulations of the ETRs,
- that the ELDR and EKRR applications are up to date and working well,
- that data quality and scientific integrity is ensured, and
- that interests of all stakeholders are respected.

The European Transplant Registries intend to uphold three main principles, namely transparency, openness and a not-for-profit status. These basic principles will be part of the Articles of Association (AoA) that will have to be set up as one of the first steps based on this governance document.

XV.1. Contractual arrangements

In the Articles of Association not only the governance structure but also rules regarding data handling, ownership of data and the publishing of information have to be established. If specific tasks of the ETRs, for instance the hosting, are delegated to third parties, service contracts have to be setup with each of them.

The present document on governance tries to outline the key aspects that should be included in AoA and further contractual agreements. By focusing foremost on the scope of the services to be provided, the governance draft leaves the necessary degree of freedom for the final documents that have to be agreed upon.

XV.2. Purpose

The main purpose of the ETRs is to gain and increase knowledge about the consequences of living (kidney) donation and the outcomes of (kidney) transplantation. These new insights will be of benefit in several ways:

On a country-level, registry data allows for transparent information on (living) organ donation and transplantation activities including the related outcome for all participating countries. On a global level, the gain in knowledge may be the basis for adjusting the process of organ donation and transplantation, for instance in donor and/or patient selection and kidney allocation. This could ultimately lead to a reduced risk for living donors and improved outcomes for patients undergoing transplantation.

As a consequence, the European Transplant Registries are supposed to have a positive influence on future treatment decisions and subsequently on the alignment of health care throughout European

Member States and beyond. Not only for this reason, it is important that the European Transplant Registries have clear policies and safeguards to ensure data accessibility, reporting and data request handling in compliance with the registry purposes.

The European Transplant Registries will serve a variety of stakeholders (partly with different interests), including:

- national Competent Authorities (CA) of cooperating member states
- national transplant registries
- national scientific review committees
- transplant centres and individual professionals
- patients and donor (families)

It is essential for every stakeholder that the European Transplant Registries respect the interests of other participants. All stakeholders will expect from the ETRs that its data are reliable, actual and their reports and 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.

XV.3. Organisational structure: organisation, tasks and responsibilities, hosting

In order for the ETRs to function, a solid governance structure is needed. The governance structure has to address both, the political and the scientific importance and relevance of the European Transplant Registries.

A three-layered governance structure is proposed for the registries (Figure 72):

- General Assembly,
- Steering Committee and
- Hosting Organisation(s) / Registry Staff

It is especially for the levels of the General Assembly and the Steering Committee, that scientific and political representation and input are considered utterly important. In the General Assembly, all Member States contributing to the ETRs as well as European Scientific Organisations are represented. Its main function is to approve policies and to monitor the overall execution of tasks. The smaller Steering Committee with members appointed by the General Assembly is the link between the General Assembly and the Hosting Organisation(s) / Registry Staff. The Steering Committee is involved in the development of policies and in the supervision of the ETRs. The Hosting Organisation(s) with the Registry Staff are responsible for the day-to-day business of the ETRs.

This proposal takes into account that the organisation of the ETRs should be lean and efficient, both in terms of costs and results. Therefore, it is proposed to join efforts by building a common General Assembly and Steering Committee and to carefully evaluate, whether one hosting organisation for both registries is feasible. This will be described in more detail later in this document.

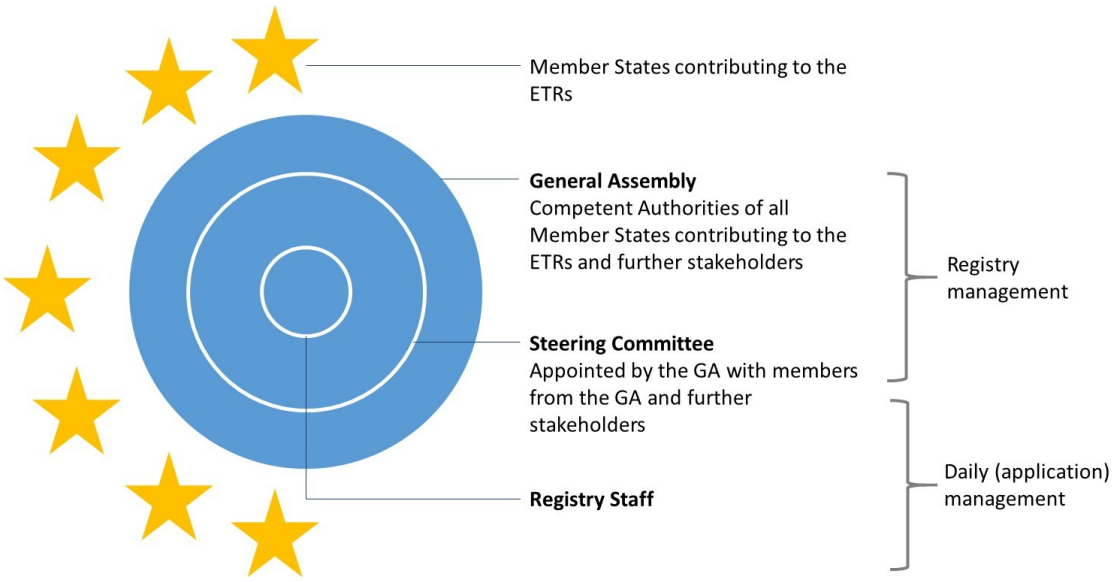


Figure 72: organisational structure of the ETRs

In the context of the governance structure and the distribution of tasks and responsibilities of the different stakeholders, the modes of data delivery to the registries – that are somewhat different between EKRR and ELDR – have be taken into account. As a standard, data delivery to both ETRs is done by the staff(s) of the national registries of the Member States typically via file upload, as an alternative direct key entry is possible. For the ELDR, professionals from the donation / transplant centres and even organ donors themselves can enter data, the latter only by direct key entry. Competent Authorities of participating countries can decide on how the data delivery is organized.

Every Member State that participates in the ETRs has certain tasks and responsibilities:

- It has to be ensured that all data that is uploaded or directly entered in the European Transplant Registries is actual and reliable. For data sent by the national registry of a Member State, this is the responsibility of the national registry. For data entered to the ELDR by centres and organ donors, mechanisms for checking data completeness and integrity and for data validation should be developed in close cooperation with the Competent Authorities of the respective member states.
- The conversion of data from an existing national registry to the dataset of the European Transplant Registries as well as the actual data entry will be under responsibility of the participating countries. The European Transplant Registries only provide a tool to collect and aggregate data. The collection and entry of data has to be performed by the participating countries. For the ELDR, this task can be delegated to the individual transplant centres.

The tasks and responsibilities of each party involved are given in the following tables (Table 46, 47, 48). In the next paragraphs the composition, the tasks and the responsibilities of the General Assembly, the Steering Committees and Registry are described in detail. Finally, the last paragraph of this section is dedicated to the role of the Hosting Organisation(s) / Registry Staff for the European Transplant Registries.

Table 46: Structure-related tasks and responsibilities in the registry organisation

Structure		
Task	**Responsible party**	**Supervision**
Proposition of new member countries to the ETRs	Steering committee	
Approval of new member countries to the ETRs	General Assembly	
Appointment of the representative in the General Assembly	Member State / Competent Authority	
Appointment of the members of the Steering Committee	General Assembly	
Monitoring and control of the Steering Committee	General Assembly	
Approval of policies	General Assembly	
Development of policies that are directed at developing and controlling the execution of data collection / data definition; data protection / safety; quality standards; data ownership / usage	Steering Committee	General Assembly
Major changes in the ETRs' data set (proposals for extra items, proposals for other definitions et cetera)	Proposal by: Member States / General Assembly / Steering Committee / European Transplant Registries	General Assembly
Finance and budget control	Steering Committee	General Assembly
Management of registry staff members	European Transplant Registries	Steering Committee
Authorization for access to the ETRs for national co-workers	European Transplant Registries	Steering Committee

Table 47: Tasks and responsibilities in the registry organisation related to the collection of data

Data collection		
Task	**Responsible party**	**Supervision**
Specification of valid formats for data entry	European Transplant Registries	Steering Committee
Communication concerning requests for data	European Transplant Registries	Steering Committee
Conversion of data from an existing living donor registry or recipient follow-up registry to EDITH dataset and dictionary	Member State / National Registry	National Competent Authority / Registry
Data entry, review and correction	Member State / National Registry	National Competent Authority / Registry
Data integrity	Member State / National Registry	National Competent Authority / Registry
Data completeness	Member State / National Registry	National Competent Authority / Registry together with ETRs
Overall monitoring and feedback on completeness and integrity of the data	Steering Committee	General Assembly

Table 48: Tasks and responsibilities in the registry organisation related to data operations

Data operations		
Task	**Responsible party**	**Supervision**
Daily support, helpdesk, database management, (technical) development and improvements, releases, etcetera	European Transplant Registries	Steering Committee
Data safety and security	European Transplant Registries	Steering Committee
Bugfixes and minor technical improvements in the ELDR/EKRR	European Transplant Registries	Steering Committee
Standardized Reports	European Transplant Registries	Steering Committee
Evaluation of requests for data	Steering Committee	General Assembly
Data analysis	European Transplant Registries	Steering Committee

XV.3.1 General Assembly

Tasks

The General Assembly acts as governing body for the European Transplant Registries and is responsible to ensure that the registries can function in compliance with the existing legal, scientific and ethical regulations.

The main tasks of the General Assembly will be the governance of the registries, including the approval of new member states and the appointment and supervision of the members of the Steering Committee. The Steering Committee in turn is directly responsible for the supervision of the technical and functional performance of the registries.

The General Assembly will bear the strategic responsibility for the functioning of the registries including its underlying policies and procedures (e.g. data request handling), financing, and content (e.g. datasets and data definitions). Therefore, the General Assembly will have to supervise and approve all changes to the structure and policies of the ETRs as well as to its data sets. Requests for adaptation of the registry from e.g. Member States or the Hosting Organisation(s) / Registry Staff, will be collected by the Steering Committee and forwarded to the General Assembly. The Steering Committee will facilitate all of the General Assembly's decision-making by preparing target-compliant measures.

Membership

Given the central political as well as scientific role of the General Assembly, it is important that a broad representation of both, the Member States as well as international scientific expertise is present in this body. Therefore, the General Assembly shall be composed with one representative for each of the following parties:

- EU Member States, that supply data to the European Transplant Registries
- One or more European scientific organisations, like ESOT or ERA-EDTA
- European donor (family) association
- European patient association
- European Commission – DG SANTE (Directorate General for Health and Food Safety)

Every EU Member State, that is willing to supply data, can join the European Transplant Registries. As a prerequisite for joining, a letter of support from the Ministry of Health or the responsible Competent Authority has to be provided by the Member State.

The General Assembly takes decisions by an absolute majority of votes cast. Each Member State delivering data to at least one of the registries (ELDR / EKRR) shall have one vote. If the General Assembly is in charge of both registries as proposed here, the agenda of the General Assembly meeting shall be divided in general, EKRR and ELDR topics; voting rights for registry specific topics will be limited to countries that report data to the respective ETRs. Members States that do not supply data to the registries may participate in the meetings of the General Assembly, but without voting rights.

Given the fact that 28 countries are currently member of the EU, the General Assembly could theoretically consist of 28 Member State representatives. For greater cost efficiency, the delegation of voting rights shall be possible. In the future it might become possible for other (non-EU) countries to join the European Transplant Registries, as long as the candidate country adheres to the rules and regulations of these registries.

The General Assembly elects a chair from the members of the General Assembly. The chair of the General Assembly will be the point of contact for the group of Competent Authorities (CA meeting) and the Steering committee, and should have a broad understanding of clinical, technical and regulatory issues. The chair of the General Assembly will be appointed for a period of three years and is eligible for re-appointment for a second term of three years. Therefore, the chair of the General Assembly can be appointed for a period of maximum six years. General Assembly membership is not limited to a specific term.

Meetings

The General Assembly will meet once a year. For efficiency reasons it is recommended to compose the General Assembly with members from the Competent Authorities and link the General Assembly meeting to the yearly Competent Authorities meeting. An alternative could be to link the meeting of the General Assembly to an annual congress, for instance from ERA-EDTA (European Renal Association – European Dialysis and Transplantation Association) or ESOT (European Society for Organ Transplantation).

XV.3.2 Steering committee

Tasks

The General Assembly is quite large and only meets once a year, which makes it difficult to make easy and fast decisions. Therefore, the Steering Committee is the linking pin between the General Assembly and the Hosting Organisation(s) / Registry staff and is responsible for supervision of the registry management.

The Steering Committee evaluates the scientific functioning of the registry, and formulates proposals for changes to the data collection (procedures), reporting facilities and standard reports like the annual report. It might also develop policies and recommendations for major changes to the ETRs, including adaptations of the Articles of Association. All changes have to be approved by the General Assembly prior to being implemented.

The Steering Committee is furthermore responsible for reviewing (and granting) requests for data or non-standardized reports. Decisions on whether or not a data request will be granted, should be made within four weeks. The Steering Committees therefore will have to discuss The Steering Committee works in close collaboration with the Hosting Organisation(s) / Registry Staff. It supervises the implementation of decisions by the General Assembly and takes care of decisions regarding minor changes and maintenance of the ETRs. The Steering Committees supervises the budget and the finances of the ETRs and reports to the General Assembly on this. It will receive administrative and secretarial support from the Hosting Organisation(s) / Registry Staff.

Membership

The ETRs' General Assembly will appoint and supervise a Steering Committee that represents political as well as scientific practice. The Steering Committee shall be composed with representatives of the following parties:

- European scientific organisations (2)
- General Assembly, representing ELDR data suppliers (2)
- General Assembly, representing EKRR data suppliers (2)
- European donor (family) association/ European patient association (1)

The Steering Committee consists of 7 members. The members will be appointed by the European Scientific organisation(s) and the General Assembly.

Membership to the Steering Committees will rotate every three years on a rolling basis (so that not all committee members are retiring at the same time). The General Assembly should ensure that at least one of the top 3 countries for the kidney recipient registry and one of the top 3 countries for the living donor registry are represented in the Steering Committee. The definition of this ´top 3´ is: countries that have included the highest absolute number of donors and/or recipients yearly in the ELDR / EKRR. The benchmark should be performed when necessary.

The chair of the General Assembly cannot be a member of the Steering Committee.

Meetings

The Steering Committee will meet in person at least two times a year. In addition, it will report about its activities in the yearly General Assembly meeting. In case of major decisions that cannot wait until a next General Assembly meeting, the Steering Committee can arrange additional consultation possibilities.

Registry Staff from the Hosting Organisation(s) have to be present at the Steering Committee meetings.

XV.3.3 Hosting Organisation(s) / Registry Staff

Tasks

The Hosting Organisation(s) / Registry Staff will be responsible for

- providing and maintaining the technical infrastructure of the ETRs
- technical support for users of the registries
- maintaining, intensifying and enlarging contacts with Member States delivering or potentially delivering data to the ETRs
- data collection (including reminders), data hosting, monitoring of the quality of the data
- preparation of an Annual Report and basic descriptive statistical analyses
- providing data (extracts) for analytical statistical analysis (after prior approval by the Steering Committee)
- implementation of all agreed policies and operating procedures
- human resources within the financial budget.

Extended, specialized specific data analysis is not the key task of the Registry Staff, it can be provided against payment of a fee.

The European Transplant Registries are considered too small for a self-supporting organisation. Therefore, the ETRs are preferably situated in one or two Hosting Organisation(s) that have experience and personnel related to the maintenance of a registry and data management.

Considerable advantages are expected to be realized if the European Transplant Registries are hosted by an existing organisation that has experience in organ donation, allocation and transplantation and that is already working on an international level.

The Hosting Organisation(s) will be contracting partner to the data supplying Member States and will need to cover following areas of competence:

- Technical application management
- Functional application management and data management
- Daily technical support (application management, help desk, contact with all data suppliers)
- Administrative support

Technical application management will provide a functioning technical infrastructure to the registry. Based on the tools, which have been developed within the EDITH project, the technical operator/s will deploy a technical interface for the data supplying countries. The technical application management involves all functionalities and applications for security control and back-up systems.

The functional application / data manager will be responsible for the combined tasks of (functional) application management and data management for the registry application(s) as well as the registry website(s). These employees will have to work closely together with the technical application manager/s. The functional application manager plays an important role in registry maintenance and development to improve the possibilities, functionalities, and features. Suggestions for improvements can originate from (daily) contact with users, but also from contacts with formal national representatives or Competent Authorities. In case large financial investments (investments that exceed a regular maintenance budget for the registries) are needed to maintain or develop the registries, the Hosting Organisation(s) will need to ask the Steering Committee for approval. The Steering Committee will discuss this with the chair of the General Assembly. The General Assembly will decide on major changes. In case a new Member State is approved to work with the ETRs, the registry staff is informed by the Steering Committee and the functional application manager will have to make the necessary preparations to make this possible. Another important task for the registry staff is data request handling and data analysis. Standardized reports will be made available on the registry websites. The reports can be renewed every year with updated registry data. Non-standardized requests for data, granted by the Steering Committee, will be handled by or delegated to the Registry Staff.

The last important task for the registry staff is daily technical support and helpdesk as well as user management (users and passwords), which will need continuous attention.

Within the presented structure, the (overhead) costs can be kept as low as possible. The registry staff members and technical management employees should preferably be employed in the same Hosting Organisation(s) (shared services and personnel), which makes daily (hierarchical) control and continuous support possible.

Meetings

The staff members of the registries are functionally accountable to the Steering Committee and will be required to attend their Steering Committee meetings twice a year.

XV.4. Temporary organisation during EDITH project phase

This paragraph describes the Governance structure during the EDITH project (01.2017- 12.2020), starting from the implementation of the new registries for use by the EU Member States. Only discrepancies in the project phase from the Governance Proposal are described here.

In the project phase we propose a slightly different governance structure:

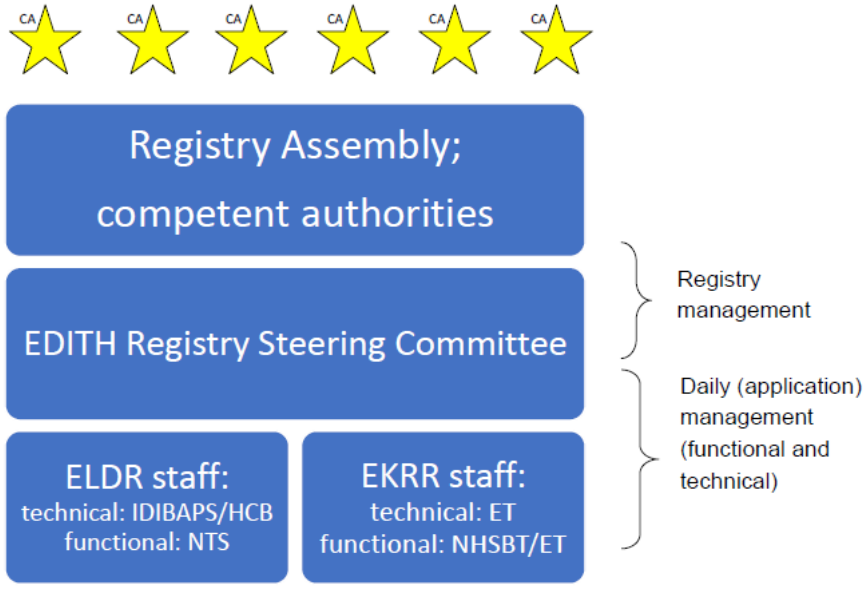


Figure 73: Governance structure of the EDITH registries during the project phase

- During the project, the EDITH Steering Committee will be responsible for major decisionmaking regarding the content and financing of the registries. This responsibility will be passed to the new General Assembly after the project finalization.
- During the project, the ETRs' staffs are actually Work Package (WP) 5 and WP 6 project members. They are responsible for the development and implementation of the registries. The responsibility of running the ETRs will be passed to the new Hosting Organisation(s), once EDITH has ended.
- During the project, WP 5 and WP 6 project members will contact the EU Member States that have indicated to be willing and able to participate in (at least one of) the new European Transplant Registries. They will facilitate the entry to the registries and enable access to the designated persons. On a functional and technical level, there will be contact with the national registries and/or centres that will deliver the data and if needed they will receive functional and/or technical help to realize this.
  All responsibilities regarding the admission of new Member States will be passed to the ETRs General Assembly, once EDITH has ended.
- During the project phase, the General Assembly will not be formally established. Therefore, the proposed governance structure will be presented to all Member States during a Competent Authority meeting for approval.

XV.5. Funding

The development of the ELDR and EKRR were part of the project EDITH and have received funding from the EU. In order to provide financial sustainability to the European Transplant Registries, once EDITH has ended, different financing options need to be examined and finalized. Possible financing options include:

- the acquisition of a sponsor
- the collection of user fees
- the use of alternative forms of financing.

In order to keep the maintenance costs the ETRs as low as possible, the aim of the present governance proposal is to combine tasks and responsibilities of the ELDR and the EKRR wherever possible (see SUSTAINABILITY paragraph).
See section XVI Recommendations for sustainability of the EDITH-build registries (D5.6/D6.8): Sound financial structure.

XV.6. Dissemination of information, data accessibility

It is planned to establish two ways of data access for internal and external users of the ETRs:

- direct access via standardized reports or downloadable standardized data extracts
- access via specific data requests

Table 49: Different approaches of data request handling

Categories of data requests		**Data release to**
A	Standardized reports and related data requests that do not require specific authorization	All Registry stakeholders, authorization by Registry Staff
B	Ad hoc data requests (which always require specific authorization)	Authorized stakeholders, authorization by Steering Committee

For the direct access, standardized reports / data extracts have to be developed by the Hosting Organisation(s) / Registry Staff in close collaboration with the Steering Committee that will be approved by the General Assembly. These reports and data extracts can be released – depending on the requesting party – without the need for authorization. Limited supranational reports will also be made available for the general public, and as a first step, the development of an Annual Report with supranational data is planned.

More detailed standardized reports / data extracts are restricted to the data suppliers (see chapter on the Organisational Structure). Since they are responsible for data quality and completeness, they should not only be able to see their data, but also be able to monitor, correct, complete or delete their data. Member States will be able to access detailed information from their own country only.

To support scientific research, it is necessary to establish optimal access to information from the ETRs for different stakeholders by providing a report facility and/or by granting data / information requests. The registries must respect the confidentiality on national / regional level. For data requests going beyond the standard reports and analyses, authorization has to be given by a committee of experts. For the European Transplant Registries this is a role for the Steering Committee. This committee is responsible for assessing whether or not data requests are complying with the approved policies and general principles of the registries. These general policies on the European Transplant Registries data disclosure need to be developed and approved by the cooperating Member States (represented by the General Assembly) and their national registries. Rules for authorship regarding publications on European Transplant Registries data will be described in this disclosure policy. The disclosure policy will be added to the next version of the governance document as an appendix.

Several prerequisites for data delivery and analyses exist. Data has to be:

- complete and of adequate quality
- processed in compliance with national and European data protection and data safety legislation and regulations.

These general procedures will safeguard against unauthorized usage of national data and prevent wrong interpretation due to incomplete extraction and/or inadequate data quality.

XV.7. Data quality/ data completeness

This section gives more information on data quality / completeness and the legal data protection requirements. The quality of a registry is defined by two measurable parameters: data quality and data completeness. In order to obtain optimal data quality some quality assurance measures can be implemented in the European Transplant Registries (functional application management):

1) Plausibility checks during data entry / upload: the data supplier should be alerted by the computer system when the data that he wants to enter (in case of data entry) or deliver (in case of data upload) are not correct. In the application this could be achieved by defining minimum and maximum values or predefined pull-down menus.
2) 2) Screening of data quality by registry data management: the data manager will perform cross checks on the completed data and discrepancies will be reported back to the individual centres / registries that delivered the data. The data suppliers have to correct the data. In case of file upload, data should be corrected in the National / local registry before a new file upload is possible again.
3) 3) The establishment of a system of regular audits by a national audit committee should be organized by the CA of EU Member States. It is advised to install a national audit committee and to develop a sound audit system to ensure the validity and accuracy of the data collected in the registries.

Next to data quality also data completeness is essential to determine which items can be used in registry reports and information request handling. In order to monitor data completeness, the individual fields in the EDITH registries must be awarded a percentage of minimal required completeness. These completeness definitions should be defined by the Steering Committee.

Finally, all Member States should provide the number of transplantations and donations in their country, for the Registry Staff to be informed about data completeness on transplant patient and donor level.

XV.8. Legal requirements

XV.8.1 General Data Protection Regulation (GDPR)

The General Data Protection Regulation (GDPR) 2016/679 of the European Parliament and of the Council of 27 April 2016 [GDPR 2016] on the protection of natural persons with regard to the processing of personal data and on the free movement of such data went into force on 25 of May 2018. This Regulation strengthens and harmonizes the rules for protecting individuals' privacy rights and freedoms within the European Union. The GDPR contains general principles to be observed in any context of personal data processing, including in research.

'Processing" means any operation or a set of operations which is performed on personal data or on sets of personal data, whether or not by automated means, such a collection, recording, organisation, structuring, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, restriction, erasure or destruction. See Article 4 (2) GDPR.
"Personal data" means any information relating to an identified or identifiable natural person (data subject); an identifiable natural person is one who can be identified directly or indirectly, in particular, by reference to an identifier such as a name, an identification number, locations data, an online identifier or to one or more

factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person. See Article 4(1) GDPR.

Organisations that process personal data must have a lawful basis for any processing activity. Article 6(1) GDPR delineates the lawful bases for processing, which include the data subject's consent and processing that is necessary for the legitimate interest of the controller.

Like in the previous Directive 95/46/EC [Directive 95/46EC 1995] the GDPR states that personal data:

shall be processed lawfully, fairly and in a transparent manner in relation to the data subject;

- shall be collected for specified, explicit and legitimate purpose and shall not further be processed in a manner that is incompatible with that purpose;
- shall be adequate, relevant and limited to what is necessary in relation to the purpose for which it is processed;
- shall be processed accurate and, where necessary, kept up to date;
- are erased or rectified without delay in case personal data are inaccurate with regard to the purposes for which they are processed;
- are kept in a form which permits identification of data subjects for no longer than is necessary for the purpose for which the personal data are processed.

The GDPR adds two principles to the existing privacy legislation [Chassang 2017]. The first principle regards the data integrity and confidentiality. According to this principle the data must be processed in a manner that ensures appropriate security of personal data, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organisational measures. The second principle is the accountability principle. This principle imposes a responsibility upon the controller of the data to be compliant and be able to demonstrate compliance with the general principles of data processing according to the GDPR.

Article 9 of the GDPR defines rules on the processing of sensitive personal data, such as data concerning health or genetic data. The basic rule is that is prohibited to process sensitive personal data unless an exception according to article 9(2) of the GDPR is applicable. According to this article the processing of personal sensitive data for archiving purposes in the public interest, scientific or historical purposes or statistical purposes shall be necessary, for the benefit of natural persons and society as a whole, and base on Union or MS law "which shall be proportionate to the aim pursued, respect the essence of the right to data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interest of the data subject."

XV.8.2 Consent

The GDPR prohibits processing of sensitive personal data unless:

- the data subject provides explicit consent "or
- the data was "manifestly made public by the data subject" (see Art. 9(2) (a) and Article 9(2)(e) GDPR).
- In addition, article 9(2)(j) GDPR allows a researcher to process sensitive data where "processing is necessary for research purposes in accordance with article 89(1) based on Union or MS law which shall be proportionate to the aim pursued, respect the right for data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interest of the data subject".

Since it is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection, Recital 33 of the GDPR allows data subjects "to give their consent only to certain areas of research or parts of research projects to the extent allowed by the intended purpose". An alternative ground for processing is the legitimate interest of the controller. According to article 6(1)(f) GDPR a controller can process personal data "for the purpose of this legitimate interests, except where such interest is overridden by the interest or fundamental rights and freedoms of the data subject". Although research is not explicitly mentioned in the GDPR as a legitimate interest the Article 29 Working party has recognized research as a context in which the issue of legitimate interest may arise.

A privacy impact assessment (PIA) is a tool to identify privacy risks concerning the collection and use of sensitive personal health data. The process involves the evaluation of privacy implications of the registries in compliance with relevant privacy legislation, through describing how data will be obtained, processed, retained and published. In order to reduce and avoid risks, solutions will be proposed by consultation of the stakeholders if potential privacy risks have been identified. To be effective, a PIA will be conducted during the EDITH project as soon as possible, prior to, or directly after, launching the ETRs, ensuring that potential risks are identified at an early stage, with regards of reducing costs and the reputational impact of a data breach.

XV.9. Sustainability of the EDITH registries

Please see section XVI Recommendations for sustainability of the EDITH-build registries (D5.6/D6.8)

XV.10. Recommendations

Directive 95/46EC 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. Official Journal L. 1995; 281:31-50.

Chassang G. The impact of the EU general data protection regulation on scientific research. - *ecancermedicalscience.*2017;11:709

GDPR - Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regards to the processing of personal data and on the free movement of such data, and repealing Directive 95/46EC (General Data Protection Regulation) Official Journal L.2016;119(1).

XVI. Recommendations for sustainability of the EDITH-build registries (D5.6/D6.8)

Responsible partner: EDITH partners
Document. 2020-10-13 - EDITH SUSTAINABILTY DOCUMENT from 13.10.2020

To improve existing knowledge about the short and long term outcomes of organ transplantation and the impact of living donation on the donors, comprehensive follow-up data collection together with presumably relevant donor and recipient factors is an important tool. The following requirements are considered essential for the sustainable functioning of a European registry, especially in light of the fact that data delivery to the European registry by the different partners is currently not mandatory and will take place on a voluntary basis:

1. Visible benefits to all stakeholders

- Continuous collection of reliable and comprehensive data from national or local registries
- Straightforward data accessibility and standardized reporting

2. Simple technical framework

- Easy-to-use application that allows smooth operations and offers support
- Adaptable system, which supports tailored solutions and enables continuous further development and improvement

3. Transparent governance

- Fixed rules regarding data handling, data ownership and publication of reports
- Clear structure, which ensures scientific, political as well as patient group representation, participation and oversight
- High standards of data protection

4. Sound financial structure

- Cost efficient set-up of the registries and the organisational overhead including the General Assembly and Steering Committee
- Appropriate maintenance costs in relation to the number of participating countries

XVI.1. Visible benefits

To allow a comprehensive pan-European data collection on transplant and living donation outcomes, it is considered crucial to include as much and as comprehensive data as possible. By the continuous collection of reliable and comprehensive data from as many national or local registries as possible, major benefits will become evident quickly. This applies to follow-up data not only from living donors, for which the collection of follow-up data is legally obliged according to Art. 15 of Directive 2010/53/EU, but also for transplant recipients, where the collection of follow-up data is not mandatory within the EU yet. The more reliable data is collected in a registry, the more accurate conclusions and appropriate strategies can be drawn and implemented on national level as well as on European level. A European database that allows Member States to easily register or upload data, while also providing access to their data via standardized reports or downloadable standardized data extracts, increases transparency and can thereby facilitate further improvement of donation and

transplantation across the Union, particularly for countries which less experience in donation and transplantation.

The EDITH project takes up on this by providing European follow-up registries for transplant recipients (EKRR=European Kidney Recipient Registry) and living donors (ELDR=European Living Donor Registry). In addition, the project also provides support to Member States to build or adapt national follow-up registries, with the possibility of international data sharing.

XVI.2. Simple technical framework

To facilitate the continuous data delivery to a pan-European transplant registry, it is recommended that data can be transferred and updated easily, with minimal resource utilisation. In view of the different situations in the European Member States regarding the existence of registries and the data collected by them, it is furthermore recommended that the European registry provides support to the participants and allows for flexibility to adapt to the needs of the data providers.

Within the Pilot Project EDITH, two registries have been developed: the ELDR and the EKRR. These two registries have been developed within two different work packages by different partners, which have chosen for different development platforms. Both technical solutions are characterised by their user-friendliness:

- ELDR provides a web-based application, approachable by common internet surfing programmes
- EKRR uses an open-source platform, that can be used both for data collection where needed and a seamlessly delivery of data to the central EDITH registry

In order to maintain and increase the usability of both registries, in the following referred to as ETRs (European Transplant Registries), it is foreseen that the two registries closely cooperate. Opportunities will be explored to combine both registries, building on the experiences and approaches of both. By the merging of the registries and the migration to one single platform, economies of scale are expected, especially with regard to staff needs of the operating unit (registry staff).

XVI.2.1 ELDR

See section III Report on the ELDR specifications (D5.2)

XVI.2.2 EKRR

See section V Description of the functional design and on technical needs, reporting requirements and IT (D6.3/.4/.5)

XVI.3. Transparent governance

See section XV EDITH Governance (D5.3/D6.6).

XVI.4. Sound financial structure

To obtain broad acceptance and to motivate countries to deliver data and to benefit from a pan-European transplant registry, a cost effective set-up is considered advisable. An efficient organisation is necessary as well as appropriate and realistic maintenance costs.

The development of the ELDR and EKRR were part of the EDITH pilot project, which have received funding by the EU. By the end of 2020, two operating registries will be delivered. Both registries as well as their underlying governance have been developed with the ultimate objective that the two registries

- will be hosted by one existing organisation to reduce the overhead costs of management
- provide for realistic and appropriate costs of maintaining, that are in relation to the number of participating countries
- uphold a non-for profit status

XVI.4.1 EKRR

Expected costs of maintaining the EKRR depend on the technical solution that is chosen. Two options are possible:

1. Scenario Better Platform
   The costs for the Better platform scenario are based on the Better license fee for the Better SAAS platform. It includes all the tools and cost for installation, maintenance and support. The total technology cost (calculations based on a three-year contract, details are subject to negotiations, and the volume of patients included in the registry): approx. 430.000 euro build up over the years, with the assumption of the following number of patients:
   - Year one (75.000 patients): 25%
   - Year two (150.000 patients): 50%
   - Year 3 and further (300.000 patients): 100%

   Risk is in this scenario reasonably low as the main component is supported by a commercial party and contract. Also, no applications need to be custom build.

2. Scenario Open Source An open source solutions does not have license costs but a budget for technical support is needed. Also, budget is reserved for setup, installation and software development in the first year. These are additional costs that are not needed in scenario 1. The total technology cost (300.000) and the technical support amounts to 390.000 EURO. A yearly budget for upgrades and further development will enable development of improvements. A server needs to be hired to run the solution on.
   - Year one: 230.000 Euro
   - Per year after: 80.000 Euro

   Risks are considerably higher because the exact costs for installation and additional tools are unknown. Support is based on the open source community model, which might be a risk depending on how active the community is.

Table 50: Comparison of technical scenarios for a three-year period

	Scenario 1 Better	**Scenario 2 Open source**
Technology		
Open EHR Platform	Better Saas Platform	Ethercis or EHRBase
Setup	Included	150.000 (one time)
Server	Included	20.000 (yearly)
Maintenance and Development	Included	30.000 (yearly)
3 Year cost	430.000	300.000
Support (yearly)		
Management	10.000 (0.1 fte)	10.000 (0.1 fte)
Data management	40.000 (0.6 fte)	40.000 (0.6 fte)
Helpdesk	20.000 (0.3 fte)	20.000 (0.3 fte)
Services	20.000	20.000
Tech support	Included	30.000 (0.5 fte)
3 year cost	270.000	360.000
TCO 3 years (in EURO)	**700.000**	**660.000**

It is recommended to start the first period with the Better platform. When the platform is not used to its full capacity the Better platform has a lower cost of ownership (till about 50% use). Risks are lower in the crucial first years of the registry and the registry can be established quickly based on the current registry.

In case the EKRR should grow fast in the first year, it is recommended that Scenario 2 is again taken into consideration. After the registry is well established the risk and the startup costs of an open source openEHR CDR can be evaluated against the commercial openEHR CDR again.

In both scenario's the registry will need staff to support users with data delivery as well as retrieving data from the registry and assuring data quality.

1. Personnel
    a. 0.6 Full Time Equivalent (FTE) for data management and functional application management,
    b. 0.3 FTE for daily support (help desk, contact with all data suppliers),
    c. 0.1 FTE for management of the registry
    d. Optionally Statistical analyses 0.25 FTE (not included)
    e. 0.5 fte technology support for installation, upgrades and maintenance only in scenario 2 (open source)
2. Services (privacy, security, legal issues) Support for such services must be assured for the office and registry management.

XVI.4.2 ELDR

For the maintenance of the ELDR the following items need to be realized:

1. Personnel
   The personnel needed will partly depend on how many countries are actively participating in the ELDR. In the final stage, when (almost) all European countries report to the ELDR and frequent scientific requests are forwarded, the following, rough, estimate for what is needed yearly can be made:
    - 0.5 Full Time Equivalent (FTE) for data management and functional application management,
    - 0.25 FTE for biostatistical analysis and data quality (optional),

- 0.5 FTE for daily technical support (application management, help desk, contact with all data suppliers),
- 0.5 FTE for administrative support.

In the start-up phase the focus will be more on the different support functions and these are in part dependent on the number of countries delivering data. The staff must from the beginning also be able to manage data reporting, which is an important feature of the ELDR. Therefore, the exact number of FTE needed will have to be evaluated (repeatedly) when the ELDR is up and running. In September 2020 the registry contains donor data, national or center based, from 11 countries. A few more countries/centers are about to start supplying their data, which is however delayed due to Sar-CoV-2 pandemic outbreak.

2. Infrastructure (hardware) and connectivity The main tools that are necessary for accessing the registry have to be in place. The office should be equipped with hardware and have proper connectivity to the Internet
3. Services (privacy, security, legal issues) An administrative support for such services must be assured for the office and registry management
4. Additional development costs for new features (standard reports and a living donor self-reporting facility) as well as improvements based on the experiences with the ELDR from participating MS
5. Work space Work space is mandatory for smoothing the work flow and providing the facilities to the employees

To translate the need for personnel and further elements needed in euros the following cost estimation can be made for the final stage, when almost all European countries participate in the ELDR (based on estimations of IDIBAPS; costs calculated in 2019):

Table 51: cost estimation ELDR

	Year 1	**Year 2**
Personnel	42.000	42.000
Infrastructure (Administrative, Hosting and communications)	23.000	23.000
Statistical analysis	12.000	12.000
Services (technical support: Registry management)	25.000	20.000
Additional development (technical evolution)	15.000	15.000
TOTAL	**117.000**	**112.000**

In the first year extra budget (€ 5000) is reserved for starting-up the ELDR (including the development of standard reports and the living donor self-supporting facility). When fewer countries participate in the ELDR some functions can be combined.

XVI.4.3 Funding option

There are several candidates for the future sponsorship of the ETRs. Not all candidates are equally suitable for sponsoring the registries. Following overview tries to point out the advantages and disadvantages of the candidates:

- Participating EU Member States
  A form of sponsoring would be a contribution of the participating MS in the ETRs. There are some pros and cons to be addressed if this option would be implemented. The advantage of

making countries pay is that together they would share and feel responsibility for the quality and use of the registry. However, it will be a challenge to find the best way to finance the registry in a fair way for all participating countries. For instance should the fee be in relation to the number of donors/recipients included (drawback: MS with large number of donors/recipients already indicated that a ETRs for them is less useful, because they have sufficient numbers themselves for statistical analysis; paying a great deal of the fee is for them not an option) or should each MS pay the same fee (drawback: countries with only a few donors/recipients indicated that they are not willing to pay the full fee for only a few cases). Nevertheless this form seems to be a useful possibility. The main supervising body of the ETRs is the Assembly (each participating country is represented by one National Competent Authority (NCA)). The Assembly should decide whether MS should pay a fee for participation in the ETRs and in what form.

- European scientific organisations
  As a foreseen partner of the ETRs General Assembly and Steering Committee, a European scientific organisation could also be sponsor for the ETRs. This way, hosting and financing could be under the same roof, which could leverage the scientific representation. Several attempts have been undertaken to get European Scientific Organisation interested in sponsoring the EDITH registries.
- Other European and national organisations
  With other European organisations is meant for instance Eurotransplant, IDIBAPS, ERA-EDTA, etc.
- The EU Commission
  The EU indicated in the beginning of the project that structural EU financing was not an option. Nevertheless, it has to be closely monitored whether new financing options in the framework of new EU projects, become available. Of course the search for other funding sources should continue without any delay simultaneously.
- Pharma industry
  This kind of sponsoring is merely dependent of the use of pharmaceutical agents. This is the case for transplant recipients who will need immunosuppressants, but not for living donors who are healthy persons and don't use specific drugs. Moreover there is a general reluctance to get involved with the pharmaceutical industry in these types of database, also due to the fact that most of the time the pharmaceutical industry wants data back from the registry, which is not always desirable or feasible. Nevertheless, the living donors are crucial for kidney transplantation in general and sponsoring of the combination of ELDR and EKRR is an alternative.
- As an alternative (additional) form of financing, a fee could be asked for the use of the data of EDITH by organisations not contributing to the EDITH registry. This option however would only become possible in the longer term when there is sufficient coverage of the registries. Another problem would be that this form of sponsoring is not structural, and depends heavily on the number of requests from outside the EU. It therefore can only be a form of additional sponsoring.

A financing model that combines different elements – e.g. a yearly funding/sponsoring/contribution (by one or more European scientific, pharmaceutical, etc. organizations) with a contribution by the participating member states – could join the positive aspects of the different options while at the same time reducing the (financial) risks. Therefore the members of the EDITH consortium are of the opinion that such a combined model should be preferred.

In any case, each MS should cover its own costs for meeting attendance. In addition, there is no fee foreseen for members of the Steering committee.

XVI.5. Conclusions

A sustainable functioning of a European registry, which is based only on voluntary data delivery, needs to fulfil several prerequisites in order to gain acceptance, participation and commitment.

Apart from above-mentioned requirements that need to be met by the registry itself, some external support is needed as well. As long as the collection of data is not mandatory, the ETRs are dependent on third parties' willingness to supply data. By encouraging the systematic collection of data on transplantation activities and outcomes on a national basis and by permitting the submission of standardised data sets to an international registry, countries would provide valuable political support. While the systematic collection of transplant data can make an important contribution to proper risk assessment as well as SAE/SAR reporting, it could also support the performance of duties with regard to documentation. For instance, the fulfilment of legal obligations as requested in EU-Directive 2010/53/EU Art. 15 on quality and safety aspects of living donation.

Besides the political, also scientific support is needed to enable the sustainable development of an international registry. The endorsement by professional organisations and national registries can act as an external amplifier with regard to new data providers. Furthermore, it also facilitates the derivation of practical recommendations regarding the treatment choices that are offered to individual patients with end-stage organ failure

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