Kidney Exchange Practices in Europe

First Handbook of the COST Action CA15210: European Network for Collaboration on Kidney Exchange Programmes (ENCKEP)

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FOREWORD

This handbook is the first deliverable of the **European Network for Collaboration on Kidney Exchange Programmes** (ENCKEP).

ENCKEP brings together policy makers, clinicians and optimisation experts in Europe to (i) exchange best practices and scientific state of the art with respect to national KEPs (ii) develop a jointly-used, common framework for data and optimisation; (iii) develop and test a prototype for transnational KEPs; and (iv) stimulate European policy dialogue.

This handbook provides information on the current practice of kidney paired exchange programmes in Europe and some countries outside Europe. It describes the incidence of active Kidney Exchange Programmes (KEPs), including details of country specific schemes and identifies the interest and aims of countries that have yet to develop a KEP.

The handbook aims to support countries and transplant centres that wish to extend their living donor kidney transplant (LDKT) programme by introducing a KEP or wish to improve an existing KEP. It provides detailed information on current programmes, criteria for success and identifies the risks and opportunities associated with KEPs.

The information was collected using a pre-structured questionnaire, concerning the starting year of the KEP (if existing) until 2016, which was sent to all European countries participating in ENCKEP, and discussed in two workshops (Tallinn, 12-13 January 2017 and Paris, 27-28 March 2017) with representatives of the participating European countries.

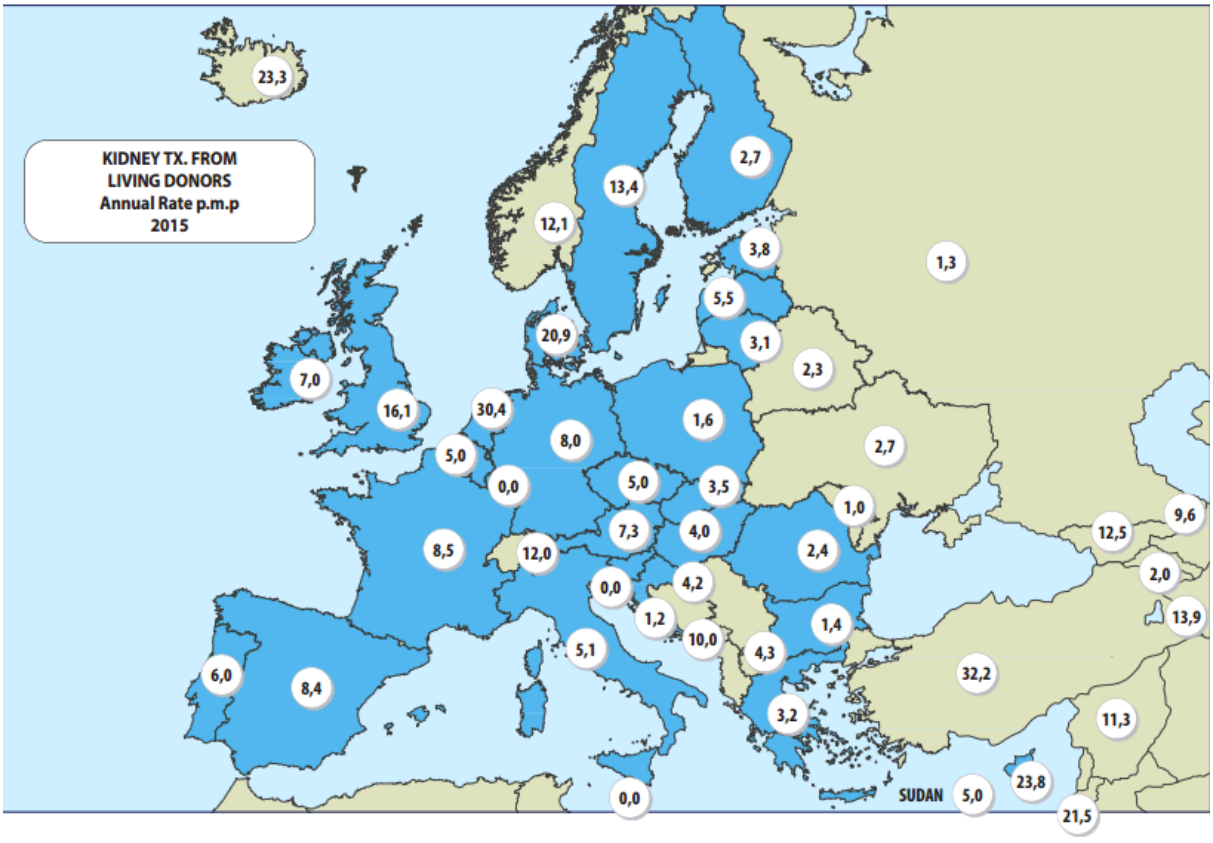
We would like to thank all country representatives for sharing their information and data and for their active participation in the workshops.

1. INTRODUCTION

1.1. LIVING KIDNEY DONATION AND KIDNEY EXCHANGE PROGRAMMES IN EUROPE

Approximately one in a thousand European citizens suffer from end stage renal disease (ESRD) [1]. For patients who are suitable for a transplant, LDKT offers the best outcomes for both patient and graft survival in comparison with deceased donor kidney transplantation (DDKT), see [2],[3], and it also contributes to the expansion of the overall donor pool. This, together with the ability to plan a transplant before dialysis, means that LDKT has become increasingly accepted as a treatment of choice for patients with ESRD. We depict the LDKT activity in Europe with two maps, first by per million population (pmp) in Figure 1 from [3] and then compared with the total number of kidney transplantations in Figure 2 based on the ENCEP questionnaire.

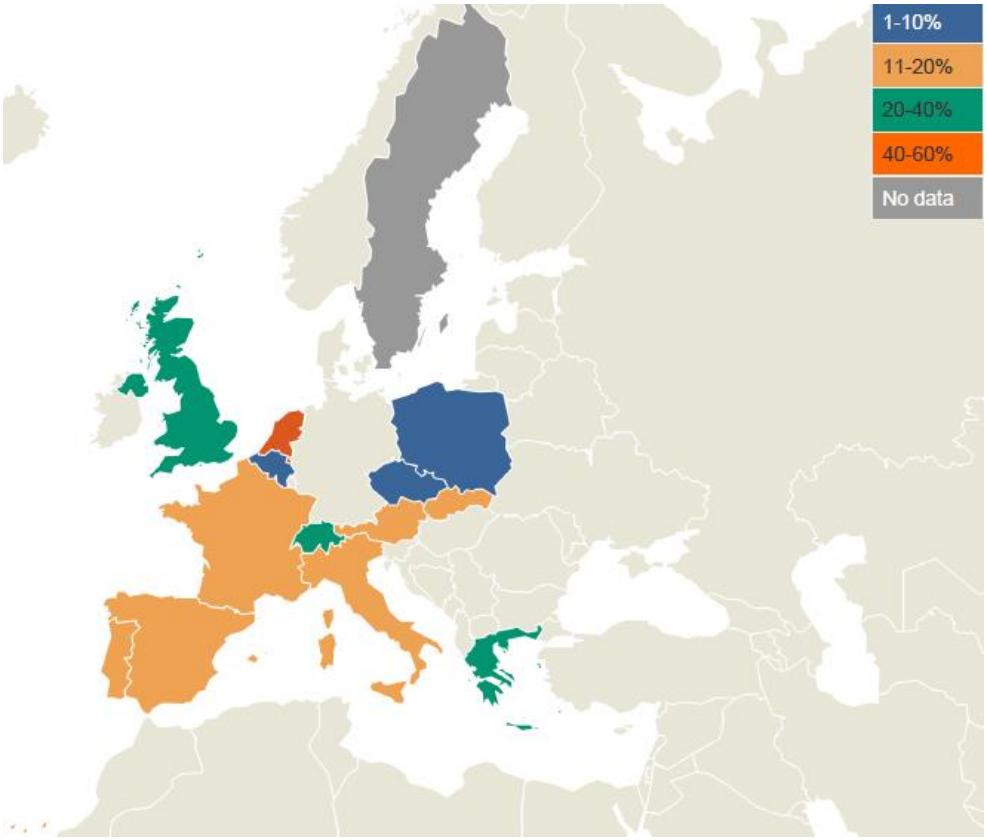
Figure 1: LDKT activity by country per million population (pmp) from [3].



In 2015 more than 41% of the almost 80,000 kidney transplants performed worldwide were from a living donor [3]. As Figure 2 reveals, this percentage is (considerably) lower for most EU countries for which we have data. In absolute terms, the annual rate of LDKT in the EU in 2015 varied from 0 to 30.4 pmp. Taken together, these data suggest that by optimising the use of living donor kidneys, overall

kidney transplantation rates could substantially increase in many European countries, yielding improved access to transplantation, better patient outcomes, and reduced dialysis costs.

Figure 2: Map on the proportion of living donor transplants compared to the total number of kidney transplantations, reflecting the living donor transplant activity of a country (data from our questionnaire)



Historically, LDKT was only an option between genetically related donor recipient pairs (blood relatives). In the mid-1990s however, evidence showed that kidneys from non-genetically related donors achieved comparable outcomes [1]. As a result, some transplant programs started to consider a wider set of donors, to the benefit for patients who lacked a compatible genetically related donor.

Compatibility is defined on the basis of blood group (ABO) and human leucocyte antigen (HLA). Certain combinations of blood types of the recipient and the donor, as well as donor human leukocytes and recipient HLAs will cause the transplanted organ to be rejected by the recipient. In such cases, the recipient donor pair is said to be incompatible. Hence, even when a patient finds a (genetically) related donor, incompatibility may still prevent LDKT. While antibody removal therapy is an option for the

individual patient nowadays, a compatible transplant is still considered preferable to an incompatible transplant as it yields better outcomes [4].

The introduction of kidney exchange programmes (KEPs) has formed a next step to increase LDKT. In addition to improving the likelihood of successful transplantation for individual patients – and especially immunologically complex patients - an effective KEP increases transplant opportunities for all patients by reducing the number of patients waiting for a deceased donor kidney.

1.2. Aim of Kidney Exchange Programmes (KEPs)

Several European countries have independently developed KEPs, to address the incompatibility issues which arise as approximately 40% of living donors are incompatible with their specified recipient. The established KEPs aimed to offer an alternative to antibody removal for immunologically complex patients (i.e., incompatibility due to Human Leucocyte Antigen (HLAi) and ABO blood group (ABOi)). To this purpose, they form a pool of recipient donor pairs, and consider the assignment of donors to recipients other than their initially specified recipient. KEPs aim to match donors to recipients in optimal combinations for kidney exchange within the pool.

While KEPs have contributed significantly to LDKT volumes, they struggle to become effective in countries where the pool sizes remain small and hence exchange options are limited. Among the possible barriers to increasing pool sizes are small population size, legal constraints, ethical concerns and fragmentation of KEP pools within a country. As a result, potential recipients are relatively disadvantaged.

1.3. Kidney Exchange Programmes in practice

As is clear from the above, recipients benefit from the practice of organising one pool of recipient-donor pairs within a country, as opposed to the common practice of separate pools for each of the transplant centres. The Netherlands was the first country to establish a national KEP in Europe, in 2004.

Subsequently more countries followed. Currently, ten European countries are operating KEPs, with four more programmes awaited.

KEPs vary in structure and approach according to country specific characteristics and/or limitations in several domains:

I. Policy (prioritisation, equity, and accessibility)

II. Clinical (clinical practice and evidence)

III. Optimisation (methods to solve the complex multi-factorial matching opportunities, taking clinical evidence and health policy into account).

In practice, this means that programmes differ in their organisation, as we have learned from our questionnaire. For instance, while some countries have scaled up to a national programme, others take a regional or single centre approach. In most countries, the organs travel from the donor to the recipient centre but in others the donor travels. Moreover, there is variation in the organisation of matching with regard to selection and inclusion of donor-recipient pairs, the frequency of the match run, and the optimisation criteria. The proportion of transplants achieved as a result of KEPs varies between 0 and more than 20 % of overall LDKT activity per country.

1.4. Challenges for Kidney Exchange Programmes

Although KEPs are acknowledged as an effective solution to addressing immunological incompatibility and, in some countries, offering opportunities to improve HLA or age matching between compatible donor-recipient pairs, there are also challenges in enhancing/extending programmes. One of these is the limited pool of donor-recipient pairs at the start of a scheme, or a decreasing pool in terms of quantity or diversity of pairs (e.g. increasing numbers of blood group O and/or highly HLA sensitised recipients). Other available options for incompatible pairs, such as antibody removal for both ABO and HLA incompatibility, may also compete with KEP despite poorer outcomes. This may also be driven by a lack of confidence in the effectiveness of a national or local KEP or by clinician and/or donor-recipient preference for 'direct' donation, which can be scheduled within a more precise timeframe. Experience in current programmes suggests that a larger pool size benefits the most immunologically complex recipients.

Emerging programmes experience different challenges and risks in comparison with established programmes, but all existing KEPs could improve and would benefit from shared knowledge and experience between individual countries. In fact, as a next step, recipients might also benefit from

merging national pools. As a starting point, the COST action ENCKEP has therefore made an inventory of current KEP practices in EU member states participating in ENCKEP.

1.5. LEGAL AND ETHICAL CONSIDERATIONS

Risks to the donor

In countries where living organ donation is governed by a legal framework, the primary purpose of the framework is to protect the donor and safeguard the interests of the individual who wishes to donate. The benefits of LDKT for the recipient are well described but there is legitimate concern about the risks of donation and impact on long-term health, both physically and psychologically, for the healthy donor. The risk-benefit analysis between the healthy donor and the patient in need of a transplant takes into account the direct benefit (or lack of it) to the donor in comparison with the potential benefit for the transplanted recipient. This includes the proximity of the relationship between donor and recipients and the likely benefit that may be derived from a close relationship between the two. Most countries have adopted a legal framework that puts limitations on the relationship between donor and recipient, placing an intrinsic value on those between blood (genetic) relatives and close emotional relationships, usually within families. KEPs facilitate a form of *indirect* donation in which the relationship between donor and recipient is reciprocal i.e., all donors donate a kidney and their recipients receive a transplant but the transaction is not *directly* between the donor and their intended recipient. KEP is only possible if the national legislation allows living organ donation between non- blood or emotionally related donor-recipient pairs, or if the legislation explicitly allows for the cross-donation through a KEP.

Risks to the recipient

As previously described, LDKT offers a recipient the best chance of a successful transplant outcome. However, there is always a risk that a donor may withdraw consent or is unable to proceed to donation for a clinical reason at a late stage or, rarely, on the day of surgery itself, leaving the recipient without the transplant they had anticipated.

In the context of KEPs, this risk is enhanced by the involvement of multiple donors and recipients in any one exchange and often mitigated by policies to minimise distress (e.g., when an exchange collapses) by conducting transplantations simultaneously and by prioritising recipients for transplantation who miss out during the course of an exchange (i.e., once donor and recipient surgery is underway). In emerging programmes, donor-recipient pairs may initially be reluctant to participate in a KEP because of emotional anxieties about the donation not being made *directly* to the intended recipient and logistical concerns (e.g., the donor travelling to another centre for surgery; impact of cold ischaemia if the kidney travels between centres; lack of confidence in the system). Established

programmes have developed policies and procedures to mitigate against these risks and minimise impact on the overall success of the schemes (see Sections 1.6 and 1.7).

No financial gain

Globally, there is ethical consensus that donations of organs by living donors are to be voluntary and unpaid. The principle of non-payment does not prevent living donors from receiving reimbursement for legitimate expenses and loss of income related to the donation. In Section 1.7 we describe national policy which aims for 'cost neutrality' to the donor.

1.6. Prerequisites for a Successful Kidney Exchange Programme

In addition to the legal and ethical principles, KEPs rely on agreed protocols, clinical standards and operating procedures for the stakeholders involved. Among these stakeholders are participating transplant centres, Histocompatibility and Immunogenetics (H&I) laboratories, and donor and recipient pairs. Central coordination and mechanisms to minimise the risk of identified transplants not proceeding due to the collapse of an exchange are essential. Hence there is much attention for evidence-based, complete and up-to-date screening of both donors and recipients regarding clinical, immunological and psycho-social status.

The behaviour of participating donors and recipients affects not only their individual interests but also those of other donor-recipient pairs in the KEP, especially if they decide not to proceed after an exchange has been identified. Whilst it is impossible to predict every eventuality (e.g., change of circumstances for the donor; unforeseen recipient illness), KEPs aim to address reasons for non-proceeding transplants that could have been foreseen. This is a challenge for all KEPs but particularly for those that involve multiple centres and laboratories, large numbers of donor-recipient pairs and emerging programmes where there is a learning curve. The impact of a high non-proceeding rate may be significant, because of distress to donors and recipients, loss of confidence in the KEP and reduced participation (see Section 1.5).

Effective KEPs increase the opportunities for patients, particularly those with immunological complexity, to receive a compatible transplant, as is nearly always the preferred option. In countries with permissive legal frameworks, supportive policies and established KEPs, the patient benefits of the KEP can be further enhanced by the inclusion of compatible pairs (e.g., for improved HLA or age match; for the greater good) and unspecified (non-directed altruistic) living kidney donors to augment the pool. Experience suggests that such a strategy maximises the benefit for all the donors and recipients involved, including recipients on the national transplant list with no living donor of their own. As well as utilising unspecified living donors to initiate a chain of transplants within the KEP, some countries

are considering using deceased donor kidneys to achieve a similar outcome, as we understood from the templates of the national representatives.

1.7. ORGANISATIONAL ASPECTS

A KEP programme requires a multidisciplinary and, in most cases, a multi-centre approach. Therefore, KEPs have defined a structure to coordinate and monitor all activities which can be national, regional or centre-based. The key components of effective KEPs that our research has identified are:

a) MEDICAL, PSYCHOLOGICAL, SOCIAL, LEGAL AND ETHICAL FRAMEWORKS FOR DONOR AND RECIPIENT CARE – to ensure consistent, high quality, safe clinical practice in line with international standards and best practice guidelines. Agreed protocols are required for:

I. Criteria for donors and recipients who wish to be included in the KEP, including clinical, immunological and psycho-social requirements
II. Donor and recipient assessment protocols and pathways, including completeness of assessment and timeframes for updating essential clinical and H&I information prior to matching runs
III. Registration procedures and information/legal permissions required
IV. Timing and organisation of matching runs, including allocation criteria and optimal use of donated kidneys
V. Arrangements for surgery, including timeframes and logistics associated with how the donor or kidney travels
VI. Special considerations within the KEP, e.g., anonymity requirements, indirect donation and reciprocity, management of non-proceeding transplants and management/listing of recipients for transplantation who may miss out within the KEP
VII. Donor and recipient follow-up arrangements

b) INFORMATION FOR PATIENTS – to ensure that the options for LDKT, individual donor and recipient risks and benefits are presented clearly and at an early stage to maximise opportunities for timely, successful transplantation/re-transplantation. This includes specific information about the KEP, highlighting key differences, risks and benefits in comparison with other options for transplantation

e.g., DDKT, AiT (antibody-incompatible transplantation), appropriate to the particular donor-recipient pair.

c) TECHNICAL STANDARDS FOR LIVING KIDNEY TRANSPLANTATION – Equitable clinical and surgical expertise to ensure consistent quality for all donor and recipient pairs.

d) CAPACITY AND CAPABILITY – Effective operation of a KEP requires a sufficient and appropriately trained multi-disciplinary workforce. In particular, clinical and scientific expertise, and central coordination are needed. Immunological testing is central to successful KEPs and is performed by accredited H&I laboratories using standardised testing and reference criteria in every laboratory for every donor and recipient pair. Central coordination from dedicated living donor coordinators (LDCs) in nephrology and transplant centres is effective in supporting donors, recipients, and family members throughout the process of donation and transplantation. The LDC role in facilitating successful KEPs is essential to managing the additional logistical and clinical complexities of the programme.

e) FINANCIAL INFRASTRUCTURE –LDKT is a cost-effective treatment for ESRD in comparison with dialysis, offering significant financial savings to the health economy. Sustainable funding through state or privately funded insurance arrangements is necessary to support national LDKT and KEPs. Clinical and personnel costs associated with the coordination and management of national programmes, together with the reimbursement of out-of-pocket expenses and loss of earnings of the living donor, are the responsibility of the respective governments in participating countries.

2. SUMMARY OF THE QUESTIONNAIRES AND OVERVIEW OF KEY POINTS

In this chapter, we summarise the results of the questionnaires and highlight the key points:

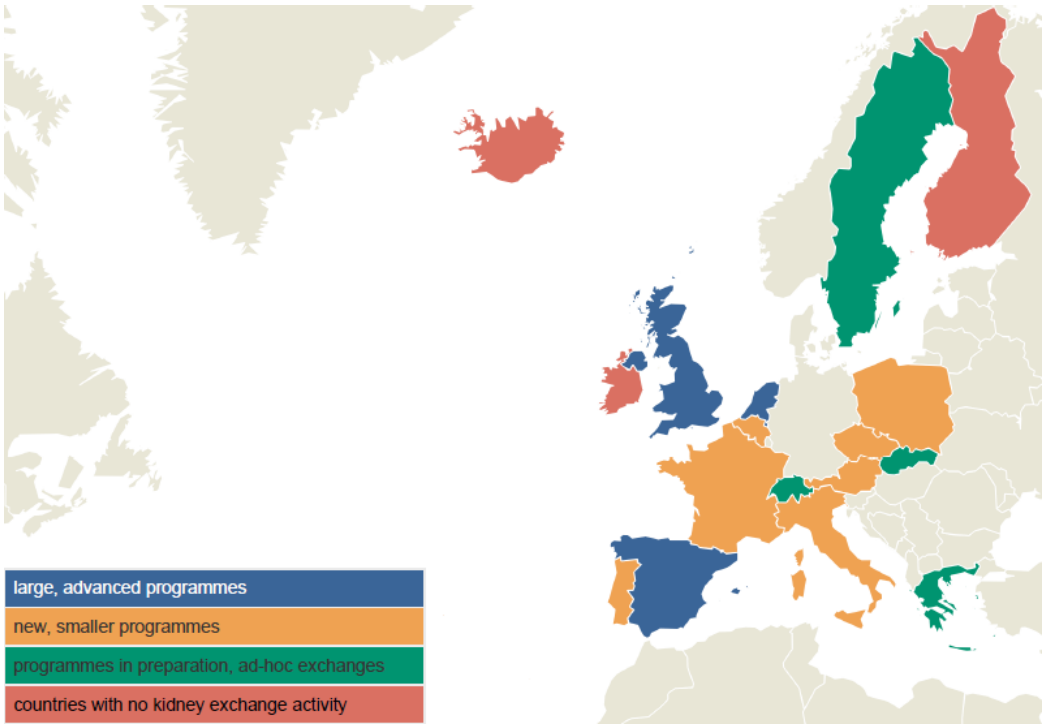
- In Section 2.1, we start with general descriptions of the KEPs in different countries, classified according to their level of development.
- In Section 2.2, we provide statistics and comparisons regarding the main properties of the KEPs.
- In Section 2.3 we summarise the key points on how to improve the effectiveness of KEPs.

Note that we only considered the countries whose representatives filled out our questionnaire.

2.1. COUNTRY DESCRIPTIONS

We classify the countries according to the level of development of their KEPs into four categories: 1. large, advanced programmes, 2. smaller operating programmes, 3. programmes in preparation, and 4. countries with no KEPs; see Figure 3. Note that in some of the countries with no KEP the patients can still get involved in kidney exchange activities in other countries, e.g., in Ireland the incompatible pairs are routinely referred to the UK programme.

Figure 3: Development of KEPs by country (based on our questionnaire)



2.1.1. LARGE, ADVANCED PROGRAMMES

Netherlands. The Dutch national programme has been in operation since 2004 and is organised by the Dutch Transplant Foundation with eight transplant centres and a single Central Reference Laboratory for histocompatibility testing. The Netherlands has the highest number of living kidney donations in Europe pmp, and they were the first country in Europe to establish a KEP. They reported a total of 284 transplants performed between 2004 and 2016 with an average of 25 transplants per year from exchanges. Further transplants are achieved through altruistic donor chains (involving one altruistic donor, one pair from the KEP pool and one patient from the deceased waiting list (9 in 2015)). This means that approximately 6% of all living donor transplants in the Netherlands currently are contributed by their KEP. In some cases, compatible pairs are also included. The donors travel and anonymity is required throughout the process, including post donation and transplantation. Donor operations are carried out simultaneously by protocol. The maximum number of pairs included in an exchange is four. The optimal solution generated by the matching run is based upon virtual cross matching. The actual cross matching in the laboratory may result in one or several iterations of matching to change the combinations of pairs when incompatibility is identified among initially matched donors and recipients. The performance of the programme has been analysed in several scientific publications [1],[7],[8],[9],[10],[11],[12],[13],[14], [15],[16],[17],[18].

United Kingdom. The UK programme includes all four countries (England, Wales, Scotland, Northern Ireland) and has been in operation since 2007. It was made possible by the Human Tissue Acts 2004 and 2006 (for Scotland) and is organised by NHS Blood and Transplant (NHSBT) involving 23 transplant centres and 20 H&I laboratories. It has become the largest operating KEP in Europe, with 250 recipient-donor pairs registered per matching run, a total of 658 transplants reported (including those initiated through altruistic donor chains) and an average of 135 transplants per year. Compatible pairs are used to improve HLA or age mismatching and non-directed altruistic donors are encouraged to opt in to the KEP. The KEP started with two-way exchanges, which involve two recipient donor pairs. In recent years, most transplants are from three-way exchanges (involve three pairs) and altruistic donor chains. A mix of two- and three-way exchanges is allowed, the organs are mostly shipped, simultaneous transplants are the default (unless there is justification for an exception under full agreement by all participants), multiple donors can register for one patient, and transplants after antibody removal (desensitisation) for low risk ABOi or HLAi are considered within the KEP. Anonymity is required prior to donation and transplantation but can be broken post donation and transplantation if donors and recipients agree. The results of the programme are documented in the following publications [19], [20], [21].

Spain. The Spanish national programme was developed in 2009 by Organización Nacional de Trasplantes (ONT) with 25 of the 39 transplant centres in the country currently participating and 18 H&I laboratories. This is the second largest KEP in Europe after the UK with 110 donor-recipient pairs

registered per matching run, a total of 147 transplants reported (including those initiated through altruistic donor chains) and an average of 35 transplants per year. Their policies are similar to the UK, with minor differences in frequency of matching runs, no limit on the lengths of altruistic donor chains and the inclusion of a re-matching policy to provide flexibility within the KEP.

2.1.2. NEW, SMALLER PROGRAMMES

Austria. The national Austrian KEP started in 2013 with four participating transplant centres coordinated by the Medical University of Vienna, where the immunological testing also takes place [22]. After conducting 11 transplants through four two-way and one three-way exchange cycles between 2013-2016, they decided to join pools with Czech Republic and the first reported transnational exchange was performed in September 2016 [23].

Belgium. The Belgian Living Donor Exchange Protocol was accepted in 2008 and the national KEP started in 2013, organised by the Kidney-pancreas Committee and the Belgian Transplantation Society. There are seven participating transplant centres and one H&I laboratory involved. Currently the coordination is also helped by Eurotransplant and the matching software was provided by the Dutch Transplant Foundation, but they are no longer actively involved. The size of the pool is still very limited and seven transplants have been reported through two two-way cycles and one three-way cycle.

Czech Republic. This national KEP was started in 2011 and is organised by a single centre, the Institute for Clinical and Experimental Medicine (IKEM) Prague. Despite the limited pool, they have performed 60 transplants [24]. The reasons for this high number of transplants are: the flexibility in performing long exchanges non-simultaneously (they have conducted 6- and 7-way exchanges), the fast laboratory testing that facilitates re-matching in response to positive crossmatch tests, the involvement of altruistic donors and compatible pairs, and the possibility of performing ABOi and HLAi transplants after desensitisation within the KEP. Since 2016 they have shared their pool with Austria and they have already performed their first transnational exchange [23].

France. The national French KEP started in 2013, organised by the Agence de la Biomédecine. 67 patients have been registered with a total of 10 transplants performed in two-way exchanges only. Altruistic donation is not legal, cycles involving more than two pairs are not yet allowed, compatible couples cannot be included and ABOi or HLAi transplants are not possible within the KEP. Indeed, the policy follows the traditional approach of enabling recipients with an incompatible donor to create a compatible exchange. Incompatible pairs are often treated outside of the programme through desensitisation (antibody removal), creating competition with the KEP. Possible improvements are expected by allowing longer exchanges within the new Bioethic Law (to be passed in 2018), and through international collaborations with Belgium and Switzerland.

Italy. The national KEP, run by the Italian National Transplant Centre (CNT), was established in 2006, but between 2005 and 2014 only single centre exchanges were performed in the Pisa and Siena centres, achieving a total of 15 transplants. Since 2015 a further 16 transplants were conducted through long, but almost simultaneous, altruistic donor chains, involving up to 11 centres (out of 40). Compatible pairs are not involved in the pool and many incompatible pairs choose desensitisation treatment, resulting in a relatively small KEP pool (around 50 registrations so far). Negotiations have started with Spain to join their programmes under the framework of the South Transplant Alliance.

Poland. The national programme started in 2015, organised by surgeons from the Department of General and Transplant Surgery, Medical University of Warsaw. Five transplants (through one two-way and one three-way exchange) had been performed in a single centre (Warsaw) by 2016 and the first inter-hospital exchange was performed in 2017 between two centres. Three centres (out of 21) are participating in the KEP. The pool size is still relatively small (around 40 donor-recipient pairs), but growing. Altruistic donation is not legal and desensitisation treatment is not yet available in the country. The low number of patients registering for the waiting list and for LDKT is likely due to the practice of offering dialysis as the default treatment for ESRD.

Portugal. The national KEP in Portugal started in 2010 by Instituto Português do Sangue e da Transplantação (IPST). Five transplant centres (out of eight) and three H&I laboratories are participating. 50 patients have been registered and a total of nine transplants reported, until the end of 2016, through three two-way exchanges and one three-way exchange. Compatible pairs cannot join the pool and altruistic donation is not yet regulated, although it is not legally forbidden. International collaboration is planned with Spain.

2.1.3. PROGRAMMES IN PREPARATION, AD-HOC EXCHANGES

Greece. The national KEP will be established in Greece by the Hellenic Transplant Organisation (EOM) in the near future, involving five kidney transplant centres. The legislation has allowed kidney exchanges since 2011, but not altruistic donations.

Slovakia. There is no national KEP yet, but there have been seven ad-hoc two-way exchanges between 2005-2015. Among those, six were performed in single centres (within three of the four transplant centres in Slovakia) and one exchange was between two centres. Desensitisation is rarely used.

Sweden (and Scandiatransplant). Sweden started its national KEP in 2016. In 2017, the initiative was taken up by Scandiatransplant, involving Denmark and Norway. A matching policy has been agreed and two-way exchanges are currently allowed [25]. However, no transplants have been performed as

yet in Sweden. All four transplant centres and their H&I laboratories are participating. Desensitisation is common for ABOi pairs, which competes with the KEP.

Switzerland. The first kidney exchange in Europe was performed in Basel in 1999 between a Swiss and German couple. Kidney exchange has been regulated by the Swiss Transplantation Law since 2007, but only ad-hoc two- and three-way exchanges have been performed so far. The national KEP is expected to start in January 2018 [26]. Desensitisation is routine in the country and will be harmonised with the KEP. Altruistic donation will also be allowed within the KEP. International collaboration is desired with European countries, like the one signed with France.

2.1.4. COUNTRIES WITH NO KIDNEY EXCHANGE ACTIVITY YET

Finland. Finland is part of Scandiatransplant but does not participate in the Scandinavian KEP and kidney exchange is not legally allowed as yet. The Helsinki centre performs all LDKT in the country.

Iceland. Iceland is part of Scandiatransplant and, potentially, they can also be involved in the joint Scandinavian KEP. Iceland has a small population and is equidistant between mainland Europe and the USA. The LDKT programme is supported by a visiting surgeon from the USA. Patients travel to Norway for DDKT.

Republic of Ireland. Recipient-donor pairs can register through a UK transplant centre for entry into the UK KEP. Six transplants have been performed through that scheme. Altruistic donation is not legal in the Republic of Ireland.

2.2. STATISTICS AND COMPARISONS

In this subsection we provide detailed information, statistics, and comparisons of the KEPs and kidney transplantation in general, extracted from the questionnaire responses.

Table 1 summarises the information obtained from the questionnaire on system and society. The active KEPs in all 10 countries are organised centrally, although the programmes have started to operate in the capitals of Czech Republic and Poland, but now they are enlarging. The KEP is organised locally in one centre in Prague, but with agreement and supervision of the national body Coordination transplantation centre (KST), where the base is. The Warsaw centre is now collaborating with other centres, and an exchange between two centres have already been conducted. We shall also remark that regarding the other eight nationwide KEPs, the coverage is not yet national in many countries with recently established programmes. We can see this in Figure 4, where the total number of centres and the number of centres participating in KEP is shown for each country. (We note that in France all of

the 34 adult transplant centres have signed an agreement for participating in KEP, but so far only 19 of them registered pairs.)

2.2.1. SYSTEM AND SOCIETY

Table 1: Summary table on system and society. The ten countries with operating KEPs at the time of writing are coloured with blue in the table.

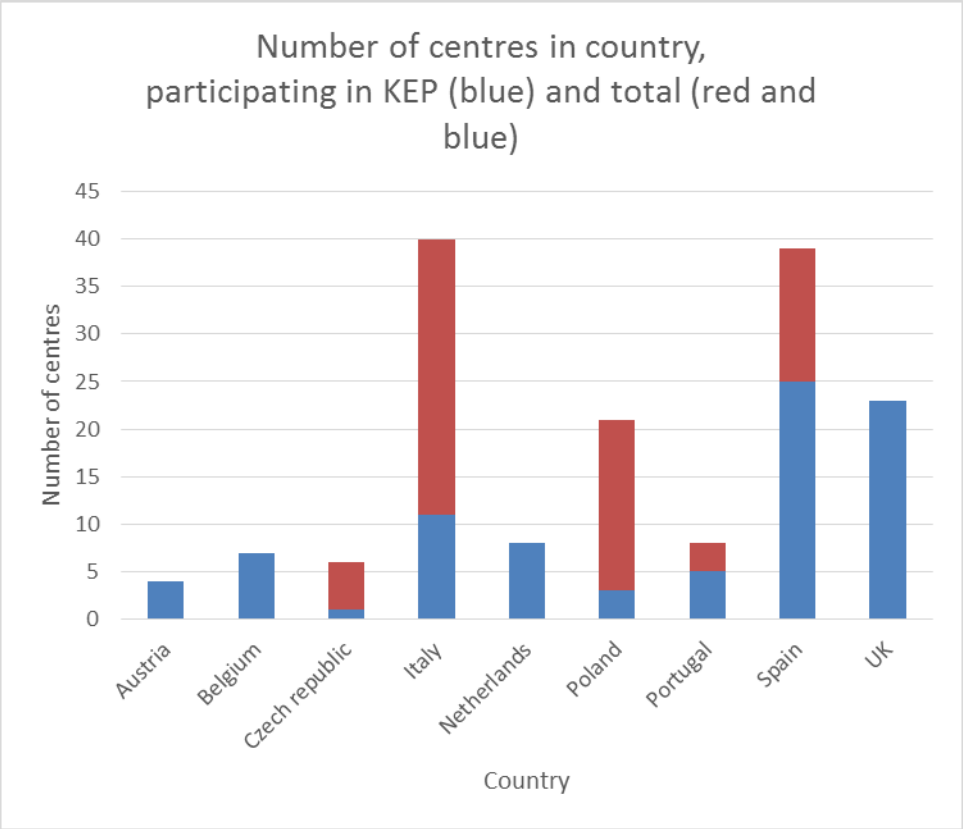
	Austria	Belgium	Czech Republic	France	Italy	Netherlands	Poland	Portugal	Spain	UK	Greece	Slovakia	Sweden	Switzerland
Public funded health system?	✓	mix	✓	mix	✓	×	✓	✓	✓	✓	✓	✓	✓	×
Incompatible transplants routine in the country?	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	×	✓	ABOi Only
National KEP system?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	×
First exchange in KEP: 20XX	13	14	11	14	07	04	15	13	09	07				
Can foreign couples be included?	✓	✓	✓	✓	✓	✓	✓	×	✓	✓				
Is anonymity a requirement for KEP? Legal (L) or by protocol (P)	P	P	L	L	L	P	×	L	L	P		L	P	P
Altruistic donor chains possible?	✓	×	✓	×	✓	✓	×	✓	✓	✓				

Regarding legal restrictions, altruistic donation is not possible in France, Poland, Greece and Switzerland. In France and Portugal, only incompatible pairs can participate in the KEP. In France, only two-way exchanges are possible.

In principle, non-resident donor-recipient pairs can be involved in the majority of the KEPs except Portugal, where only resident recipients can join the KEP, and Belgium, where the recipient must be resident in a Eurotransplant country. The international collaborations are described in detail in section 2.3.1.

Anonymity is a legal requirement in most countries and it is part of the protocol in all countries, except Poland. In some countries, it can be broken following donation and transplantation with full agreement from the donors and recipients involved.

Figure 4: the proportion and number of transplant centres participating in a KEP at national level by country (for those countries that reported)



2.2.2. DONORS AND RECIPIENTS

Table 2 summarises the information obtained from the questionnaire on donors and recipients. In most countries, there are nationally agreed criteria for becoming a living kidney donor, while criteria for who is eligible to become a recipient may vary at centre level in some countries. All the donors and recipients are fully assessed before inclusion in a KEP and in some countries special rules apply for clinically complex donors. The practice regarding formal arrangements for reimbursing the expenses and loss of earnings of living donors varies between countries, but the countries with the most advanced KEPs have cost neutral reimbursement policies.

Table 2: summary table on donors and patients/recipients

	Austria	Belgium	Czech Republic	France	Italy	Netherlands	Poland	Portugal	Spain	UK	Greece	Slovakia	Sweden	Switzerland
Nationally agreed transplant suitability criteria for recipients?	✓	×	×	×	×	×	✓	✓	✓	✓	✓	✓	×	✓
Nationally agreed living donor suitability criteria?	✓	×	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fully assess donors & recipients before entering process?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Special requirements for registering complex donors to KEP?	✓	✓	×	✓	×	✓	×	×	✓	✓		×	×	×
Formal reimburse-ment of living donors? (C=cost neutral)	×	✓	✓	✓	×	✓ C	×	✓ C	✓ C	✓ C		×	×	?

2.2.3. ORGANISATIONAL ASPECTS OF THE KEP

Table 3: summary on organisational aspects of KEPs

	Austria	Belgium	Czech Republic	France	Italy	Netherlands	Poland	Portugal	Spain	UK	Slovakia	Sweden	Switzerland
Paediatric recipients participate?	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Paediatric donors participate?	×	×	×	×	×	×	×	×	×	×	×	×	×
Compatible pairs/ couples participate?	×	×	✓	×	✓	✓	✓	×	✓	✓	✓	✓	✓
Organs usually travel (O) or donors (D)?	D	O	-	O	O	D	O	O	O	O	D	O	D
Simultaneous surgery required for an exchange in KEP? (E=with exceptions)	✓	✓	×	✓	✓	✓ E	×	✓	✓ E	✓ E	✓	✓	✓ E
Simultaneous surgery required for altruistic donor chain? (E=with exceptions)	na	na	×	na	✓ E	✓ E	na	na	×	✓ E	na	na	na

Table 3 summarises the information obtained from the questionnaire on organisational aspects of KEPs. Paediatric (<18 years old) recipients can participate in KEPs in almost every country; exceptions are Belgium and the Czech Republic. Compatible pairs can participate in KEPs in the advanced programmes. In Spain, both paediatric recipients and compatible pairs are prioritised within the KEP. Usually organs travel rather than donors, except in the Netherlands, Slovakia and Switzerland, where the donors travel according to the protocol. Simultaneous surgeries for exchanges are required

everywhere by protocol, except in the Czech Republic and Poland due to large exchanges and lack of operating theatres, respectively. Non-simultaneous exchanges can also happen in the most advanced programmes with full agreement by all parties, although the default remains simultaneous surgery. This allows flexibility in organising surgery. Regarding altruistic donor chains, simultaneous surgery is not required in the Czech Republic and in Spain, and exceptions can also be made in other countries.

2.2.4. CLINICAL ASPECTS OF THE EXCHANGE PROGRAMME

Table 4: summary table on clinical aspects of KEPs

	Austria	Belgium	Czech Republic	France	Italy	Netherlands	Poland	Portugal	Spain	UK	Slovakia	Sweden	Switzerland
National guideline for consent of donor and recipient?	×	✓	×	✓	✓	×	✓	✓	✓	×	×	✓	
Single lab carries out cross matching after virtual matching?	✓	✓	✓	×	×	✓	×	×	×	×	×	×	✓
Are matches identified based only on virtual crossmatch?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓
Matching run alterations if +ve cross match result?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		?	✓
Nationally agreed definition of HLAi?	✓	✓	×	×	✓	×		×	✓	✓	✓	✓	×
Common MFI thresholds used?	✓	✓	✓	✓	✓	×	✓	×	×	×	×	✓	×
Historical samples also considerd?	×	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓

Table 4 summarises the information obtained from the questionnaire on clinical aspects of KEPs. In most countries, there are national guidelines for donors and recipients to enter the KEP. Usually large countries have multiple laboratories to carry out crossmatch testing and smaller countries use one laboratory only. In all of the KEPs the exchanges/chains are identified after a virtual cross match and then these are confirmed in a laboratory cross match. Most countries have nationally agreed definitions of HLA incompatibility and a commonly used Mean Fluorescence Intensity MFI threshold (between 2000-3000). Almost all countries consider results from historical samples as well, but the current ones are deemed most relevant.

2.2.5. THE MATCHING PROCESS

Matching runs are conducted at regular time intervals (usually every three months) in the large programmes. In smaller programmes the runs are more ad-hoc, depending on the size of the pool.

Software is used to identify transplants in all KEPs. Table 5 contains detailed information on the matching processes.

Table 5: summary table on the matching process

	Austria	Belgium	Czech Republic	France	Italy	Netherlands	Poland	Portugal	Spain	UK	Slovakia	Sweden	Switzerland
Matching process every x months (NR=not regular)	NR	NR	3	3	NR	3	1	3	4	3	NR	na	3
Matching process uses automated algorithm matching?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	na	✓	na
Altruistic donors considered in same process?	na	na	✓	na	✓	✓	na	na	✓	✓	na	na	na
Altruistic chain – max no of transplants?	na	na	No	na	No	4	na	na	No	3	na	na	na
Longest chain already conducted	na	na	6	na	6	?	na	na	6	3	na	na	na
Max number of transplants in one exchange?	3	No	No	2	No	4	3	No	3	3	na	2	na
Longest exchange already conducted	3	3	7	2	2	4	3	3	3	3	na	na	na
Multiple donors registering for one patient?	✓	×	✓	×	✓	×	✓	✓	✓	✓	na	✓	✓
Incompatible transplants allowed within KEP?	✓	×	✓	×	×	×	×	×	✓	✓	na	✓	✓

The matching criteria used in the algorithms are enlisted in Table 6. The main optimisation criterion within the algorithms is typically the maximum number of transplants identified but multiple criteria are used in most of the programmes. Regarding the donor and potential recipient, the HLA-match is important, the blood group identical transplants can be prioritised, the donor-recipient age-difference is aimed to be small and sometimes extra priority is given when the matched pairs are from the same region. In the UK donor-donor age difference is used as a tie-breaker between possible matches. The sensitisation, blood group and the waiting time of the patient can also matter. Shorter exchange cycles are generally preferred in the solution.

2.2.6. DATA ON THE EXCHANGE PROGRAMME

The following charts show the cumulative registrations and transplantation activity in each of the programmes from 10 countries (Figure 5) in comparison with activity in each of the programmes in the most recent year (Figure 6). This demonstrates the improvements in the proportion of transplants achieved as programmes mature, particularly within the more advanced programmes.

Table 6: summary table on the criteria used in the matching algorithms

	Austria	Belgium	Czech Republic	France	Italy	Netherlands	Poland	Portugal	Spain	UK	Sweden	Switzerland
Maximum possible transplants?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Waiting time of patient? (D=dialysis)	×	D	×	×	×	D	×	D	✓	✓	×	D
Blood group compatible vs identical?	×	✓	×	✓	×	✓	×	✓	✓	×	×	✓
Recipient HLA sensitisation level?	×	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓
Length of chain/size of exchange?	✓	×	×	×		✓	✓	✓	✓	✓	×	×
Embedded exchanges?	×	×	×	×	×	×	✓	×	✓	✓	na	×
HLA match between donor and recipient?	×	✓	✓	✓	✓	×	✓	✓	×	✓	✓	×
Donor-recipient age difference	×	✓	×	✓	✓	×	✓	✓	✓	×	×	?
Distance/ geography?	×	×	na	×	✓	×	×	×	✓	×	×	×

Figure 5: KEP activity for all years until end of the most recent year for 10 countries

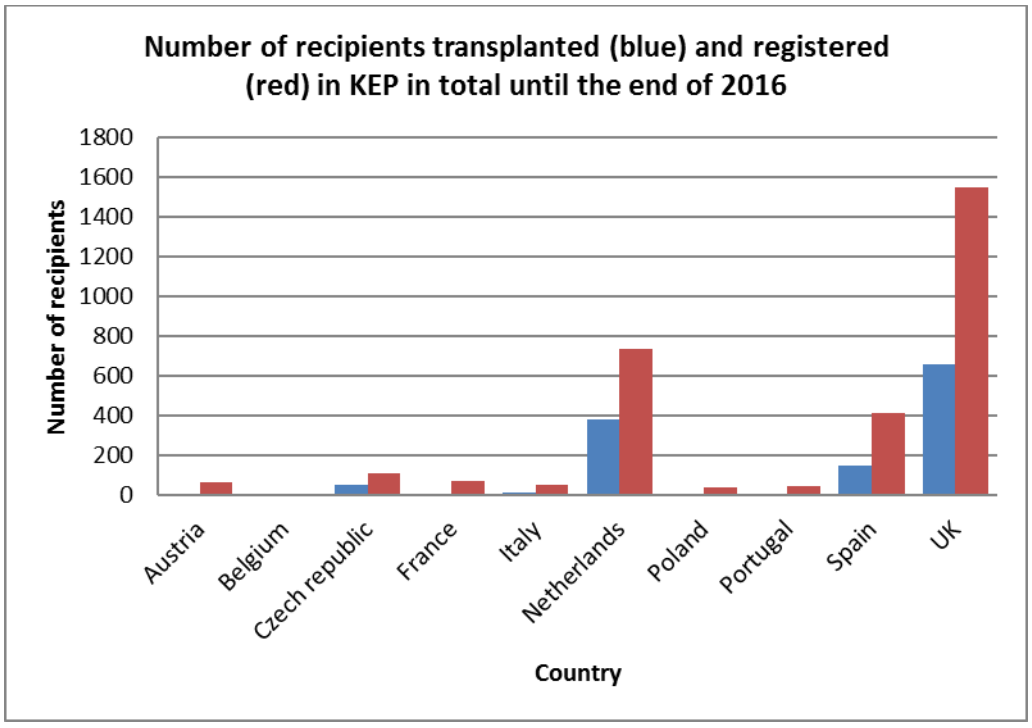
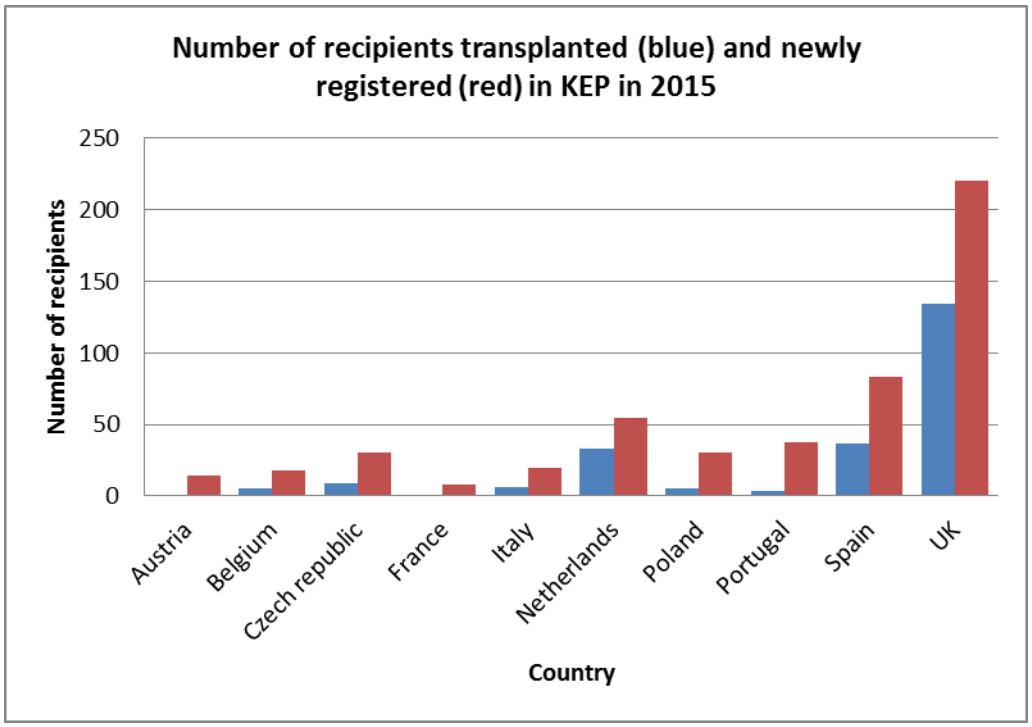


Figure 6: KEP activity: number of proceeding transplants and the number of new recipients registered in 2015 by country.



The proportion of recipients registered in the KEP with different incompatibilities (ABOi, HLAi, ABOi and HLAi) is shown in Figure 7. Influencing factors in individual countries may include active antibody removal programmes for ABOi and HLAi, maturity of the national KEP and confidence to achieve transplants for the most immunologically complex recipients.

Figure 7: Proportion of ABOi, HLAi, and both ABOi & HLAi, compatible pairs registered in KEPs

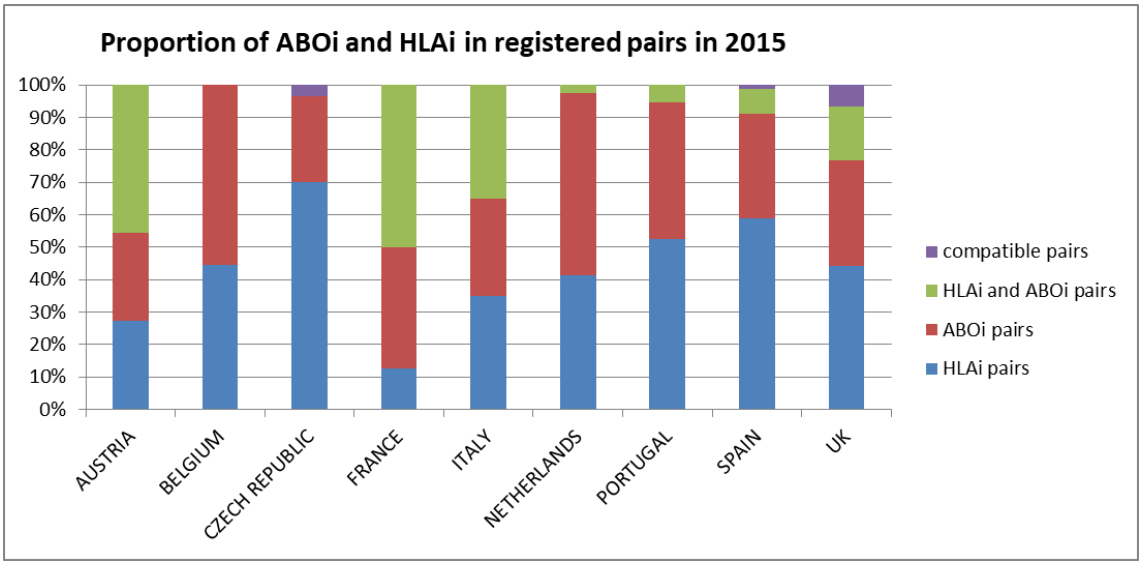


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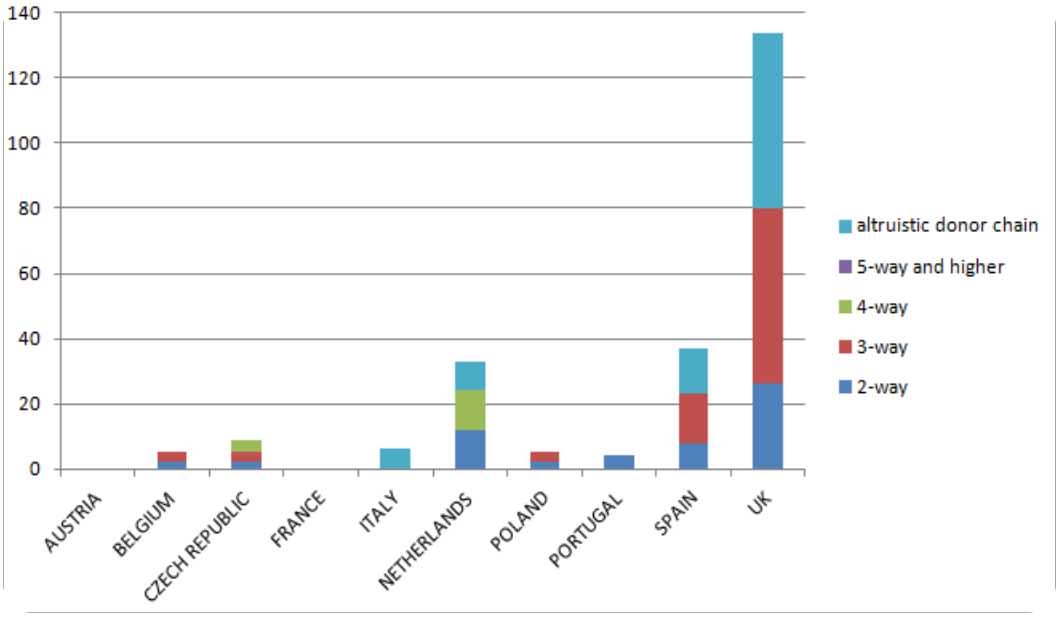
Figure 8: Proportion of exchanges: 2-way/3-way/4-way or longer exchanges/altruistic chains in 2015



2.2.7. COUNTRY SPECIFIC CHALLENGES

A key challenge reported by all countries is to maintain or increase the KEP pool size by encouraging new registrations and/or introducing initiatives to enhance the scope of the pool and maximise transplant activity. The accumulation of highly HLA sensitised recipients in the pool is an issue for many countries, making it difficult to find suitable matches for immunologically complex recipients. In addition to these, individual countries describe specific challenges:

Austria: there is no reimbursement or dedicated personnel for the organisation of the KEP.

Belgium: altruistic donors are currently not included in the KEP and collaborations with other countries have yet to materialise within or outside Eurotransplant.

Czech Republic and Poland: patients approaching ESRD and/or on dialysis are not well informed about the benefits of transplantation and, outside the capital, incompatible pairs are often not referred to the KEP.

France: the legal regulations restrict exchanges to two-way and altruistic donation is not permitted. The pool size is also limited due to preference for incompatible transplantation, which is the same in the KEPs in **Italy** and **Sweden**.

Netherlands: the altruistic donor chains are currently being incorporated into the national KEP matching runs by developing the necessary computer software but this has not been the case historically. Maintenance of the pool size is a challenge due to the combined impact of HLAi and ABOi removal programmes and small population size.

Portugal: compatible pairs and altruistic donors are not permitted in the KEP but a change in the legislation is anticipated.

Spain: only the half of the transplant teams register their patients in the KEP. Highly HLA sensitised patients are accumulated in the pool and the desensitisation and DDKT programmes compete with the KEP.

UK: the programme needs careful organisation and monitoring because it is large and increasingly complex with ongoing innovation and development. This presents local logistical challenges that impact at a national level.

Sweden-Scandiatransplant, Switzerland, Slovakia and Greece: in these four countries with KEPs under preparation, the legislative foundation, medical processes and computer software are still to be established or finalised.

2.2.8. FINAL NOTES: MISSING COUNTRIES AND KEPS OUTSIDE EUROPE

We finish this section by giving notes on some countries in the COST Action area with kidney exchange activities that we could not cover due to lack of appropriate contacts, and a short overview on KEP activities outside Europe.

Romania had a single centre KEP in Cluj-Napoca from 2001, as documented in [27] and [28]. Between 2001-2005, their medical team performed 56 transplants through 23 two-way exchanges, 2 three-way exchanges and 1 four-way exchange. The operations were simultaneous for two- and three-way exchanges and non-simultaneous but, on the same day for the four-way exchange. Anonymity was not feasible due to logistical reasons. When optimising the matches the HLA-matching was considered as a crucial factor, although no details were provided on the exact matching criteria. In Israel two KEPs are operating, but we have no information about their nature (private communication by Itai Ashlagi).

There are several countries outside Europe where KEPs are operating, e.g., South Korea, USA, Canada, Australia. For further information, we recommend two recent surveys [29] and [30] on KEPs around the world. Here, we only include a short description on the US situation, and information on one of their nationwide KEPs, United Network for Organ Sharing (UNOS), which was established in 2010. This information was provided in a questionnaire response by a representative of UNOS, who is a participating member of our Action.

In the US, UNOS, operated under the (Organ Procurement and Transplantation Network (OPTN), the National Kidney Registry (NKR) and the Alliance for Paired Donation (APD) are the three KEPs operating nationwide but, besides these many regional and single centre programmes exist within the

approximate 250 living donor transplants centres. 70 centres are actively participating with UNOS from the 160 centres registered with them. Note that around 200 centres have conducted at least one transplant in an exchange through an internal hospital programme, a regional programme, or one of the national programmes in the US.

Some of the large transplant centres perform the majority of their exchanges in-house and report only their hard-to match patient-donor pairs to the national programmes. One of the organisational implications of this fragmented system is that the national KEPs do not wait to build up their pools, which is common practice in Europe. UNOS conducts matching runs every week and NKR and APD search for exchanges immediately after each registration. Simultaneous transplantation is a requirement at UNOS (the donors have to donate with 24 hours of the other donors in the exchange; and the transplantations in chains are completed within 3 weeks in a sequential way). UNOS allows two- and three-way exchanges and four-way chains for logistical reasons. Among the 173 transplants performed between 2010-2015, 52 were through two-way exchanges 75 through three-ways and 46 through altruistic chains.

The high (90%) failure rate is the main issue in the US system. Until the end of 2015 UNOS had 1628 registered patients and they identified 2246 matches in virtual crossmatch tests. Only 173 transplants proceeded, which is partly due to the practice of centres registering only hard-to-match patients and the lack of consistency in the HLA-lab testing. Another problem is that The National Organ Transplant Act (NOTA) only allows the participation of biologically incompatible pairs in the KEPs, so blood type and crossmatch compatible pairs cannot register, unless hospitals define incompatibility in a very strict way regarding age, ABO, HLA mismatch or something else. They allow HLAi transplants through the UNOS KEP, but not ABOi transplants, which also restricts the pool size. Finally, the financial arrangements are complicated: the recipient's insurance pays for the nephrectomy and hospitalisation costs of the actual donor, which requires a financial contract with each hospital for every exchange.

2.3. KEY POINTS ON IMPROVING KEP EFFECTIVENESS

As we have seen, there are many KEPs in Europe, but apart from the largest programmes (Netherlands, Spain and UK), the others have difficulties with small pool sizes. In this section, we discuss possibilities for overcoming difficulties and for further improving the effectiveness of the programmes.

2.3.1. INCREASE POOL SIZE

The options to enlarge the pool size and create more transplant opportunities internally (within a single country) are:

- Inclusion of compatible pairs to achieve better HLA or age match.
- Inclusion of incompatible pairs in preference to antibody removal to avoid the costs and higher risks associated with desensitisation programmes.
- Inclusion of altruistic (unspecified) donors to trigger KEP chains, where the transplants can be non-simultaneous or 'never ending' chains.
- Extending the length of simultaneous exchange cycles.
- Allowing multiple potential donors to register for one patient to improve the chances of identifying exchange cycles.
- Improving the effectiveness of the selection of exchanges by the interaction between optimisation and the virtual and laboratory crossmatch tests. Flexibility with finding alternative exchanges in the context of a positive crossmatch is important in order to maximise transplants.

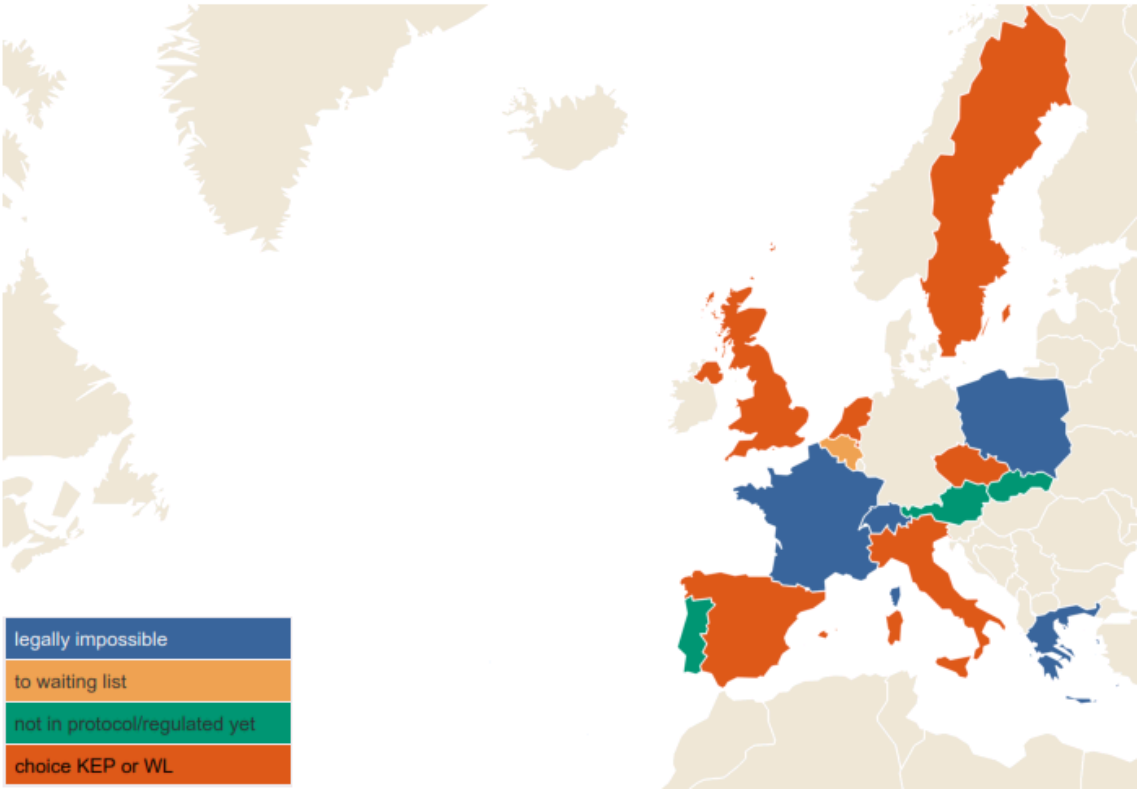
Inclusion of compatible and incompatible (ABOi and HLAi) pairs; harmonisation between desensitisation and KEP. The traditional context for the development of KEPs, namely to enable recipients with ABOi and/or HLAi donors to exchange them for compatible and/or better matched donors, the inclusion of compatible donor-recipient pairs to improve age and/or HLA-match and the role of AiT for ABOi and HLAi donor-recipient pairs, is discussed in Section 1.4. Inclusion of all combinations of these donor-recipient pairs benefits the other participants in the KEP by giving more opportunities for exchanges.

In the advanced programmes (e.g., Netherlands, Spain and UK) the options for desensitisation and the KEP are harmonised to avoid competition between the two programmes and maximise patient and transplant outcomes. The incompatible pairs are largely recommended by transplant centres to join the KEP for between 1-4 rounds (maximum 1 year) and, if they cannot get matched in the KEP their suitability for desensitisation is reviewed. In other countries, (e.g., in France, Italy and Sweden) desensitisation is the primary choice in practice, creating competition with KEP and contributing to small pool size.

Altruistic (unspecified) donations and chains. Altruistic kidney donations are not legally permitted in many European countries, including France, Poland, Switzerland, and Greece. Elsewhere, altruistic donors can only donate to the waiting lists (Belgium) or the question has not been considered yet (Austria, Portugal, and Slovakia). Some other countries have already conducted short chains starting with an altruistic donor and involving one or more pairs from the KEP pool, with a patient on the deceased donor waiting list completing the chain (Czech Republic, Italy, Netherland, Spain, UK). In these countries, the altruistic donors are encouraged to start a chain with KEP participants, but they

currently also have the choice to donate to the waiting list. In the UK, the default position for all altruistic donors will be to donate into a chain from next year. The selection of short altruistic chains is part of the same matching process to identify exchange cycles in the Czech Republic and in the UK. This maximises transplants across the two types. In the Netherlands, altruistic donors have recently been added in the KEP algorithm to increase efficiency. Due to limitations of the software, altruistic chains were previously selected after the matching run. In Italy and Spain altruistic chains can be started at any time, so it is not coordinated with the KEP run. In the joint KEP of Denmark, Norway and Sweden, coordinated by Scandiatransplant, the new policy allows the inclusion of altruistic donors to create short chains. Never ending chains have not been used so far, but the Czech Republic, Italy and Spain already have performed relatively long non-simultaneous chains and their regulations allow never ending chains.

Figure 9: Map of current state of development of altruistic (unspecified) donation (based on the questionnaire)



International collaborations. As an alternative to increasing pool size nationally, KEPs may seek international cooperation. There are a number of different models for current international collaborations and plans: some are led by an advanced KEP, other countries are joining their small pools in order to create large pools, and finally, Eurotransplant and Scandiatransplant also plan to establish international KEPs. In the UK, patient-donor pairs from Ireland are welcome to participate, and six recipients have already received transplants. Spain, with the second largest KEP in Europe, has

started co-operation with Italy and Portugal. The Netherlands helped the establishment of the Belgian KEP by sharing their software. France is in negotiation with both Switzerland and Belgium. Austria and the Czech Republic have already joined their pools and performed their first transnational exchange in September 2016. Following the Swedish initiative, Scandiatransplant has just started the coordination of a joint KEP involving Denmark, Norway, and Sweden. Eurotransplant is helping the organisation of the Belgian KEP and, theoretically, it is possible for a resident of a Eurotransplant country to join a KEP in another Eurotransplant country. Eurotransplant has plans to lead the coordination of a joint KEP for the member countries. European collaborations still require many legislative, medical, financial, and practical issues to be resolved.

2.3.2. INCREASE POSSIBLE MATCHES WITHIN THE POOL

Length of exchange cycles. Among the large programmes, Spain and the UK allow two-way and three-way exchanges only, whilst in the Netherlands the upper limit for the exchange cycle length is four. Most of the small programmes have only conducted two- and three-way exchanges so far. The upper limit is two in France and Sweden, but Austria, Belgium and Poland allow up to three-ways. There is no theoretical limit in Italy and Portugal, and the most notable exception is Czech Republic, where seven, six and five-way exchanges have been conducted non-simultaneously. When comparing the Czech practice with the advanced Spanish and UK programmes, we find that reasons for not considering longer exchanges in the latter programmes include logistical complexity, the general requirement for simultaneous transplantation (even with some flexibility to perform non-simultaneous surgery over a few days in some countries) and the high risk of cancellations of long exchanges for various reasons, with minimal or no options to find alternative solutions if positive crossmatches occur.

Frequency of match runs. The frequency of matching runs is determined by the characteristics of country specific programmes and the way in which they are organised- e.g., single centre or multi-centre, pool size, stage of development. Regarding the advanced programmes, the Netherlands and the UK have quarterly matching runs, whilst Spain has a matching run in every four months. The rationale for determining the frequency of matching runs is to allow sufficient time for the pool size to increase with newly registered recipient-donor pairs. This benefits all the participants in the pool but particularly the most immunologically complex recipients, by maximising the number of potential donors available to create a transplant opportunity in each matching cycle. The frequency must also be balanced against practicalities - extended times between matching runs will discourage recipients and donors from participating in KEPs because of the risks of delay and uncertainty about timeframes, whilst matching runs occurring too frequently is logistically challenging, particularly in advanced

programmes with large pool sizes that generate a significant number of transplants from each matching run.

Optimisation and crossmatch tests. The typical method of selecting the exchange cycles is to first identify HLA and ABO matches that are acceptable, based upon blood group matching and virtual HLA crossmatch tests (based on reported HLA antibodies). This is followed by laboratory crossmatch tests for the identified transplants. If a crossmatch test is positive then the exchange cycle has to be cancelled but it is possible that new exchanges can be identified and tested. This iterative re-matching process depends significantly on the size of the pool and the availability of the quick laboratory crossmatch tests.

In the UK the pool is large, the process is complex and laboratory testing is not centralised. The only contingency is to prioritise 3-way exchanges with embedded 2-ways in the matching process to minimise the impact and allow a possible 2-way exchange if an identified 3-way exchange cannot subsequently proceed (for any reason, not just due to positive crossmatch).

In Spain, they also test all the exchanges in the laboratory that were first identified by virtual crossmatches, and fix the cycles found to be negative in the laboratory testing. If exchanges cannot proceed, there is more flexibility for finding new exchanges. In the Netherlands, the pool is smaller and laboratory testing is very quick due to their single laboratory system, so more iterations are possible. They first test the recipient-donor pairs in the first exchange cycle of the solution and, if this is satisfactory, then they fix this and move to the second exchange cycle, and so on. If any of the exchange cycles in the ordered list is not suitable, they completely change the rest of the optimal solution and restart the testing again. The system in Prague is very similar to this, due to the single centre model and the relatively small pool. Regarding the other programmes, the small pool size often allows the complete laboratory testing of all recipient-donor pairs.

SUMMARY AND CONCLUSIONS

From the surveyed countries, we have achieved a comprehensive review of KEPs and have identified the key characteristics of the active programmes in Europe. Our findings clearly reveal the complexity of the (inter-organisational) structures and processes of KEPs. Moreover, they display a wide variety among KEPs in the participating countries, which each develop in different context and take unique approaches to addressing the challenges arising in these country specific contexts. The most advanced programmes with a longer history have already learned how to advance by continuous review and improvement, whilst the emerging/developing programmes can also learn from other countries to develop a model that is suitable for their requirements. Recognising the differences in legal frameworks, clinical practices, geography, population size, et cetera, it is clear that solutions that appear to be work best in one country may be suboptimal in another and vice versa. One size does not fit all.

The key characteristics that define KEP effectiveness are:

- A permissive legal and regulatory framework with few restrictions on donor participation and selection
- Consistent and responsive systems and processes including matching software, immunological testing, organisational framework, and coordination).
- Clinical leadership to establish confidence in the KEP as the treatment of choice for immunologically complex recipients and compatible recipient-donor pairs seeking a better age or HLA match and to ensure that recipients and donors are appropriately informed about their treatment options.
- Recipient and donor awareness to inform their decision-making and encourage participation in the KEP.
- A culture of continuous improvement to develop the KEP in response to innovations in the field, clinician and patient choice and actively manage potential risks (e.g., diminishing pool size, non-proceeding transplants, low uptake of the KEP).

The variety and dynamics highlight the potential for shared learning and collaboration across international boundaries to address some of the challenges that exist within individual country KEPs. In particular,

- Sharing knowledge and expertise to support new, emerging and developing programmes.
- Effective cross-border collaborations to improve pool size and optimisation.

- Advanced cross-border schemes to maximise options for immunologically complex recipients who remain unmatched within their own country KEPs.

In conclusion, effective KEPs ultimately benefit all patients: immunologically complex recipients, compatible recipient-donor pairs seeking a better age or HLA-match and, in countries where altruistic donor chains are permitted, those without a living donor of their own who receive a transplant at the end of a chain. It is hoped that the detailed description of current KEP practices in this handbook will inform future advances in practice, foster international cooperation, and maximise access to transplantation across Europe for all patients with ESRD, regardless of where they live.

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APPENDIX: THE QUESTIONNAIRE USED IN OUR SURVEY

Questionnaire ENC Kidney Exchange Programmes Working Group 1

Existing Kidney Exchange Programmes

Representatives from each participating country are asked to provide the following information:

Note KEP = kidney exchange programme

A INTRODUCTION

1	Country:	
2	Name and brief description of the organisation coordinating the (national) KEP:	
3	How and why did the KEP start in your country?	
4	Relevant website(s) for more information:	
5	Relevant publications from / including your country:	

B SYSTEM AND SOCIETY

1	Type of health system in your country – public / private (health insurance) / other (please explain).	
2	Are there any legal restrictions to the possibilities for kidney exchange in your country? Please describe.	

3 Is your KEP organised: a. Centrally (nationally) b. Regionally c. Multiple transplant centres together d. Single transplant centres working alone	
If not national, please describe briefly, noting any differences between programmes	
4 If not centrally organised, is there an organisation which could organise KEP nationally? Y/N (please explain)	
5 Can foreign couples be included in the programme? Please describe.	
6 Please describe any past, current or future planned collaborations internationally for kidney exchange.	
7 How many kidney transplant centres are there in your country?	
8 What is the policy on anonymity in kidney exchange in your country? Is this a legal requirement? Please describe briefly.	
9 Are incompatible transplants routinely undertaken in your country?	
No; yes – ABO only; yes – HLA only; yes - both.	
10 What are the clinical preferences for transplantation in the case of an incompatible pair? (Exchange or ABO incompatible? Exchange or HLA incompatible?) Why is that the case?	

C DONORS AND PATIENTS / RECIPIENTS

1	Are there nationally agreed criteria for suitability to be a kidney transplant recipient? (please provide link where possible)	
2	Are there nationally agreed criteria for suitability to be a living kidney donor? (please provide link where possible)	
3	Please describe briefly how patients learn about the possibilities of kidney exchange in your country. Are there any public awareness initiatives?	
4	Please describe briefly how potential altruistic donors learn about the possibilities of donating to the waiting list or through kidney exchange in your country (if relevant).	
5	Do altruistic donors have a choice about whether to donate to a chain or to the waiting list (if relevant)?	
6	Are donors and recipients fully assessed (pass all clinical tests/suitability criteria) before they can enter the matching process?	
7	Are there any special requirements for registering clinically complex donors in the exchange programme (eg complex anatomy, relevant donor history)? Please describe	

8	Are there any formal arrangements for reimbursing expenses and loss of earnings for living donors? Please describe.	

D ORGANISATIONAL ASPECTS OF THE EXCHANGE PROGRAMME

1 a. b. c. d. e.	What are the options for altruistic donors in your country? Not legally permitted Donate to waiting list only Donate to chain only Donate to chain or waiting list Other (please specify)	
2	How many transplant centres participate in the kidney exchange programme in your country?	
3	Can paediatric recipients participate (<18 years)?	
4	Can paediatric donors participate (<18 years)?	
5	Can compatible pairs / couples participate in the scheme? Is there any incentive / reward for them to participate?	
6	What is the maximum number of transplant centres that can be involved in one exchange / chain?	
7	Do donors or organs usually travel? Is this always the case? Please describe any constraints eg travel times	
8	Is simultaneous surgery required for an exchange (eg 2-way, 3-way)? Are there any exceptions to this? Please explain.	

9	Is simultaneous surgery required for an altruistic donor chain? Are there any exceptions to this? Please explain.	
10	How are pairs registered for the matching run?	
11	How are results of matching runs communicated to transplant centres? Telephone, email, post, other.	
12	What is the average time until transplants happen after the matching process?	
13	Are any reports relating to the exchange programme produced for governance bodies? Please describe briefly what information is required and provide the name of the governance body.	
14	Is there a clinical body / group with oversight over the exchange programme? Please describe the group briefly.	
15	How is the performance of the scheme assessed? How often are there reports?	

E CLINICAL ASPECTS OF THE EXCHANGE PROGRAMME

1	Is there a national guideline for donor and patient consent to enter the exchange programme? Please explain the process briefly.	

2	How often are recipients followed up post-transplant?	
3	How often are donors followed up post donation?	
4	Where is follow up provided? Transplant centre, local renal unit, GP/doctor.	
5	How many laboratories carry out the cross matching of donors and recipients after the matching process? How are results coordinated and communicated?	
6	How are cross-matches performed? a. Virtual cross match prior to run followed by laboratory cross match to confirm identified transplants b. Lab cross match carried out prior to run on all possible matches c. Other (please specify)	
7	If a positive crossmatch is identified, is it possible to change the result of the matching run to identify other matches?	
8	Is there a nationally agreed definition of HLA incompatibility?	
9	What MFI thresholds are generally used to define incompatibility?	
10	Are historical samples considered in addition to current samples?	

F THE MATCHING PROCESS

1	How often is the matching process performed? Are there regular matching runs or is it on an ad hoc basis?	
2	Is the matching done manually or through software with a matching algorithm?	
3	If software (computerised):	
a.	What is the origin of the software?	
b.	Who maintains it?	
4	Are altruistic donors considered in the matching process?	
a.	If yes,	
	i. can altruistic donors create chains at any time or only in the regular matching process?	
	ii. Is there any benefit / incentive to the centre for registering an altruistic donor?	
b.	If altruistic donors are not included in the matching process, please describe the process for altruistic donors	
5	If altruistic donor chains are permitted:	
a.	What is the maximum length that can be identified?	
	i. Is the limit logistical or legal?	
b.	Are 'never ending' chains used? Please explain/describe	
6	What is the maximum number of transplants that can be identified in	

	one exchange in the matching runs? Eg only 2-way exchanges (two pairs, two transplants)	
	i. Is the limit logistical or legal?	
7	Can a recipient be registered with more than one donor? (eg with two brothers as potential donors). If yes, what is the maximum?	
8	Are any situations considered where a deceased donor may start a chain of transplants? Please describe.	
9	Are any restrictions imposed in the matching process (other than to achieve blood group and HLA compatibility)?	
a.	If yes, what are those restrictions eg age differences, ABO match priorities	
10	Are incompatible transplants allowed through the exchange scheme?	
a.	No, yes – ABO only, yes – HLA only, yes – both. Please describe the criteria.	
b.	If yes, are these identified manually or automatically? Please describe.	
11	Please indicate which of the following criteria are used to determine the optimal set of transplants in the matching process and explain the appropriate priority / weighting of factors (provide a website link or document if available):	
a.	Number of recipients matched	
b.	Waiting time of recipient (how is this calculated?)	
c.	Recipient characteristics (blood type, sensitization)	

d.	Length of cycles/chains (e.g. preferences for short cycles)	
e.	Embedded cycles (e.g. 3 way exchanges with embedded 2-way exchange).	
f.	Age differences between donors and recipients (explain how)	
g.	Blood group compatible vs identical	
h.	Incompatibilities (ABO, HLA)	
i.	HLA match between donor and recipient	
j.	Location-based criteria (geographic distance between donor and recipient)	
k.	Any other criteria – please describe.	
Brief description of prioritisation		
12	Are the matching criteria different for altruistic donor chains? Please explain	
13	Are the matching criteria different for compatible pairs? Please explain	
14	What happens when an identified match cannot proceed?	
15	How soon after the matching run are transplant centres notified of matches (where applicable)?	
16	How soon after the matching run do the crossmatch tests happen?	

G DATA ON THE EXCHANGE PROGRAMME

Please provide the following information:	

1	Population of country in 2015/2016 (millions)	
2	Number of deceased, living and total kidney transplants in your country in 2016 (2015 if 2016 not possible).	
3	Total number of living donor ABO and HLA incompatible transplants in 2016 (2015 if 2016 not possible).	
4	Total number of patients on the active waiting list for a kidney transplant at the end of 2016 (2015 if 2016 not possible). Please include adults and children and kidney plus other organ transplants.	
5	Total number of patients on dialysis in 2016 (2015 if 2016 not possible).	
6	Total number of patients with a functioning transplant (living + deceased donor) in 2016 (2015 if 2016 not possible).	
7	Number of altruistic donors donating (by any means) in 2015 and 2016.	
8	Year of first kidney exchange transplant	
9	Year of start of formal programme (first matching run)	
10	Year of first transplant through formal programme	
11	Number of recipients included in first matching run	

12 Number of matching runs by end of 2016	

13 For the following information, please provide total over the duration of the programme to last matching run in 2016 and number in latest full year (2015 if possible):
For transplants in 2015, please count those that were identified in 2015 that resulted in a transplant (mostly transplanted in 2015 but some may be transplanted in 2016 and these should be included).

		Total (by end of 2016)	2015
a.	Number of recipients joining the KEP		
b.	Number of pairs joining the KEP (this may be higher than number of recipients if more than one donor can be registered for a recipient)		
c.	Number of pairs that are:		
	i. HLA incompatible		
	ii. ABO incompatible		
	iii. HLA and ABO incompatible		
	iv. Compatible		
d.	What % of patients registering for KEP have HLA sensitisation >=85%?		
e.	Average pairs (and patients) per matching run		
f.	Average new pairs (and patients) per matching run		
g.	Number of transplants **identified** (include altruistic donor chains including the recipient on the waiting list at the end of the chain)		
h.	Number of transplants **identified** that are:		
	i. 2-way		
	ii. 3-way		
	iii. 4-way		
	iv. 5-way and higher (include any never ending)		
	v. Altruistic donor chain (include patient on waiting list at end of chain)		
i.	Number of transplants **proceeding** through programme (include altruistic donor chains including the recipient on the waiting list at the end of the chain). See note above		
j.	Number of transplants **proceeding** that are:		

i. 2-way		
ii. 3-way		
iii. 4-way		
iv. 5-way and higher		
v. Altruistic donor chain (include patient on waiting list at end of chain)		
k. Number of transplants **proceeding** that are for recipients who are:		
i. HLA incompatible		
ii. ABO incompatible		
iii. HLA and ABO incompatible		
iv. Compatible		
l. Number of transplants **proceeding** that are for recipients who are:		
i. Adult (>=18 years)		
ii. Children (<18 years)		
m. Number of recipients leaving the scheme without a KEP transplant		
i. Number of these who received an alternative transplant		

H CHALLENGES AND OPPORTUNITIES

1 Our challenges in the domain of government/policy are (comment briefly when applicable):	
a) Legal:	
b) Financial/reimbursement:	
c) Resources/Processes:	
d) Other regulations:	

2 Our challenges regarding other stakeholders are (comment briefly when applicable):	
a) Surgeons/nephrologists:	
b) Patients (e.g. education):	
c) Public:	
3 Pool size & composition (indicate all that apply)	
a) Enrolment	
b) Highly sensitized patients	
c) Altruistic donors	
d) Inclusion of (in)compatibilities (e.g. HLA highly sensitized)	
e) Inclusion of Non-resident recipient/donors/pairs	
f) Inclusion of compatible pairs	
g) Interactions with deceased donor(s)/waiting list	
h) Other (please elaborate)	
4 Competition /existing business models for providers of other treatment modalities (dialysis, AiT, deceased donation)	
5 Coordination with other modalities (deceased donation, living donor donation,...):	
6 Coordination issues between centers and labs:	
7 Program sustainability (acceptance, funding):	
8 Any other issues	