



Alliance-O Work Package 3 - Deliverable #1

Position Paper on Best Practices for Organ Allocation in Europe

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1. Introduction

▷ Organ allocation is a complex and composite process interfacing organ retrieval and organ transplantation. Most candidates to transplantation experience a life threatening functional organ failure. Facing a crucial need of supply, organ procurement has been organized from the mid-eighties, but fails to cover the increase of demand [First92].

For example, the 4661 liver transplantations performed in France, Germany, Italy, Spain, Hungary and UK in 2004 cover to the need of the 4544 patients registered on the national waiting lists on December 31, 2003 but cover only 43% of the 10 906 candidates for liver transplantation (4544 + 6362 new patients registered in 2004). Seven hundred and sixty-eight patients died while awaiting for a graft in 2004 and 4457 patients were still registered on the waiting lists on December 31, 2004 [table 1].

Liver 2004	France	Germany	Hungary	Italy	Portugal	Spain	UK
Pop	61,26	82,2	10	56,3	10	42,72	59
<i>Waiting for a liver by 2003, 31st December</i>	460	1613	42	1544	-	631	254
Registered in 2004 (2)	1160	1427	81	1359	-	1460	875
Death on the waiting list (3)	103	288	15	137	-	163	62
Removed from waiting list	112	346	20	274		187	83
Transplanted in 2004 (4)	931	881	43	1035	205	1040	731
<i>Waiting for a liver by 2004, 31st december (5)</i>	474	1525	47	1457	-	701	253
Increment	+14	-88	+5	-87		+70	-1

Table 1 - Liver waiting lists in participating countries (source Newsletter Transplant Vol.10. N°1)

The Collins Cobuild English dictionary defines the "allocation of something" as "the decision that it should be given to a particular person or used for a particular purpose".

The allocation of an organ is indeed a decision with positive individual results, supplying a vital resource to a patient with an end-stage disease and providing a necessary resource to the transplantation procedure. In a more collective perspective, the selection of a given patient for transplantation means the exclusion of other patients, still awaiting transplantation and thus exposed to the hazards of their end-stage disease. Cadaver organ retrieval has obvious societal implications; the scarcity of organs and the discriminating aspect of organ allocation are other issues for the society. From a societal point of view, organ allocation policies indeed occupy a central place between the need and supply, requiring a transparent approach and a strong guarantee in terms of justice, equity and efficiency [Houssin97].

For organ procurement organizations, the allocation process is triggered by the identification of a donor and it comprises the distribution of all organs and tissues retrieved to a set of recipients. The process addresses all logistical issues and interactions related to the management of offers to transplant teams. Feasibility, simplicity, rapidity and robustness of allocation procedures are indeed also crucial issues. For the transplantation medical staff, two points are particularly important: the place of the medical decision within the allocation process and the importance of the so-called "local priority", linking the level of transplantation activity to the level of organ retrieval activity in the area of the transplant program.

This document aims at providing a conceptual toolbox for public health policy makers and institutions involved in organ allocation in Europe. It attempts to promote Quality Assurance for organ allocation. The first part is a "state of the art" giving a picture of the actual situation in the Alliance-O participating countries, with a descriptive summary of the allocation process in each country and a comparative analysis section. Two study cases have been selected to illustrate the variations of allocation procedures in each country: liver and kidney. The second part sets out proposals for best practices in organ allocation.

2. State of the art

2.1. Organ Allocation in France

2.1.1. Aims, General Principles and Organization

2.1.1.1. Historical and legal context

▷ During the eighties, progress in surgical procedures, immunology and immunotherapies prompt transplant professionals to create a non profit organization, France-Transplant, to maintain organ waiting lists and to coordinate organ donation and transplantation.

The Public Health law 93-43 of January 1994 created a new agency, the *Etablissement français des Greffes* (EfG) and defined organ allocation among its attributions. EfG was in charge of "patients registration on the national waiting list, management of this list and allocation of all organs, harvested in France or outdoors". More precisely, ministerial order 94-870 of October 1994 gave to EfG the charge of "the good application of the rules related to the management of the National Waiting List, the distribution and the attribution of the cadaver organs". In 2004, with the revision of the bioethical laws in France, the EfG was integrated into a new agency, *l'Agence de la Biomédecine*, with new attributions in the field of embryology and procreation.

2.1.1.2. Dealing with Societal concerns

▷ No public opinion poll has ever been performed in France. Instead, a public consultation was organized in 1996, ruled by a specific committee. The members of this committee were two lawyers, two Hospital board and public health professionals, one journalist and four medical doctors of whom one was not working in the field of transplantation. All of them had a wider scope than their initial professional culture, and were experienced in interfacing with other connected fields such as public health policy, bioethics, sociology or ethnology.

The president of the committee, a counsellor of the cassation court, was the vice-president of the *Conseil National d'Ethique*. The committee audited medical research and public health institution's officials, personalities and politicians involved in bioethics or sociology, representatives of transplanted patients and organ donation promotion associations, transplantation medical societies members and surgeons or internists involved in transplantation, physicians and nurses in charge of organ retrieval and allocation, in France or in Europe. The committee report was published in July 1996 and was used as a basis to an interactive debate between transplantation medical teams and the Medical and Scientific Advisory Group of the EfG in charge of the preparation of the new corpus of allocation rules.

2.1.1.3. Allocation Policy Definition and Improvement

▷ Allocation practices and procedures applied at the time of France-Transplant were then turned into a corpus of written rules and ratified on a temporary basis in November 1995. The final corpus of rules was ratified by a minister order the 6 November 1996, and completed with a detailed Allocation Procedures Guide inside EfG.

Minor changes to allocation procedures give birth to a new version of the Allocation Procedures Guide. Organ specific committees propose changes in allocation policies, according to the results of evaluation studies or to significant changes in end-stage diseases management. Major changes are ratified through ministerial orders. The last major update of the allocation system in France underwent in June 2004.

With the creation of the *Agence de la biomédecine*, patients associations get a wider place in the institution.

Until recently, allocation rules were mainly discussed with the professionals. The experimentation of a scoring system for kidney allocation associates now transplant teams, patients associations and hospital boards representatives.

2.1.1.4. Allocation system objectives

▷ Objectives of the allocation system are featuring with the allocation rules ratified by minister order: "In respect with justice, equity and medical ethics, the allocation system is required to improve the quality of health care. A compromise has to be done between equity, technical constraints related to organ retrieval, logistic, preservation of organs and quality of the results." The main objective of the allocation system was defined as "to take into account some specific patients conditions such as emergency or low probability to access to a graft, and to optimize graft utilization".

2.1.1.5. Allocation principles

▷ The allocation system in France is organized around a set of principles and rules. Rules shared by any solid organ are referred to as "common rules" whereas "specific rules" are established for each organ. Allocation principles respond to the common rules. Specific rules will be described for liver and kidney in the study cases section.

Common rules feature in the appendix of ministerial order of the 6th Nov 1996, (unmodified in June 2004):

- 1) Organs concerned by allocation rules are heart, lung, liver, small bowel, kidney and pancreas;
- 2) Any patient who needs transplantation is mandatory registered on the national waiting list;
- 3) The medical registration is made by the transplantation medical staff and confirmed by the EfG after examining the administrative records;
- 4) Any potential graft harvesting is reported to the *Agence de la biomedecine* with no delay;
- 5) The *Agence de la biomedecine*, through one of its six regional coordination offices or its national coordination office proceeds to the organ offer; the proposal is made for a patient or a group of patients referred to a transplantation medical staff (organ distribution);
- 6) the final decision of the graft attribution to a patient, is under the responsibility of the transplantation medical staff. The staff informs the *Agence de la biomedecine* of its local attribution procedures which can not be in contradiction with the specific and common rules stated hereby ;
- 7) Four levels of allocation are considered : local, regional, national and international ;
- 8) Retrieved organs may be proposed in priority to the following groups of patients : (i) patients who need an emergency transplantation, (ii) patients with low probability to access to a graft such as patients with AB or B blood typing or with high levels of HLA antibodies and (iii) children ;
- 9) Any graft has to be performed in priority with recipient and donor pertaining to the same blood group. When no such recipient is identified, the organ is then proposed for ABO matched recipients.
- 10) When a patient requires a national or regional priority for reasons that are not yet defined, the dossier is submitted to an expert-advisory group.

2.1.1.6. Waiting list Registration Procedure

▷ Any patient who needs transplantation is mandatory registered on the national waiting list. The medical registration is made by the transplantation medical staff and confirmed by the *Agence de la biomédecine* after examining the administrative records. A patient can't be registered for the same organ in more than one transplant team at the same time. Non-resident patients are request to attest that they are not registered in their own country on another waiting list. The medical registration is confirmed by an administrative registration. Once the procedure is complete, the patient receives a notification of his/her registration by mail. He/she gets a unique identification number in the information system.

For kidney recipient, transplant medical staff can specify minimal HLA matching (A, B, DR), identified antibodies and forbidden antigens.

2.1.1.7. Allocation Rules Application

▷ EfG and now the *Agence de la biomédecine* is in charge of the application of allocation rules through one of its six regional coordinating units or its national regulation unit.

Any potential donor identified is mandatory registered by the regional coordination in CRISTAL, the *Agence de la biomédecine* computerized database. A set of algorithms developed according to the allocation priorities defined above, is used to match each organ with potential recipients. As a result, an ordered list patients is established according to allocation priorities levels and complementary allocation criterions. It is used as guide to propose the organ to the transplantation team in charge of a selected patient. Each transplantation team has the possibility to decline the offered organ. When a retrieved organ triggers no national or regional priority, it is proposed to the local transplantation team and allocated according to its local procedures. In this case, CRISTAL can be used as a decisional advisory system.

2.1.1.8. Information System

▷ When a donor becomes available CRISTAL helps select the most eligible transplant patients via the implementation of the legal criteria in a series of programs that also take into account the ongoing regional and national priorities.

After transplantation the information that the patient has been transplanted with a specific organ of a specific donor is recorded in CRISTAL. A detailed report of concerning the peri-operative and 1 month post operative period are recorded.

There are currently about 6500 patients on the waiting list. The number of post transplant patients is around 50 000. Post transplant follow up information are entered annually. The data entry confirms that the patient is living and indicates the occurrence of important episodes over the past year (complications, treatment changes).

CRISTAL is a centralised system. A single copy of the software runs on a powerful, secure, computer based near Paris. For the time being users run a terminal emulation session on their computer and communicate over a modem-to-modem direct dial link with the central computer. CRISTAL is used to administer the national transplant waiting list, records patient details and pre and post transplantation follow up and is also used to record donor information, provides guidance concerning patient priority and emergency situations and records the proposition of organs to transplant teams (with their responses) as well as the final allocation of the organ. Each patient is identified in the table Patients and has one or more transplant dossiers containing pre and post-transplant information and a series of visit reports.

At transplantation the donors' organs are linked to the various recipients in a transplants and organs table. The donor is recorded in the donor table and the donor's dossier is recorded as a set of data in an associated table.

CRISTAL helps match recipients to donors' characteristics according to the applicable allocation rules. Given the age and blood group of the donor (and the HLA for kidney recipients) the donor matching program produces ordered lists of recipients and transplant centres that the regulators in the regional coordination offices use to pilot the organisation of the procurement process.

2.1.1.9. Allocation Process Evaluation

▷ The ministerial order specifies that "An evaluation of the consequences of this corpus of rules on recipients waiting time and transplantation results is needed as a guide to improve the procedure with technical improvements". The *Agence de la biomedecine* comprises a Medical and Scientific Department in charge of the evaluation of transplantation activities. The evaluation of the allocation process is reported in the French transplant activity annual report:

- number of transplantations performed per organ and categories of priority (paediatric patients, urgency, hypersensitised patients)
- waiting time per organ and categories of priority;
- graft and patient survival per organ and categories of priority [figure 2];

Regional coordination offices also edit regional reports for the transplant teams in their area.

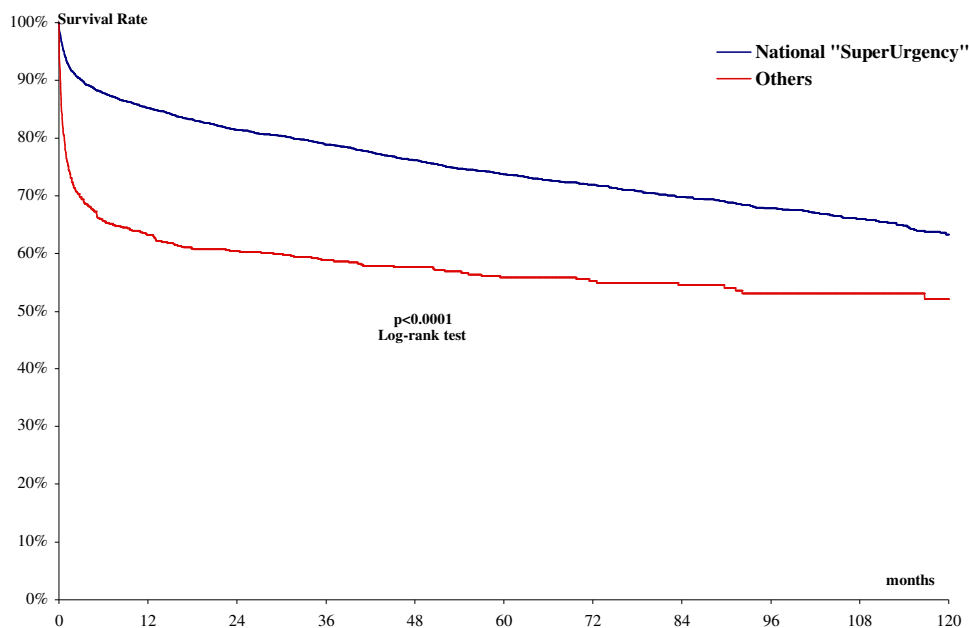


Figure 1 - Survival Rate after Liver Transplantation in France according to Allocation Priority.

2.1.1.10. Non Resident

▷ Non resident patients can be registered on the national waiting list in France. Some non specific constraints exist: (i) according to the native country, some patients outside EU require a sanitary visa to cross the border; (ii) when there is no pre-established agreement with health insurance, the transplant candidate will have to provision the cost of the scheduled health procedure.

There is a specific constraint for transplantation: non resident patients are required to produce a certificate from their home Health Ministry attesting that there is no possibility for the relevant organ transplantation in the homeland. Last, transplant teams in France have been asked to limit the registration of non resident patients “at the lowest level”.

When a patient is registered on the national waiting list, his “non residency” has no impact on organ allocation.

Last, the liver “SU” priority is shared by French and Swiss liver transplant candidates according to an agreement with Swiss-transplant.

2.1.2. Allocation systems in use: study cases

2.1.2.1. Kidney allocation

▷ Kidneys retrieved are sequentially proposed according to the following allocation priorities:

a. Priority 1- Emergency:

In case of emergency such as the impossibility of dialysis due to vascular complications, a patient may have a national priority. The registration of patients in this priority group is under the control of the kidney allocation advisory group.

b. Priority 2: Acceptable antigens program:

Any patient with panel reactive antibodies greater than 80% that is included within the "acceptable antigens" program get a national allocation priority when there is no A and B mismatch and less than 1 DR mismatch with the donor antigens completed with the defined acceptable antigens.

c. Priority 3: Hypersensitised National Priority:

Any patient with panel reactive antibodies grade greater than 80% get a national allocation priority when there is a maximum of 1 HLA mismatch with a donor.

d. Priority 4: Zero miss-match National Priority:

Any Patient with panel reactive antibodies grade greater than 5% get a national allocation priority when there is no HLA mismatch with a donor.

e. Priority 5: Immunized National Priority:

Patients with panel reactive antibodies greater than 5% that obtained a national allocation priority (with or without a dispensation to the ABO identity rule) from the kidney allocation advisory group because they were shown to have a low probability to access to transplantation.

f. Priority 5: Immunized Regional Priority:

Patients with panel reactive antibodies greater than 5% that obtained a regional allocation priority (with or without a dispensation to the ABO identity rule) from the kidney allocation advisory group because they were shown to have a low probability to access to transplantation.

g. Priority 6: Paediatric Priority

Children less than 16 years old will be proposed in priority any kidney retrieved on a donor less than 16 years old in the national level and any kidney retrieved on a donor less than 30 years old at the regional level.

h. Other priorities:

Apart from these allocations priorities, the kidneys are proposed to the local level and then to regional level according to procedures accredited by the *Agence de la biomedecine*. If not accepted for a patient in a region, the organ is proposed at the national level according to a procedure defined by the *Agence de la biomedecine* which takes into account the time spent on the national waiting list and the HLA matching with the donor.

2.1.2.2. Liver allocation

a. Priority 1: National "Super-urgency":

A national allocation priority is given to the patients with a short term life threatening conditions such as fulminant hepatitis including some acute presentation of a Wilson's disease and for patients who require an early re-transplantation during the eight days after initial transplantation. In this case, the graft may be performed with any ABO matching donor. Registration of patient in this type of priority is under the control of the expert advisory group.

b. Priority 2- Regional Urgency:

A regional allocation priority is given to the patients with biliary atresia complicated with ischemic necrosis or with some acute functional failure in metabolic disease or with liver failure after transplantation. Registration of patient in this type of priority is under the control of the expert advisory group and the graft may be performed with any ABO matching donor.

c. Priority 3- Pediatric Priority:

Children less than 16 years old will be proposed in priority any liver retrieved on a donor less than 16 years old at the national level and any liver retrieved on a donor less than 30 years old at the regional level.

Other priorities:

When no recipient is identified at the local level, the liver is proposed to each transplantation team of the region in turn. If not accepted for a patient in the region, the organ is proposed to each other region in turn.

2.1.3. Living Donor and non heart-beating donor Organ Allocation

In France, living donation is restricted by the law to family and emotionally related persons. Organs from living donors are allocated to their related recipient. In case of ABO incompatibility during living donor evaluation/screening, there is no possibility for donation.

Until recently, non-heartbeating donor retrieval was very limited in France. An experimental study is in progress. Allocation of organs from non-heartbeating donors is based on the local priority to minimize cold ischemia duration.

2.1.4. Summary and Perspectives for the current allocation system

▷ The actual French organ allocation system is a compromise between a patient-driven allocation system and a transplant centre-based allocation system. Regional and national priorities defined by the patient's condition (emergency, poor access to transplantation, children) are patient-driven procedures. When no priority is triggered, the organ is proposed to the local team and the allocation relies on the medical decision that has only to conform to general rules (blood group compatibility, patient registered on the waiting list).

Regional and national priorities ratified by ministerial order are limited to those that reached a national consensus. For example, fulminant hepatitis and early re-transplantation get a national priority whereas severe cirrhosis do not get any priority. This lack of prioritization to the sickest patient has been corrected in one region, with the elicitation of an additional regional priority. Results obtained with the MELD score in the US, not only for liver allocation but also to identify patients that have an individual benefit from liver transplantation (thus avoiding "futile" transplantation) [Merion05] must indeed be taken in consideration.

Major concerns about the French Allocation system emerge from the evaluation of the results showing regional and centre discrepancies in the access to transplantation for patients registered on the waiting list.

▷ A retrospective study showed huge regional and centre discrepancies in time spent and death rate on the liver waiting list [Figure 2, Table 2]. Variations in the balances between number of transplant candidates and number of organs proposed at regional and centre levels appeared as a determinant of the variations of regional and centre death rates adjusted on patient's severity. A prospective study has been conducted to assess if the MELD score permits to predict death on the waiting list in the French context (robustness of the MELD) and assess alternative scoring systems. Results from this prospective study will be soon available and discussed with all transplant teams. The use of a scoring system within the allocation procedure seems the most relevant solution. Simulations are under construction to compare the results various allocation models to the historic liver allocation results.

Another issue that is emerging is due to the rarefaction of young donors that might lead to base the paediatric priority onto morphological criterion rather than age and to promote split-liver.

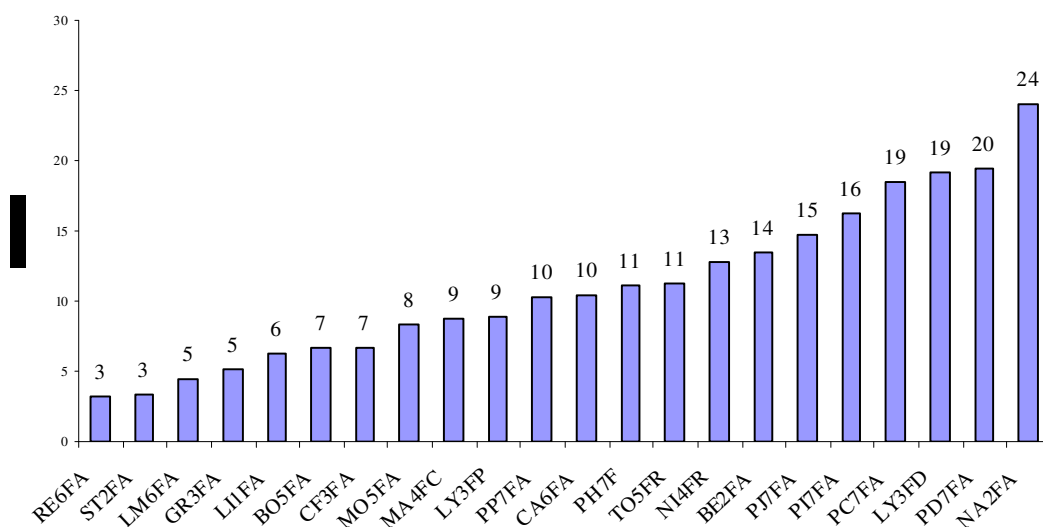


Figure 2 - Liver waiting lists death rates (1996-2000)

	Median (months)	95%-Confidence Interval
Northern Allocation Region		
Lille (A+P)	1,8	1,5- 2,1
Est		
Besançon (A+P)	4,1	3,4- 4,8
Strasbourg (A+P)	1,6	1,4- 1,7
Middle-East/La Réunion Island Allocation Region		
Region		
Clermont-Ferrand (A+P)	4,3	3,5- 5,1
Grenoble (A+P)	1,7	1,4- 2,3
Lyon Croix Rousse (A)	6,2	5,2- 6,8
Lyon Edouard Herriot (A+P)	4,3	3,6- 4,8
Western Allocation Region		
Caen (A)	1	0,9- 1,2
Limoges (A)	4,4	2,7- 7,0
Rennes (A+P)	0,9	0,7- 1,0
Paris and Antillas Allocation Region		
Clichy Beaujon (A)	5	4,4- 5,5
Creteil Henri Mondor (A)	4,3	3,8- 4,9
Le Kremlin Bicêtre (P)	4,4	3,4- 5,3
Paris Cochin (A+P)	7,2	6,2- 8,5
Paris Necker-Enfants Malades (P)	7,2	4,2- 10,6
Paris Pitié-Salpêtrière (A)	5,9	4,6- 7,4
Paris Saint-Antoine (A)	6,9	5,9- 7,4
Villejuif Paul Brousse (A+P)	4,5	4,1- 5,0
Southern Allocation Region		
Bordeaux (A)	2,6	2,2- 3,0
Marseille Conception (A)	3,4	2,8- 3,8
Marseille Timone enfants (P)	5,2	3,5- 7,2
Montpellier (A+P)	2,9	2,4- 3,7
Nice (A)	2,7	2,2- 3,4
Toulouse (A+P)	2,3	2,0- 2,7

Table 2 - Time spent on the liver waiting list for patient registered from January 1993 (A: adult, P: paediatric)

▷ Kidney allocation also meets regional variations. Three regions systematically exchange one kidney to improve donor-recipient matching; each region elicited additional regional priorities to deal with long waiting patients or with immunized patients. Priorities are different from a region to another. The magnitude of the local priority depends on the consensus the transplant teams and the *Agence de la biomédecine* can reach about the composition of local organ retrieval networks and about the amount of kidneys shared in regional and national priorities. In three allocation regions, the two kidneys are mainly allocated locally. In two regions, there is a payback to balance kidney exchanges.

The political consensus around the kind of priority to promote and the way to implement it is widely influenced by the consequences of any change in the allocation system on centres activity. For example, the introduction a national priority for young adults awaiting a kidney-pancreas transplantation encounter criticism of teams that do not perform this kind of transplantation. This example pinpoint a pitfall in organ allocation revision procedure: on one hand, the complexity of the problematic implies deep interactions with the professionals, on the other hand, their fear of variations in their transplant activities jeopardizes the scope of changes that can be expected from consensus based revision process.

In summary, the French kidney allocation system is an heterogeneous patchwork of nationwide allocation rules comprising regional and national priorities, regional allocation procedures comprising surrogate

regional priorities and local allocation practices. The allocation system applies allocation priorities sequentially: such an approach implies to sort the patients according to categories of priority that can be ordered with no overlap- and they are a few. These categories do not take into account time spent on the waiting list; they only take into account patients supposed to have a poor access to transplantation on the basis of their amount of Panel Reactive Antibodies (PRA) or their blood group.

For patients with PRA<80%, an expert system was built to assist human experts in their decision to give or not a priority to a given patient on the demand of the transplant team. This system computes for a given transplant candidate the number of donors retrieved during the past 5 years, at a local, regional or national level, with no unacceptable antigen, with the same blood group or with ABO compatibility, classified according to the number of mismatches. Using this expert system, we found that the number of regional donors retrieved during the past 5 years, with less than 3 mismatches and having blood group identical to the transplant candidate was a relevant measure of the access to transplantation. Patients with a high 5 years regional flux of iso-blood group donors with no unacceptable antigen and less than 3 HLA A, B, DR mismatches have the best chances to get a well matched donor. In contrast, patients with few donors have limited chances to get a well matched donor in their allocation region. Thus we refer this measure as to "Kidney Transplant Access Expectancy" (KTAE). The percentiles of KTAE for a given blood group can be used to systematically identify patients with the lowest access to transplantation. Because KTAE takes into account the frequency of HLA phenotypes and the frequency of blood groups into the real allocation region together with the consequences of declared unacceptable antigens, it is a more accurate measure than PRA level. Some patients with high PRA but a very frequent HLA phenotype and unacceptable antigens that are not frequent in the regional donor population can have a good access to transplantation. Conversely, patients with rare HLA phenotype and/or unacceptable antigens that are very frequent within the allocation area may have low PRA but a poor access to transplantation.

Taking lessons from the past period, a new kidney allocation scoring system is under construction in France. It aims to optimize simultaneously efficiency through donor-recipient matching on HLA and age, equity through waiting time and KTAE, logistics and cold ischemic time through proximity between transplant and retrieval centres. Such a scoring system also allows overlap and competition between categories of patients that is not possible with a sequential priority based allocation system.

The scoring system is in experimentation since April 2004 in the region of Paris. It will be progressively extended to other regions. Preliminary results show that it improves significantly the access to transplantation for long waiting patients, with a slight lower HLA matching during the first year. It also minimizes centre differences in access to transplantation, improving the equity between patients and centres at the price of slight variations in transplant activities.

Another emerging investigation topic is to find methods for the control of cold ischemia in the allocation of kidney coming from at risk donors.

2.2. Organ Allocation in Germany

2.2.1. Aims, General Principles and Organization

2.2.1.1. Historical and legal context

▷ Prof. Dr. Jon J. van Rood founded Eurotransplant International Foundation (ET) in 1967 to allow for a central registration of all patients who were waiting for a donor organ; the aim was and is to increase the chance of finding a good match between the donors and the recipients tissue groups. In doing so, the transplant results themselves would improve considerably, according to Van Rood. One of ETs most important tasks, therefore, is the registration of patients who qualify for a transplant operation. At the moment 75 transplant hospitals participating in ET have a joint waiting list of approximately 15,000 patients. Originally, ETs activities only concerned kidney transplants, but in the late seventies it also came to mediate for liver transplants. A few years later, heart, lung and pancreas transplants followed. Recently, patients qualifying for an intestine transplant operation have also joined the international waiting list.¹ Finally, the cooperation within ET has been secured by a consensus document that has been signed by the Health Ministers of the six ET members (Germany, Austria, the Benelux and Slovenia). The joint declaration regarding cooperation within the framework of ET International Foundation incorporates the following components:

- Objective allocation system according to medical criteria
- Safety and quality requirements
- Transparency and follow up
- Government involvement

Ever since Germany joined the ET community there was a co-existence of the international allocation of organs and the individual allocation performed by the transplant centres with no legally binding rules. The rapid development and improvement of transplantation medicine on the one hand and the increasing scarcity of organs on the other gave also rise to the question of allocation of this scarce good. Responding to this task it was the *Arbeitsgemeinschaft der Deutschen Transplantationszentren e.V.* that eventually passed the so called “*Transplantationskodex*” in 1987. In this codex guiding principles for organ transplantation and allocation were stipulated. It was laid down to what extend the organ harvesting hospital/centre was allowed to keep and allocate the procured organ/organs autonomously - to patients on their own waiting lists - and in what case allocation via ET was indicated. Namely in case of a full-house – HLA-matching or when there was no patient on the local waiting list with at least two HLA- matches. However there were no sanctions for violating these principles since the centres applied the codex on a voluntary basis. In the remaining cases the transplant centres were rather free to choose the patients for transplantation from their waiting list according to local policies. Thus allocation policies differed from transplant centre to transplant centre.

In 1997 when the German Transplantation Act was passed the German Transplantation System underwent some substantial changes and established legal certainty. As one of the consequences of the new transplantation act strict separation of the following activities was stipulated: Allocation of solid organs (ET International Foundation), organ procurement and coordination of the organ donation process (German Transplantation Foundation, DSO) and transplantation (transplant centres), that also maintain the waiting lists. The aim was to avoid conflicting interests and to establish transparency. This was to promote

¹ <http://www.eurotransplant.nl>.

confidence in the transplantation system that in the long run leads to a positive impact on organ donation – an indispensable prerequisite for transplantation.

ET was entrusted with the task of allocation of all solid organs procured in Germany. The tasks of the allocation agency are laid down in an agreement with the central associations of the health insurance funds, the German Medical Association and the German Hospital Foundation. This contract was authorized by the Federal Ministry of Health. One of the contract provisions is the obligation to comply with the German allocation provisions.

Step by step a patient-oriented allocation system, according to which the organ offers are made to transplant centres for a specific patient on the match list, was established. The potential recipients are ranked with the help of a point score system. The patient with the highest point score is ranked on top and receives the first offer. All following offers, firm or backup, are made in descending order. The allocation procedure is entirely objectified. The allocation agency - ET- only is provided with standard set of patient information. The parameters are the same for all patients.

Already in March 1996 a new renal algorithm - the X-COMB matching system as originally described by Wujciak and Opelz- was introduced by ET in its manual. With the entering into force of the German Transplantation Act in 1997 all kidneys procured in Germany had to be offered to ET in order to be matched to a suitable recipient using the algorithm named above. Of course the algorithm had to be modified according to changes in the national legislation on transplantation in Germany since the guidelines of the German Medical Association assessed the scoring factors slightly different and are subject to constant changes in order to meet the current medical standards. On July 26, 2000 ET finally introduced a new patient oriented allocation scheme for the liver as well (ET Liver Allocation Scheme - ELAS). This was also required by the German law. Thus also all livers procured in Germany are offered to ET in order to conduct the allocation. For the liver allocation a point score system is combined with assigned levels of medical urgency.

2.2.1.2. Dealing with Societal concerns

▷ In the legislative procedure of the German transplantation act the main focus of debate was on the brain death criterion and the pros and cons of informed consent versus presumed consent to organ donation. Apart from medical experts, legal professionals, philosophers, representatives of the major religious denominations but also patient representatives (including recipients, donor relatives and representatives of patient self-help groups) were involved in the legislative procedure. However it became also clear, that since the provisioning with post-mortem organs by far does and did not meet the increasing demand, an efficient and equitable allocation system was required. Prospect of success of transplantation and medical urgency were determined to be the guiding principles for the allocation decision. Therefore these to some extend conflicting factors have to be constantly balanced. Moreover the decision for a patient oriented allocation system that chooses the recipient from a joint (inter)national waiting list was considered fundamental to guarantee for an equal treatment of all patients.

Aware of the fact that due to the immanent lack of organs not all persons involved could be satisfied, it became apparent that the allocation of a scarce lifesaving good is not solely a medical but societal responsibility- that also has to take into account ethical and legal aspects. However with the decision in favour of a patient oriented allocation system utilizing a point score system the most difficult and challenging task remained to be solved: The weighting of the scoring factors.

Since a perfect allocation system suitable and valid for all times does not exist but rather has to advance according to current medical standards and societal development only a set of guiding principles was adopted in the German Transplantation Act. The German Medical Association was authorised to specify these principles according to current standards. This is continuously done by the “permanent commission for organ transplantation” located within the German Medical Association. It compounds approximately 20 members that represent the professions named above. Included are representatives of the DSO, the German Transplantation Society, the KfH (curatorship for home dialysis), the ministries of health, ET, the German Hospital Foundation, the insurance companies and patient-representatives. The discussion amongst these experts about weighting the scoring factors thus is a continuously ongoing one.

2.2.1.3. Allocation Policy Definition and Improvement

▷ The general rules for allocation are laid down in the German Transplantation Act. According to section 12 paragraph 3 the allocation agency is obliged to allocate solid organs to suitable patients according to the state of the art of the medical standards taking into account in particular the prospect of success and the medical urgency for transplantation. The waiting lists of the transplant centres are to be treated as a uniform national waiting list. The Transplantation Act further authorizes the German Medical Association to lay down in guidelines the rules governing the placement of a patient on the waiting list and the rules governing organ allocation as described above and below.

More over the allocation rules have to be consistent with the German constitution. Since the state holds the “monopole-position” for organ allocation and even penalizes organ trafficking. Even if the concrete allocation decision is delegated to a private institution like ET, the allocation rules applied by the allocation agency have to be consistent with German law and must not interfere with the fundamental rights laid down in the German Constitution.

2.2.1.4. Allocation system objectives

▷ According to ET an allocation system has to be objective and based on medical criteria. All post-mortem organs that become available for implantation (donor organs) in the participating countries are - taking account the respective domestic legislation - reported to ET. Using the allocation criteria arrived at on the basis of consensus; ET's task is to ensure optimum allocation of the donor organs.

The donor organs are allocated according to the following criteria:

- The most important factor is to maximise equality of opportunity for patients, and to do so by taking into account objective medical criteria (e.g. compatibility of organ with recipient, the expected transplantation result, medical urgency and how long a recipient has been waiting) as well as individual differences.
- The allocation system must be patient oriented.
- The allocation procedures must be transparent and objective.

Procedures must ensure justified, genuine distribution across the participating countries in a manner that takes account of the solidarity principle within each country. The objective is transparency of the medical criteria applied to transplantation and the moment of registration on the waiting list. The placing of patients on the waiting list and the determination of the criteria applied here are matters primarily for the doctors concerned and must take place in accordance with the most recent advances in medical science.²

² ET Manual Chapter 1; 1.2.3. p. 8

The designated kidney allocation aims in particular to reduce both the average and maximum waiting time; compensate for the disadvantages of homozygous and rare HLA-patterns and to arrive at a reasonable exchange-balance within the ET member states.

2.2.1.5. Allocation Principles

▷ The removal, allocation and transplantation of specific organs – such as heart, kidneys, liver, pancreas and intestines – is subject to specific regulations in the German Transplantation Act. For this set of solid organs general allocation principles are defined by law.

- 1) Transplantation of these organs may only be performed in transplantation centres authorised for this purpose.
- 2) Recipients have to be listed on a joint (inter)national waiting list according to the rules described in the waiting list procedure below.
- 3) Informed consent and brain death diagnosis are mandatory prerequisites for organ donation.
- 4) With the establishment of the brain death diagnosis the obligation of the donor hospital to inform the DSO about the potential donor arises.
- 5) The DSO notifies ET who perform the allocation.
- 6) All allocation decisions have to be reasoned and documented.
- 7) There exists a set of guiding principles for allocation that are the following:

As laid down in the Transplantation act the main factors to be considered for the establishment of allocation rules are the prospect of success of the transplantation and the medical urgency. Those factors have been specified by the German Medical Association in its guidelines for the allocation of solid organs. The German Medical Association defines the prospect of success of transplantation according to three factors namely the survival of the recipient, the long term graft function and the improvement of the quality of life. Medical urgency is determined by the estimated potential of harm that the patient would face without transplantation. Furthermore all patients shall be granted the equal opportunity in order to obtain a transplant. This target is supported with the implementation of a joint national waiting list. Discrimination because of domicile and registration at a certain transplant centre, social and financial status is prohibited. Since the allocation procedure is objectified this becomes already relevant with view to the regulations concerning the access to the waiting lists.

2.2.1.6. Allocation Rules Application

▷ As mediator between donor and recipient, ET plays a key role in the acquisition and distribution of donor organs for transplantations. The data of all potential recipients, such as blood group, tissue characteristics (HLA groups), cause of the disease, clinical urgency and the hospital where the patient is to be transplanted, are passed on to ET. This information is stored in a central computer database.

Subsequently, the patient is put on the (inter)national waiting list. At that point, the waiting time starts. The waiting time for kidney patients starts on the date of the first dialysis. As soon as a donor becomes available somewhere within the ET area, the regional tissue-typing laboratory determines the donor's blood group and tissue characteristics. All relevant (medical) information about the donor is then transferred on to ET's database. Subsequently, the ET staff enters the donor information into a computer program especially developed for this purpose. After the data entry, the program selects the patient most suitable to receive the organ of this donor.

All solid post mortem organs procured in Germany have to be allocated via ET. No organ can be retained by the harvesting transplantation centre for individual allocation. The concrete allocation is conducted by ET that according to an algorithm based on a point score system determines the recipient. The Allocation Rules followed by ET are laid down in the ET-Manual that is updated on a regular basis and takes into consideration the national legislation. The implantation of a solid organ that has not been allocated by ET is fined according to the penal provisions of the German Transplantation Act. Compliance with the allocation rules on ET side is monitored on a regular basis through an examination board of the German Medical Association.

2.2.1.7. Waiting List registration Procedure

▷ The waiting lists are managed by the transplant centres that are responsible for the potential recipient. All waiting lists are pooled together in a joint (inter)national waiting list for Germany respectively the ET Region. According to the German Transplantation act the transplant centre is obliged by law to place a patient indicated for organ transplantation on its waiting list unless contraindications exist. The transplant centre bases its decision upon the current state of the art of medical knowledge with particular regard to necessity and prospect of success of transplantation. Further particulars concerning the placement of a patient on the waiting list are laid down in the guidelines of the German Medical Association. There exist organ specific guidelines that are supplemented by common rules applicable to all solid organs. The guidelines are continuously revised in order to keep up with the most recent advances in medical science. The German Medical Association defines the prospect of success of transplantation according to three factors namely the survival of the recipient, the long term graft function and the improvement of the quality of life.

Before being placed on the waiting list the patient has to be informed about risks, prospect of success and all (medical, social and psychological) long term effects of organ transplantation. The individual situation of a patient is taken into account (patient-profile) and the instruction also includes information about the (centre-profile) since not every centre offers the same spectrum of medical treatment. The rules are flexible in order to give the possibility to adapt to the current medical standards. Therefore the overall physical and mental condition of the potential recipient has to be taken into account. Thus the decision whether a patient shall be placed on the waiting list remains an individual decision based on the overall evaluation (physical and psychological) of the patient including the estimation of his preparedness for compliance.

A patient must not be discriminated against because of social or financial status and background. A central body/commission that supervises the placement does not exist. Neither is it double checked by ET. If a patient is unlawfully denied access to the waiting list he can seek legal protection and in case of any damage resulting from the omission of a registration for compensation. Thus shall be ensured that the transplant centres comply with the guidelines.

The “necessity” of transplantation depends on the specific organ:

a. Kidney:

A patient is indicated for the placement on the waiting list for kidney transplantation if he suffers from an irreversible renal failure which makes dialysis indispensable for survival.

Contraindications can be for example not curatively treated malignancies, clinically manifested infectious diseases or severe additional diseases but also estimated lack of compliance.

In order to be placed in the High Urgency (HU) category the patient must successfully pass a HU audit-procedure.

b. Liver:

A patient is indicated for the placement on the waiting list for liver transplantation if he suffers from an irreversible, inexorably proceeding and life threatening liver disease and no alternative treatment is available.

Such as:

Cirrhosis; cholestatic liver diseases, genetical and metabolic indisposition, acute liver failure, malignant liver tumors and others (Neiman Pick; chronic Budd-Chiari-Syndrom).

Contraindications can be for example current alcohol abuse, expected non-compliance, extra-hepatic tumour growth.

ET has strict rules to place the potential recipient in the ET – urgency categories for liver transplantation. A remote centre cannot assign the urgency categories in ENIS but has to apply for its patients according to strict rules to be placed in a certain category. The final decision is on the ET audit committee as described in detail in the ET-Manual.

2.2.1.8. Information System

▷ In 1995 ENIS (ET Network Information System) was installed as the new registration system.

The transplant centres have to register their patients in ENIS. There is a specifically defined registration procedure. The necessary data for registration are laid down in the ET – Manual which is supplemented by the ENIS-Manual. Only after this registration a patient can be considered in the allocation process. The term (inter)national waiting list is therefore misleading. It is rather a registration system. The factor waiting time is considered by assigning a certain amount of points.

A transplant centre must register the organ transplantation as soon as possible but no later than 72 hours after the transplantation. The registration of this transplantation will remove the patient from the ET waiting list and assign him the Follow-up code. The transplant centre is required to enter immediate and long term follow up data into ENIS. Further there is a close cooperation with international scientific registries (CTS, ELTR, ISHLT and IPTR) to which follow up data is also supplied. In several agreements with ET and these registries it was decided upon a mutual exchange of this data in order to avoid time consuming duplications since most of the transplant centres supply general recipient data directly to the scientific registries.

When a donor becomes available the DSO Coordinator submits all data necessary for the allocation procedure to ET by utilizing their donor information form provided by ET. According to this donor profile a list of potential candidates who have profiles compatible with this organ is produced. Thus a suitable recipient for the organ offered is determined.

All donor data are additionally collected in the DSO database called ISYS that will be optimized by the end of 2005. It is intended to link organ donation data to the recipient follow up data. The technical requirements will be finalized in the nearest future.

2.2.1.9. Allocation Practices Evaluation

▷ The allocation practices are evaluated by ET in close cooperation with the scientific registries named above.

2.2.1.10. Allocation to non residents

▷ The German Transplantation Act does not contain any provision about the access of Non-Residents to the (inter)national waiting list. Neither do the Guidelines of the German Medical Association dealing with the access to the waiting list and allocation of organs. Hence the question of access of “non residents” to the

waiting lists and thus allocation to these patients remains unsolved. It is handled rather individually by the TX-Centres. No clear definition of who is a “non resident” in terms of transplantation is available on a national level.

The ET-Manual contains the following provisions:

▷ Non-resident patients

A non-resident patient is a patient who has his permanent address outside and is treated outside the ET region.

Before registering a non-resident patient, a transplant center has to make sure that organizational and financial matters are settled and that the necessary follow-up is guaranteed.

▷ 5% rule - Liver and thoracic organs

The number of non-resident registrations for patients (either first or repeat) for a thoracic or liver (re)transplant should not exceed 5% of the total number of post-mortem transplantations (either first or repeat) by this center in the preceding year

▷ Kidney and Pancreas

Non-resident patients are not allowed to be registered for a post-mortem transplantation on the ET kidney and pancreas waiting list, respectively.

2.2.2. Allocation system in use: study cases

2.2.2.1. Kidney Allocation

a. General procedure

▷ Kidneys are allocated according to ETKAS (ET Kidney Allocation System). ETKAS has established five urgency codes in order to classify transplant candidates on the waiting list and to prioritize patients in the kidney match and allocation procedure. The urgency codes combine the aspects of transplantability, medical urgency and the most recent level of allo-sensitization in ENIS.

HU	High Urgency	Medical urgency if the following criteria are fulfilled: - severe (uremic) polyneuropathy, - inability to cope with dialysis with a high risk for suicide; - severe bladder problems (hematuria, cystitis etc.) due to kidney graft failure after simultaneous kidney + pancreas transplantation, provided that the pancreas graft is bladder-drained and functioning adequately.
T	Transplantable	% PRA <6
I	Immunized	% PRA ≥6 and <85
HI	Highly Immunized	% PRA ≥85
NT	Not Transplantable	

The following blood group rules have to be considered:

1) AM Program

Donor blood group	Eligible recipients
A	A and AB
B	B and AB
AB	AB
O	A, B, AB and O

2) T, I, HI and HU – 000 HLA mismatch

Donor blood group	Eligible recipients
A	A and AB
B	B and AB
AB	AB
O	B and O

3) T, I, HI and HU → 1HLA mismatch

Donor blood group	Eligible recipients
A	A and AB
B	B and AB
AB	AB
O	O

The Allocation follows the following schema:

First:

Absolute priority is assigned to patients on the so called Acceptable Mismatch (AM) – Program. This program aims at allocating organs to patients who are immunologically compromised because of current and/or historical HLA-sensitization. The program identifies HLA-A, -B, -DR mismatches not resulting in a positive cross match by checking against which HLA-A, -B, -DR antigens the recipient has not yet reacted with allo-antibodies.

Patients selected by this program have priority over all ETKAS-selected recipients.

Inclusion criteria are:

Patients with a history of %PRA levels of $\geq 85\%$ in two consecutive 3-monthly screenings, after exclusion of auto-reactive antibodies, are eligible. Patients don't necessarily need to be highly immunised (HI) at the time of matching. Patients can only be accepted into the AM program by the ET Reference Laboratory (ETRL). Updates of the acceptable HLA-antigens can only be carried out by the ETRL. (Un)acceptable HLA-antigens (incl. repeated HLA-mismatches) are identified and entered in ENIS.

Minimum requirements for organ offers:

The AM program is run for every post-mortem kidney donor with a known HLA typing to select potentially cross-match negative AM recipients.

Minimum requirements:

- * Sharing of 1 HLA-B and 1 HLA-DR antigen;
- * No unacceptable donor antigens and repeated mismatches;

If any of the three requirements is not met, then the patient is not eligible for an organ offer. All eligible AM-patients are presented to and discussed with an ETRL immunologist prior to a kidney offer.

then,

to zero (000) HLA-A, -B and -DR mismatch patients (pediatric & adult) ranked according to their point score.

then,

HI, I, T and HU patients (pediatric & adult) ranked according to their point score.

The scoring factors are:

1) HLA-mismatches

The number of mismatches on the loci HLA-A, HLA-B and HLA-DR is added according to the following formula: $= 400 \times [1 - (\Sigma \text{ broad HLA-A, -B, -DR mismatches} / 6)]$

Number of HLA-A, -B, -DR mismatches	Number of points
0	400.00
1	333.33
2	266.67
3	200.00
4	133.33
5	66.67
6	0.00

Note: For paediatric transplant candidates (<16 years old at the time of registration), the points for HLA-antigen mismatch are doubled.

2) Mismatch probability

▷ Mismatch Probability is a calculation of the probability (according to a formula laid down in the ET manual) of receiving a kidney offer with 0 and 1 *broad* HLA-A, -B or -DR mismatch based on 1000 kidneys offered, taking into account ABO blood group rules and PRA screening.

3) Waiting time

▷ German Patients receive 0.137 points per day or 50 per year. There is no limit thus waiting time points can be accrued unrestrictedly.

4) Paediatric bonus

< 6 yrs	Additional 100 points
≥ 6 and < 11 yrs	Additional 33.3 points
≥ 11 and < 16 yrs	Additional 66.6 points

Note: For Kidneys there is no priority of paediatric transplant candidates for paediatric donor organs. However amendments are planned for the near future.

5) Regional factors in order to limit CIP (cold ischemic period)

▷ It is aimed to reduce CIP and transport time to a minimum. In order to include this factor in the allocation process recipients from Germany receive a bonus of 100 points when the donor is from Germany and additional 100 points if the donor is from the same DSO-region where the recipient is registered.

6) National Net Kidney Exchange Balance

▷ Once every working day, for the period of the immediate previous 365 days, the difference between the number of kidneys procured in and exchanged for transplantation in and between each ET country is calculated.

* *Export*, i.e. a negative balance, is defined as:

kidneys procured in a country > kidneys transplanted in that country.

* *Import*, i.e. a positive balance, is defined as:

kidneys procured in a country < kidneys transplanted in that country.

No compensation exists for exchanging kidneys together with non-renal organ(s) from one donor for transplantation into one patient.

The point assignment depends on the range of national balance values and is only assigned to resident transplant candidates.

[National Balance Points = (highest import balance – recipient country balance) x 10]

7) High Urgency

▷ Transplant candidates with urgency code HU receive a bonus of 500 points.

b. Exceptional procedures

Further there exist modified allocation rules for the following programs or peculiarities

ET Senior Program /Germany

The Eurotransplant Senior Program (ESP) allocates kidneys from post mortem donors ≥ 65 years old without the use of a donor HLA typing.

In order to participate in this Program the recipient has to fulfil the following criteria:

- ≥ 65 years
- (non)immunized
- awaiting a first or re-transplant

In order to keep the cold ischemic period (CIP) as short as possible the allocation follows specific national allocation rules. Hence kidneys from ESP donors are preferably allocated to patients to ESP –recipients from the donor region.

Donors < 5 years and en-bloc procurement.

Transplant coordinators (TC) are advised to contact ET as soon as possible if they have a donor younger than 5 years. The donor procedure should be discussed together with the ET medical office.

Donors < 2 years

From donors under the age of 2 years the kidneys must be procured en-bloc.

Donors between 2 and 5 years

From donors between 2 and 5 years of age it is recommended to procure the kidneys en-bloc.

2.2.2.2. Liver Allocation

▷ Livers in the ET community are allocated according to ELAS (ET Liver Allocation System). This System combines urgency-levels and a point score system.

a. Priority levels

HU	High Urgency	Acute liver failure (ALF) defined by King's College or Clichy criteria; <ul style="list-style-type: none"> - Acute graft failure (<15 days post-transplant); - Rapidly progressive Morbus Wilson; - Rapidly progressive Budd-Chiari Syndrome; - Life-threatening liver trauma; - Anhepatic state secondary to ALF with toxic liver syndrome.
CO	Approved combined Organ	Patients in need of a multi-organ liver transplant -except liver+kidney- can be assigned urgency CO
T2	Chronic disease, acute deterioration	T2 criteria <ul style="list-style-type: none"> - end-stage liver disease not eligible for HU, but in urgent need of a liver transplant; - chronic liver disease who meets the criteria of T3 and whose clinical condition acutely deteriorates. <p>The patient:</p> <ul style="list-style-type: none"> - has a life expectancy <29 days without transplantation, and - has a Child-Turcotte-Pugh (CTP) score of ≥ 11, and - ≥ 1 of the following complications: <ul style="list-style-type: none"> a) unresponsive variceal bleeding - endoscopically confirmed, needing 2 packed cells per day, recurring after sclerosing / banding therapy; b) hepato-renal syndrome - serum creatinin >1.5 mg/dl, and - urine volume <500 ml/day, <i>or</i> - urine sodium (Na+) <10 IU/ml, <i>or</i> - urine osmolality $>$ plasma osmolality, U/P ratio > 1.0; c) refractory ascites/hepato-hydrothorax - unresponsive to drug treatment, requiring large volume parenteces >1 every two weeks; d) encephalopathy grade III/IV unresponsive to medical therapy; e) repeated spontaneous bacterial peritonitis - positive culture of ascitic fluid, <i>or</i> - positive gram stain of ascitic fluid, <i>or</i> - white blood count (WBC) of ascitic fluid >300 PMN cells/ml, or a total of 500 white blood cells/ml. <p>A patient is not eligible under the following conditions:</p> <ul style="list-style-type: none"> - extrahepatic sepsis unresponsive to antimicrobial therapy; - high dose or > 2 vasopressors to maintain adequate blood pressure. <p>T2 and late re-transplantation (>14 days) In case of a late re-transplantation >14 days after the immediate previous transplantation, e.g. due to chronic rejection, recurrent HepB/HepC or ITBL, at least one of the above defined complications (see 5.1.4.1) must be present.</p>
T3	Chronic disease, complications	Patient has: <ul style="list-style-type: none"> - a CTP score of ≥ 10, or a CTP of 7, and - ≥ 1 of the following complications: <ul style="list-style-type: none"> - see 5.1.4.1 - known HCC - assessment according to state of the art rules, - tumor diameter ≤ 5 cm, - ≤ 3 nodes involved and <3 cm in diameter, - no macrovascular invasion on preoperative examination, - no extrahepatic spread.
T4	Chronic disease, no complication	All other indications for liver transplantation including patients with a CTP score of at least 7. Patient is at home in constant need of medical care. Short hospitalizations for intercurrent reasons do not change the status.
NT	Temporarily not-transplantable	

The selection of potential recipients is based on ABO blood group rules, donor weight, medical urgency waiting time and donor region

b. *There exist three different blood group rules:*

1) ABO Compatible (Applied for CO; pediatric HU, pediatric T2, pediatric T3)

Donor blood group	Eligible recipients
A	A and AB
B	B and AB
AB	AB
O	A, B, AB and O

2) ET – Compatible (Applied for adult HU; adult T2 and T3)

Donor blood group	Eligible recipients
A	A and AB
B	B and AB
AB	AB
O	B and O

3) TPG (German Transplant Act) Compatible (Applied for T4)

Donor blood group	Eligible recipients
A	A and AB
B	B and AB
AB	AB
O	O

c. *Ranking of recipients:*

The categories HU (internationally highest priority), CO (internationally second highest priority) and T2 (nationally highest priority) within ET are based on their respective medical urgency, and not the point score. Patients in these categories are ranked by the time they have spent in their current urgency, i.e. the date that they were registered in that urgency. Thus, the patient waiting longest in that urgency is ranked first. For the patients in the remaining urgency categories T3 and T4 the following point score is assigned:

1) Urgency

T3 (200 points)

T4 (100 points)

2) Waiting time

1.11 points per waiting day (incl. maximum of 30 NT-days)
(maximum of 365 total waiting days for matching)

3) Region

200 points

d. Thus the following schemes apply:

Adult donor \geq 46 kg

first,

to HU patients (paediatric** & adult)

then,

to CO multi-organ patients (paediatric & adult)

then,

to T2 paediatric & adult patients in open obligation** countries/centres

then,

to T3 and T4 paediatric & adult patients in open obligation countries/centres

then,

to T2 paediatric & adult patients in the donor country

then,

to T3 and T4 paediatric & adult patients in the donor country

then,

to T2 paediatric & adult patients in other ET countries

then,

to T3 and T4 paediatric & adult patients in other ET countries

*There exists no paediatric bonus for liver allocation (for recipients <16) – however if there is a paediatric donor (<46 kg) on each urgency level the paediatric recipient is favoured as shown in the scheme below.

** Generating an obligation

An “obligation to offer” is generated, if a liver from a donor outside the transplant centre’s country is transplanted to a patient in urgency HU or CO.

Closing an obligation

To close an “obligation to offer”, the receiving country must offer the next available liver in the same blood group. If the liver is transplanted in the donor country that procured the liver generating the obligation, then the obligation is closed.

This rule is based on ‘country to country’ and keeps national balances between the participating countries level.

Paediatric donor (< 46 kg)

first,

to HU patients (paediatric & adult)

then,

to CO multi-organ patients (paediatric & adult)

then,

to T2 paediatric patients in open obligation countries/centres

then,

to T3 paediatric patients in open obligation countries/centres

then,

to T2 paediatric patients in the donor country

then,

to T3 paediatric patients in the donor country
then,
to T2 paediatric patients in the other ET countries
then,
to T3 paediatric patients in the other ET countries
then,
to T2 adult patients in open obligation countries/centres
then,
to T3 and T4 adult patients in open obligation countries/centres
then,
to T2 adult patients in the donor country
then,
to T3 and T4 adult patients in the donor country
then,
to T2 adult patients in the other ET countries
then,
to T3 and T4 adult patients in the other ET countries

The Allocation procedure for liver is currently under review. It is being discussed to replace the Child – Turcotte - Pugh scoring system by the Model for End-Stage Liver Disease (MELD).

e. Special Programs:

Split liver transplantation (SLT)

Each liver from a post-mortem donor who meets the conditions ≥ 50 kg body weight **and** ≤ 50 years of age is considered a potential split-liver donor if additionally the liver has excellent values.

One split must be transplanted to the patient initially selected by ELAS and for which the splitting centre accepted the whole liver.

The allocation algorithm for the **second** split is as follows:

First, locally, a suitable recipient is chosen by the transplant center from its own waiting list;

then, suitable recipients selected by ELAS split liver match, **first** regionally, **then** nationally, **then** internationally.

If, ultimately, the whole liver cannot be split, then the initial patient selected by the ELAS whole liver match receives the whole liver graft.

Further the Allocation Guidelines of the German Medical Association include exceptional rules for particular cases/situations. They apply for all solid organs and allow diverging from the above stated rules. ET is obliged to implement these rules by the end of August 2005.

Modified allocation procedure:

Limited function of post mortal donated kidneys, livers, pancreas, hearts and lungs or certain pre-existing diseases may cause difficulties for the allocation of these organs.

An exact definition of ECD (extended donor criteria) to describe these possibly well performing organs is impossible due to the variety of possible causes for their partial dysfunction. However several of those organs can be successfully transplanted under favourable circumstances, such as a short preservation times.

Criteria for allocation limitations that apply to all solid organs:

Organs from donors with grave prior diseases (e.g. history of malignancy) or complications resulting from these diseases require a special allocation procedure.

For example expanded donor criteria are given when the donor suffered of one of the following diseases:

- Viral hepatitis (alternatively HBS Ag+, anti-HBC+ or anti-HCV+)
- Sepsis with positive blood-culture
- Malignant tumour in medical history
- Drug abuse

Specified criteria for extended donor criteria are only existent for liver transplantation such as (alternatively):

- Age of donor > 65 years
- ICU-treatment including artificial respiration > 7 days
- Donor adipositas >BMI.>30
- Fatty liver (histologically affirmed) > 40 %
- Sodium>165mmol/l
- SGOT or SGPT >3x average (last parameter before notification as donor) or
- S-Bilirubin >3mg/dl (last parameter before notification as donor)

Each individual case has to be evaluated by the physicians involved in the organ retrieval in order to determine whether the extended donor criteria are fulfilled or not. The organs described above are only offered to transplant centres respectively their patients that prior to the acute allocation informed ET about their willingness to accept organs with extended donor criteria and noted that in the centre- and patient profile.

Accelerated allocation procedure:

ET is further entitled to modify its allocation procedure in case of

- a repeated refusal of organs due to donor(organ) related medical criteria (liver 3 x; kidney 5 x)
- Imminent threat of loss or donor organ due to logistic and organisational aspects

The organ offer must be accepted within 30 minutes. In order to profit from regional structures ET provides the centres with a list of matched recipients. The centre picks the one that is suitable the most according to the ranking. In case of competition the patient whose centre accepts first receives the organ.

2.2.3. Living Donor and Non-heartbeating donor Organ Allocation

2.2.3.1. Living Donor

▷ According to Section 8 paragraph 1 of the German Transplantation Act the removal of organs which cannot regenerate is only admissible for the purpose of transplanting to relatives of the first or second

degree, spouses, fiancés or other persons with whom the donor obviously entertains an especially close personal relationship.

Thus no allocation of organs donated in this manner is required since the recipient is known/determined at the time of donation. The German Transplantation Act prohibits altruistic anonymous living donations. Cross-over donation and pool-models are highly controversial. One of the Federal Supreme Courts ruled on cross over living donation and declared it permissible if the respective donors and recipients develop a close relationship due to their common destiny. This judgement however is disputed. Changes on the strict regulations regarding living donation are not to be expected especially with view to the successfully performed ABO incompatible transplantations.

2.2.3.2. NHBD

▷ The removal of organs is inadmissible in the case that the final, irreversible cessation of all function of the cerebrum, the cerebellum and the brain stem is not determined according to rules of procedure which comply with the state of the art medical standards (Section 3 paragraph 2 of the German Transplantation Act). Thus the brain death diagnosis has to be established prior to removal- consequently organ procurement from the so called NHBD (non-heart beating donor) is illegal in Germany. It is also illegal to allocate organs from NHBD's from outside Germany to German recipients.

2.2.4. Summary and Perspectives for the current allocation system

▷ On the basis of the German Transplantation Act a strictly patient oriented allocation system was established in Germany that only allows for a few exceptions such as the ones described above. In the ET registration system all “waiting lists” of the individual transplant centres are merged into one joint (inter)national waiting list. All patients have equal access to this registration system regardless of their financial or social status. Medically based inequality of patients who are immunologically compromised because of current and/or historical HLA-sensitization is balanced by their prioritization. Furthermore discrimination due to residency and choice of transplant centre shall be avoided. The acceptance to the waiting list is based on necessity (indications for transplantation) and prospect of success (no contraindications) according to current medical standards.

The concrete allocation of a post-mortem organ is performed by ET according to organ specific algorithms using a predefined point score system. This guarantees an objective process utilizing the same parameters for each patient on every matching procedure. This has the clear advantage that the allocation follows transparent rules and is completely operational. The influence of the so called squeaky wheel principle or prejudices on the transplant centre side is reduced to the minimum since the allocation decision is not made by an individual but via a computer program. The decision is unbiased, quick and definitive which becomes necessary at a certain quantity of listed patients. Thus ad hoc decisions where the physician on duty faces the additional pressure to decide – often in the middle of the night- which one of his patients might be the most suitable or the one in need most for a transplant shall be reduced as far as possible.

The doctor who is responsible for every single one of his patients shall be spared of possible conflicts of interests that might burden the patient-doctor relationship.

This however can not be avoided when it comes to the allocation of organs with extended donor criteria. Due to the increasing shortage of organs and to the constant improvements in transplantation medicine the utilisation of so called marginal organs is growing.

The utilization of an anonymous, impersonal and computer based point score system guarantees best that the allocation decision is not influenced by the following (human) factors either on the patient or the doctor’s side:

- Squeaky wheel principle: Possible lobbying of the patient or other influential persons or media in order to swing the allocation decision in somebody’s favour,
- Sympathy or antipathy towards certain transplant candidates,
- Personal relationship or lack of it,
- Social status or function,
- Fidelity-principle: Possible tendency to favour patients awaiting a retransplant, due to the grown Patient-doctor relationship;
- Needs of the program principle: Possible tendency to favour transplant candidates with a scientifically interesting research-profile.

Also the lawfulness of a computer based allocation decision is easier to monitor and to evaluate because either it was taken according to the algorithm or it was not. Thus a high standard of legal certainty is guaranteed. In case legal protection is sought, it has not to be directed against the concrete allocation decision (which could lead to the absurd situation and worse case scenario that due to the time factor the

consequence might be the loss of the donor organ) but instead can focus on questioning the chosen scoring factors at an earlier stage of the allocation process.

A point score system takes into account different factors relevant for allocation and assigns each of the factors a certain weighting. The recipient with the highest point score is offered the organ first. However in spite of the advantages listed above the problem of weighting the scoring factors is not solved yet. The initial problem that efficacy (prospect of success) and medical urgency are very often conflicting factors that need to be properly balanced remains unsolved. For example the current liver allocation system with its four urgency levels – due to the enormous lack of suitable organs- does not allow for considering the patients in urgency level T 3 and T 4. Thus only the criterion of medical urgency is relevant whereas the prospect of success as the other legally defined major criterion is neglected completely.

In addition the chosen allocation system has to be consistent with a country's constitution. Since the allocation system was imposed by law every allocation decision can be ascribed to the state even if the concrete allocation decision is conducted by an individual. This becomes even more evident with regard to the prohibition of organ trafficking. The attempt to seek the organ needed on the “free market” is penalised. An Act of state (direct or indirect) however has to comply with the law and in particular with the constitution. Constitutional rights involved when an allocation decision is taken are for example the right to live and to physical integrity (in particular that of the patient left out); equality of each individual (an 70 year old patient has the same rights to be treated like an 20 year old even if the later most likely has more life years ahead of him). Discrimination because of sex, religion, physical handicap, ethnic group etc. in choosing the suitable recipient must also be prohibited.

A predefined point score system allows considering and deliberating all factors relevant for an allocation decision thoroughly. It is a crucial selection that – due to the large number of patients on the waiting lists facing an extreme shortage of organs- might even be a decision about who is to live and who is not. Such a fundamental decision can and should not be taken in an ad hoc situation by the individual physician. It is a multidisciplinary task that cannot be solved by medical professionals only. Legal, ethical and societal aspects have to be taken into consideration as well. If the scoring factors are reviewed, re-evaluated and improved continuously by a multidisciplinary commission (such as the Permanent Commission on organ transplantation at the German Medical Association) not only current standards of medical science but also societal, ethical and legal contemporary standards will be ensured. Thus the scoring factors, despite of the fact that they are written down in legally binding guidelines, shall not be understood as rigid regulations but are subject to constant changes and improvements.

Last but not least a patient oriented allocation system based on a national registration system facilitates the chance to find the “perfect match” out of the large pool of potential recipients. This is at least of considerable importance for the HLA – compatibility of kidney recipients.

However the anonymous patient oriented point- score allocation system has been subject to criticism as well. It was pointed out that it would not provide sufficiently for individual solutions that are often required in the field of medical treatment of patients. The attempt to achieve justice on a general and abstract level though tends to be disadvantageous to some individuals- in particular those who were left out. The laboratory values that serve as objective parameters according to which the point score is determined, leave no room for individual aspects (e.g. psychological, social, family) and can easily be overrated for the sake of objectivity. Thus a patient- oriented system only allows an individual treatment of the patient to a certain extend which invokes the impression of a contradiction. This objection could be attenuated by leaving room for an extra

bonus that each patient could apply for via his doctor, and a letter of motivation to a special commission for example.

Nevertheless with view to the whole ensemble an objective and transparent system is preferable even though it might seem unjust in some individual cases. This is immanent to all situations in which shortage has to be allocated.

Scientific tests prove that the reduction of the CIP to the minimum does not only improve graft performance but as a result of that is also extremely cost saving. It has to be admitted, that factors aiming to minimize CIP might not be sufficiently taken into account. It is difficult to integrate in a point score system since this can only be done by assigning major regional bonuses which partially would be a return to a centre oriented allocation system. Nevertheless this argument is brought up very often by the transplant centres that by the majority favour a transplant centre oriented allocation system. It is rather difficult to invalidate. Last but not least the major argument of the transplant centres in favour of a more transplant centre focussed allocation system can be invalidated. According to this argumentation the hospital lacks incentives to notify the DSO of a potential donor if it is not to keep and transplant the organs to its own patients. Thus donor numbers would decrease. This of course is an illegitimate argument. The hospitals are obliged by law to report a potential donor even if they do not profit from it by earning money through transplantation in the end. This is part of their assigned mission that of course is remunerated adequately. On top of this statistics prove that the alteration from the transplant centre oriented allocation to the patient oriented system was not accompanied by a decline of donation numbers. Sadly enough the figures remained constantly low.

2.3. Organ Allocation in Hungary

2.3.1. Aims, General Principles and Organization

2.3.1.1. *Historical and legal context*

▷ Cadaver kidney waiting list was established in Hungary in the HLA Typing Laboratory of National Institute of Haematology and Immunology in 1971. First selection software was implemented in 1992, which was applied for recipient selection for all over the country. Software renewal was done in 1997, with the help of RETRANSPLANT project, making regional selection available. (In Hungary there are 4 transplantation centres with associated typing laboratories). The selection criteria were based on immunological parameters (ABO identity/compatibility and HLA matching) following the former ET criteria.

The legal background for this activity was laid down in the Act CLIV of 1997 on Health and the following ministerial decrees (18/1998. (XII.27.) and 61/2003 (X.27.)).

The ministerial decree in 2003 ordered the foundation of waiting list committees organ by organ, they are responsible for the admission criteria, the selection rules, admitting and removing patients from the waiting list. There are four regional kidney waiting list committees joined by the national committee, and independent liver, lung and heart committees. The organ specific waiting lists exist separately from each other; neither common database nor central computer system is available for their synthesis.

2.3.1.2. *Dealing with Societal concerns*

▷ In all waiting list committees civil organizations are also involved, e.g. National Association of Kidney Patients, National Association of Kidney Transplant Patients, National Association of Liver Transplant Patients, National Association of Heart Transplant Patients, National Association of Lung Transplant Patients. Hungarotransplant is also member in the National Kidney Transplant Waiting List Committee and invited for the extended meetings of the other committees twice a year.

2.3.1.3. *Allocation Policy Definition and Improvement*

▷ In 2001 the volume of the kidney waiting list exceeded the 1000 patients. As the number of patients waiting more than 4 years accumulated on the list, an analysis was performed to reveal the possible causes. Based on the analysis, and the international experiences fundamental changes were introduced in the allocation system. These changes resulted in a more sophisticated ad hoc selection list of patients simultaneously for all transplant centres for every donation. The impact of these changes on the composition of waiting list lag behind the expectations because the transplant centres did not strictly follow the order of selection lists.

2.3.1.4. *Allocation system objectives*

▷ The allocation system for heart and liver transplantation is very simple because there are only one heart and one liver transplant unit; their waiting lists are the national waiting lists at the same time. So no allocation activity should be performed among centres, only the proper recipient selection should be assured.

The activity of liver transplant, and particularly the heart transplant program do not as high as it could be derived from donation activity.

That means that the utilization rate of hearts and livers is significantly lower as compared to international figures: 7% vs. 30% and 30% vs. 80%, respectively (utilization rate: rate of transplanted organs in

percentage of cadaver donors). Nevertheless we have the legal background for organ offer to abroad (CLIV. Act on Health, 1997. Chapter XVII., 243.§), the authorization for Hungarotransplant to initiate cross border organ offers and the undersigned bi- and multilateral contracts are still missing. The basic principle of the concerned law is that any organ for transplantation purposes can be offered to abroad only in that case when no suitable Hungarian recipient for the given organ is available.

The ratio of transplanted kidneys and non-kidneys is 50-50 % in “well utilizing” countries while in Hungary this ratio is 20-80% (Figure).

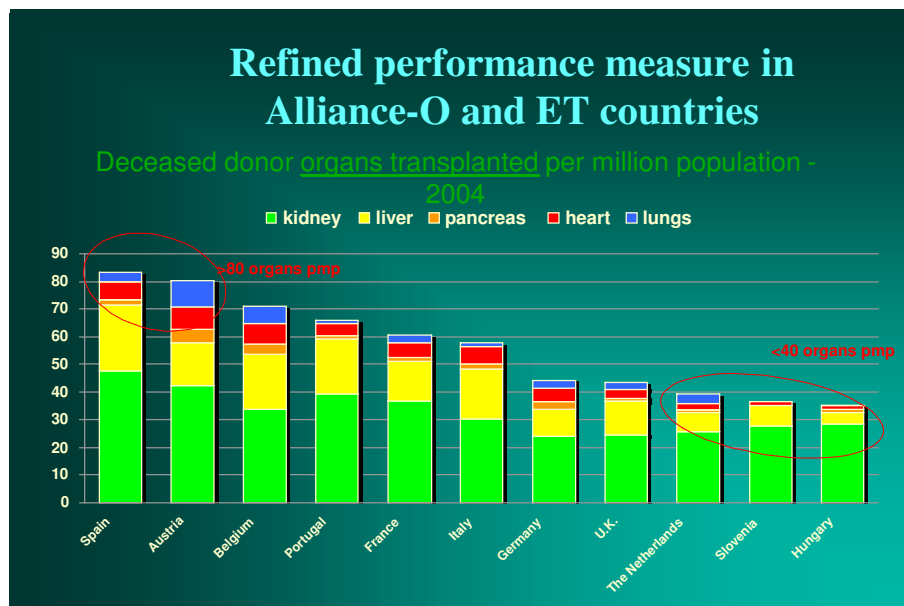


Figure 3 - Performance measure in Alliance-O and ET countries

2.3.1.5. Allocation Principles

▷ The allocation principles regarding the kidney allocation among the four centres are slightly overlapping and ambiguous. Priority of the procuring centre, ABO and HLA matching, waiting time, sensitization, age matching should be taken into account simultaneously that results in an inappropriate freedom in decision making for centres. (see detailed in case reports)

Regarding liver and heart allocation the main factor is the ABO identity or compatibility, and body weight match. Female donors in case of male heart recipients are usually excluded. If more recipients are eligible according to the blood group and size matching, the waiting time and the severity of original disease and the general condition of the patient is the decisive factor.

2.3.1.6. Allocation Rules Application

▷ According to the Decree the four regional kidney waiting list committees should be responsible for the follow up of the adherence to the allocation rules, and they have to report to the National Committee in every case of skipping patients on the selection list provided by the HLA Laboratory. To date in practice this system does not work.

2.3.1.7. Allocation Practices Evaluation

▷ According to the ministerial decree the waiting list committees are obliged to present their results twice a year on an expanded meeting, where the representative of Ministry, Hungarotransplant, insurance company and civil organizations are also invited.

2.3.1.8. Waiting List registration Procedure

▷ There are organ specific evaluation protocols, that contain those examinations that are considered necessary for registration to the waiting list. These examinations are financed by the insurance company only in some dedicated hospitals. After the completion of the protocols the doctor in charge refers the patient to the waiting list committee on its weekly meetings in case of liver and monthly in case of heart. This committee decides whether the patient is eligible to be registered on the WL. These meetings are also used to check the eligibility of previously listed patients.

2.3.1.9. Information System

▷ The organ specific waiting lists are existing separately from each other, neither common database nor central computer system is available for their synthesis. Patients waiting for combined kidney+pancreas transplant and kidney alone are listed in the computer of the National HLA Laboratory. The data stored in this system allow to evaluate the age and gender ratios, PRA values etc., and their changes on a time scale.

2.3.2. Allocation system in use: study cases

2.3.2.1. Kidney Allocation

a. Rules for ABO matching

- Donor A -> recipient A or AB;
- Donor B -> recipient B or AB;
- Donor AB -> recipient AB;
- Donor O -> recipient O or B (in case of pediatric donor the pediatric recipient could be either O, B,

A or AB group as well).

b. "Urgency" categories in Hungary:

U: „highly urgent to transplant” - based on the clinician's decision.

IM: (intelligent mismatch) for hyper immunized patients

- PRA > 85% and
- neg. crossmatch (XM) (with current sera)
- less than 1 HLA-B and 1 HLA-DR mismatch (MM)
- no non-acceptable MM (repeated previous donor antigen.)

Such patient will be ranked on the top of the list just after the category “U”.

c. "Extra" categories in Hungary:

In case of the donor is aged up 18 years a separate pediatric patient's selection is performed automatically, and it can be also requested if the donor is under 30 years of age.

Pancreas + kidney: separate selection. To date no consensus could be achieved between the two concerned centers regarding the pancreas allocation.

Liver + kidney combined transplantation: absolute priority

d. Allocation score system:

Basic: HLA mismatch calculation

Definition: an HLA mismatch occurs, when a donor HLA antigen would be recognized by the recipient as being different from the recipients' own HLA-antigens.

In case only one HLA antigen is identified, the donor is assumed to be "homozygous" for that locus. In this case only one mismatch can occur on that locus.

Advantage to DR matching:

- minus 40 points for 1 A or B MM, minus 120 points for 1 DR MM

	Score
0 ABDR MM:	400,00
1 AB MM:	360,00
2 AB MM:	320,00
1 DR MM:	280,00
1 AB, 1DR MM	240,00
3 AB MM:	280,00
2 AB, 1DR MM:	200,00
4 AB MM:	240,00
2 DR MM:	160,00
1 AB 2DR MM:	120,00
3 AB, 1DR MM:	160,00
2 AB, 2DR MM:	80,00
4 AB, 1DR MM:	120,00
3 AB, 2DR MM:	40,00
6 ABDR MM:	0,00

Mismatch probability factor:

with the kind help of ET their calculation is in use: it is an estimate of the probability of a kidney offer with 0 or 1 HLA-A, B or DR mismatch out of 100 kidney offers, taking into account the ABO blood group matching rules and the percentage of the most recent PRA screening.

- 0 and 1 HLA MM probability: on the basis of allele frequencies (Hungarian database)**
- ABO frequency (Hungarian data based on own donor population, 1990-2003)**

ABO blood group			
Recipient	Frequency	Donor Match	Match frequency
ABO-O	0,440	ABO-O	0,440
ABO-A	0,423	ABO-A	0,423
ABO-B	0,102	ABO-B + ABO-O	0,542
ABO-AB	0,036	ABO-AB+ABO-A+ ABO-B	0,561

- % PRA: the latest PRA is taken into account. Higher %PRA the lower the chance of a negative crossmatch. PRA measurement is performed monthly.**

The formula to assign points for the factor "Mismatch probability" was introduced, based on ET's system.

Waiting time:

15 points bonus/year waiting

Additional ("clinical") considerations beyond list order

- Donor age < 18 yrs, simultaneous pancreas kidney tx. (SPK) possible only under 18 yrs
- Simultaneous Liver Kidney (SLK) has absolute priority
- U, IM patients at the top
- CMV: D(-), R(-) should be preferred
- regionality: the local centre should keep the kidneys
- the recipient's actual clinical condition and the age-matching should be also kept in mind
- further logistic aspects could be preferred
- inter-centre balance should be kept in mind

2.3.2.2. Liver Allocation

▷ Hungary has one liver transplant program that operates in Budapest, in the Transplantation and Surgical Department of Semmelweis University. All potential donors referred to the Hungarotransplant's national coordinator on duty are considered potential liver donor at startup. The coordinator checks the hepatic-specific selection criteria and in case of no absolute contraindication he refers it to the Transplant Department. The final decision whether the liver is suitable or not is the responsibility of the surgeon on call. The policy of recipient selection is defined by the Liver Waiting List Committee and the Transplant Department together with the National Transplant Society.

The National Transplant Society promotes the improvement of awareness about the possibility of liver transplantation among internists and hepatologists. Even so great regional discrepancies can be seen in the patients' referral rate to the waiting list. Only patients having Hungarian insurance card can be listed.

Having only one centre the question of conflicting interests between transplant teams on their transplant activity is not applicable. Patients suffering from hepatitis B cirrhosis have poorer access because of a limit decided for them. Only three of them can be transplanted in a year due to financial restrictions because of the extra costs originating from the use of Hepatect.

There is an evaluation protocol consisted of two levels, it contains those examinations that are considered necessary for registration to the waiting list. These examinations are financed by the insurance company only in some dedicated hospitals. After the completion of the protocols the doctor in charge refers the patient to the waiting list committee on its weekly meetings. This committee decides whether the patient is eligible to be registered on the WL. Patients are grouped on the waiting list according to their blood groups. Further subgroups are defined based on the general condition of the patients and Child score. MELD score is not routinely determined. Recipient selection is based primarily on blood group and size (height and weight) matching with the donor. Further selection can be made if necessary according to the length of waiting or the Child score. There is an obligation originating from a ministerial decree that the waiting list committee has to report his activity two times a year. This is an extended meeting with the involvement of Hungarotransplant, representative of the insurance company, Ministry and civil organizations.

The waiting list committee advises changes based on the evaluation of the previous time period.

2.3.3. Living Donor and Non-heartbeating donor Organ Allocation

▷ There is no legally approved NHBD program. Only Maastricht Category IV (cardiac death in a brain dead donor) is accepted by harvesting teams.

The legal basis of living donation is well defined. Not only relatives but spouses and emotional relatives can donate. In case of no genetic relationship between donor and recipient a local ethic committee has to approve the donation. Out of four kidney transplant programs only two provide living donation, Budapest and Pécs. In Budapest only open surgery is available, in Pécs laparoscopic donor nephrectomy is also available.

2.3.4. Summary and Perspectives for the current allocation system

Critical considerations for kidney allocation (by Hungarotransplant)

- not transparent for the patients
- the „list order” is optional for the centres, no effect of any modifications
- no inter-centre balance
- big centre (Budapest) – small centres (Debrecen, Szeged, Pécs): imbalance for the benefit of Budapest
- no pay-back in case of SPK, SLK
- no real, measurable advantages of Highly Sensitized Patients
- no clearance of unsuitable patients
- lack of possibility for international collaboration (e.g. acceptable MM program)

Priority algorithm

(temporarily rejected proposal of HT) for solution

U: no access for HD, Kidney transplantation is life saving (exceptional)

- IM:
- PRA > 85% and
 - neg. XM (with current sera)
 - less than 1 HLA-B and 1 HLA-DR MM
 - no non-acceptable MM (repeated previous donor ag.)

List order: HLA-MM + waiting time + corr. factor (AB0 and HLA frequency, PRA)

Pay-back (1st, 2nd, 3rd attempt): in order to keep inter-centre balance. That means an obligation to offer giving back kidneys to the other center in three consecutive organ procurements. If the offer is rejected even in the third occasion, the debt should be cancelled.

- The priority order should be:
1. Kidney + liver simultaneous recipient
 2. Urgent (U) recipient at local centre
 3. Urgent (U) recipient elsewhere
 4. Paediatric recipient at local centre
 5. Paediatric recipient elsewhere
 6. IM recipient at local centre
 7. IM recipient elsewhere
 8. 2 HLA-A or less MM at local centre
 9. 2 HLA-A or less MM elsewhere
 10. Pay-back (1st, 2nd, 3rd attempt)
 11. According to the list order at local centre
 12. According to the list order elsewhere

No additional („clinical”) considerations!

2.4. Organ Allocation in Italy

2.4.1. Aims, General Principles and Organization

2.4.1.1. *Historical and legal context*

▷ The Italian transplant system is regulated by Law 91 dated April 1st 1999, under which Art 10 has acknowledged and inserted the Regional and Interregional coordinating structures in the national system and created the Italian National Transplant Centre. The main aim of such system is optimising the use of procured organs, ensure transparency and proper working of the whole system, issue guidelines and implement personnel training and information to the general public.

2.4.1.2. *Dealing with Societal concerns*

2.4.1.3. *Allocation Policy Definition and Improvement*

2.4.1.4. *Allocation system objectives*

2.4.1.5. *Allocation Principles*

a. *National Programs*

▷ National programs override organ allocation mechanisms in all inter-regional areas. Such programs aim at giving priority to recipients at life risk or in serious or particular clinical conditions, or for a particular age interval or under other clinical and/or immunological conditions that make transplant difficult. National programs are:

- Manage of request for urgent liver and heart
- Manage of request for organ advances
- Bowel and multivisceral transplant program
- Liver transplant in HIV-patient program
- Kidney transplant in HIV-patient program
- Paediatric program
- Kidney program for patient difficult to be transplanted
- Lung transplant program
- Pancreas transplant program.

Whenever an organization or a transplant centre allocates an organ for national programs, it is general returned within a given time for avoiding penalizing the recipients of that area.

Organ advance and return

When a patient is in serious clinical conditions, but does not fall in the categories foreseen by the protocol for urgent requests or is waiting for an organ different from those foreseen by the present protocols the transplant centre can submit a national request for organ advance. Whereas urgent request have to be met compulsorily, the Transplant Centre can decide whether to meet the advance request or not. Organs allocated for advance requests have to be returned within set deadlines and under terms that are fixed time by time when the organ has handed over to other organization.

b. Interregional programs

▷ Such programs are different from an organization to another, and in AIRT and OCST they refer to the management of surplus organs alone (organs that were not transplanted in the originating region), but are much more complex for NITp since such organization manages organ allocation at central level.

NITp has an allocation model that is directly managed by the Interregional centre which allocates organs on the basis of shared and fixed protocols, that assigns priority to clinical conditions and, only when no recipient is in serious clinical conditions, organ is allocated to the transplant centre of the area where it was originated.

Surplus organs

Surplus organs are those organs that cannot be utilized in the originating region, due to lack of transplant centre or of suitable recipients on the regional waiting list for that kind of organ. In such cases, the interregional organizations will offer the organ to its regions on the basis of fixed criteria.

As a general rule organ is offered to regions on the basis of a centre rota mechanism, and the Centre that accepts it comes then last. AIRT offers any organ to regional centres, whereas OCST applies a different rule depending on the kind of organ: hearts and livers are offered to transplant centres, kidneys, lungs and pancreas are offered to regional centres. When an organ is allocated to the regional centre and more transplant centres are present in the region, the regional transplant centre will assign the organ on the basis of its own regional criteria.

c. Regional programs:

▷ Regional programs, that are in use in AIRT and OCST as stated above, foresee that organs are allocated inside the donor originating regional territory, unless national programs are applied.

d. Standard allocations:

▷ When national programs are not applied, allocation of organs from donors detected by intensive care units in the regional territory is managed by the Regional Centre that will ascribe them to transplant centres in its Region, on the basis of shared and fixed criteria. Should more centres be present in the same regional territory, the Regional Centre will assign the organ according to in-a-row model. Once the organ has been assigned to the transplant centre, the centre itself will choose the most suitable recipient for that kind of organ.

e. Recipient choice:

When an organ has been allocated to the Transplant Centres for transplantation, personnel of the Centres will choose a recipient from official regional waiting lists using pre-established criteria. The Transplant Centre will communicate the name of the eligible recipients in the case, all the changes they act and the final selection. The clinical choice of the most suitable patient for a transplant it depends on several parameters for different organs.

2.4.1.6. Allocation Rules Application

▷ Presently in Italy there are three interregional organizations, Interregional Transplant Association (AIRT), Nord-Italy Transplant (NITp) and Centre-South Transplant Organization (OCST), that coordinate the twentyone Regional Transplant Centres (see Fig.1), whose organizational models lie upon common and shared criteria but are different for some relevant aspects. OCST and AIRT have a “regional” organizational model: the Regional Centre of the area where the donor is detected offers organs first to the transplant

centres of its region, barring the presence of national programs (urgencies, request for advances, returns and paediatric organs), that are managed directly by Interregional Centres. Moreover, AIRT and OCST allocate “surplus” organs, that means retrieved and not utilized organs in the retrieval region, either due to absence of transplant centre or suitable recipients, on the basis of predefined shared and transparent principles, through a continuous in-a-row mechanism. NITp is instead working as interregional organization and allocates available organs to the transplant centres of its regions directly.

Both models have some advantages, since the regional model allows to curb costs of team, organ and biological material transportation. Interregional model instead allows to have a larger pool of potential recipients, resulting in a better donor-recipient match.

2.4.1.7. Allocation Practices Evaluation

2.4.1.8. Waiting List registration Procedure

2.4.1.9. Information System

2.4.2. Allocation system in use: study cases

2.4.2.1. Kidney Allocation

▷ All the Centres allocate kidneys to the recipients from their waiting lists first on AB0 and HLA compatibility. AB0 and HLA related score has been assigned to the eligible recipients. On that base others secondary criteria are used: time in waiting list, donor-recipient age match, time in dialysis, PRA positiveness, etc. The regional and inter-regional organizations are free to decide the relative importance in decision making of that different secondary criteria, in respect of local autonomy.

In the following tables are shown the adopted criteria in the OCST Regions and comparing their different usage in the transplant programs.

	AB0	HLA	Pts. Age	Dialysis time	Don/Rec age match	WL time	PRA	N° Tx
Abruzzo-Molise	X	X			X	X		
Basilicata	X	X		X	X	X	X	X
Calabria	X	X	X	X				
Campania	X	X		X	X	X	X	X
Lazio	X	X			X	X	X	X
Sardegna	X	X	X	X				
Sicilia	X	X		X	X	X		
Umbria	X	X				X		

Tableau 1 - Allocation rules for kidney in OCST regions

2.4.2.2. Liver Allocation

▷ For liver transplantation the first parameters to allocate organs are: ABO compatibility, clinical state, anthropometrical dimensions. To evaluate clinical situation many centres use the MELD score, revised giving extra-points to associated pathologies or clinical situations that potentially reduce life expectancy. Every regional and inter-regional organizations have decided to evaluate differently that parameters.

In the following tables are shown the adopted criteria in the OCST Regions and comparing their different usage in the transplant programs.

	ABO	HLA	Pts. Age	Dialysis time	Don/Rec age match	WL time	PRA	N° Tx
Abruzzo-Molise	X	X			X	X		
Basilicata	X	X		X	X	X	X	X
Calabria	X	X	X	X				
Campania	X	X		X	X	X	X	X
Lazio	X	X			X	X	X	X
Sardegna	X	X	X	X				
Sicilia	X	X		X	X	X		
Umbria	X	X				X		

Tableau 2 - Allocation rules for liver in OCST regions

2.4.3. Living Donor and Non-heartbeating donor Organ Allocation

2.4.4. Summary and Perspectives for the current allocation system

2.5. Organ Allocation in Portugal

2.5.1. Aims, General Principles and Organization

2.5.1.1. Historical and legal context

▷ The first official law regulating organ and tissue transplantation dates back to 1976 (Decree-Law 553/76 of 13 July, 1976) and already regulated the criteria for procurement and transplantation of cadaveric donors, with presumed consent being established as a rule.

The Law 12/93, of April 22, which overruled the above mentioned decree-law, established the current set of rules governing the harvesting of organs and tissues of human origin for diagnosis and therapeutic purposes. The creation, within the scope of the institutions belonging to the National Health Service (Serviço Nacional de Saúde), of a network of services operating in the area of transplantation (the Decree-Law 244/94, of September 26), has regulated the organisation and functioning of the National Registry of non-Donors [Registo Nacional de não Dadores (RENDA)].

Subsequently, and with the purpose of promoting and developing the resources required for the effective organisation of the transplantation activity, the position of the national coordinator for transplantation was created (ministerial decree 17/95 of the Minister of Health), with appointment by the Minister of Health.

The experience yielded the need to improve the institutionalisation of the combination between several bodies qualified to carry out harvesting and transplantation of organs and tissues, by means of the creation of a system functionally organised, but flexible and representative, like the ones existing in other countries of the European Union.

Thus, in 1996 the Organização Portuguesa de Transplantação (OPT) was created, being acknowledged the fulfilment of the requirements that, aiming at the maximisation of the existing resources efficiency, allowed to proceed to the reform of the current scenery concerning institutional relationship, i.e. by creating a consultative council where all the institutions are represented and where all the important issues concerning harvesting and transplantation activities, namely in regard to relevant ethics aspects and outcome assessment, are debated.

The OPT has successfully established, together with the Coordination and Procurement Offices for Transplantation (CPOT), the histocompatibility labs and the procurement and transplant units, a set of rules concerning donor detection and evaluation, criteria for organ donation and allocation and waiting list management.

Kidney allocation rules were already in place as the histocompatibility labs had a tradition on this field. With the beginning of heart and liver transplantation in the nineties, recommendations for organ allocation were issued by the OPT.

2.5.1.2. Dealing with Societal concerns

▷ No public opinion poll has ever been performed in Portugal.

The allocation rules are set after an open discussion with all the participants involved in organ procurement and transplantation, under the auspices of the OPT.

No entities outside the field of transplantation are involved in these discussions, however suggestions by patients associations and others are welcome.

However and up to the present moment the contribution by entities outside the field has been negligible.

2.5.1.3. Allocation Policy Definition and Improvement

▷ The OPT consults with an Advisory Committee composed by Transplantation Units, CPOTs, Tissue Typing Labs and Transplantation Experts belonging to the National Transplantation Council.

The Advisory Committee submits the final text of the proposal or new changes, to the OPT.

After evaluation, the OPT submits to the Health Minister rules for kidney transplantation, then published as official guidelines.

For other organs (liver included) there are no official guidelines but recommendations issued by the OPT as accepted rules.

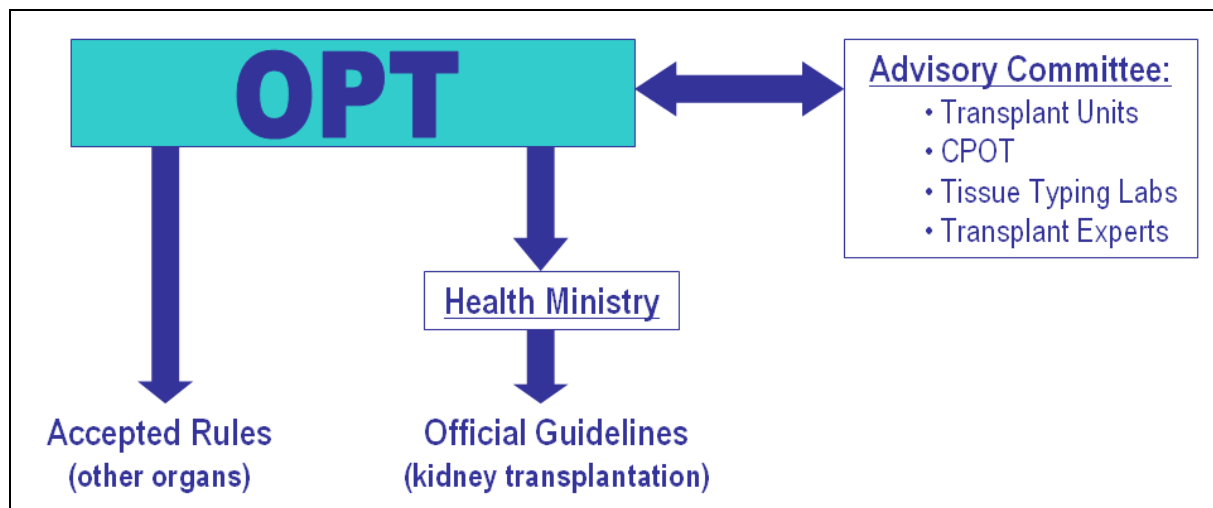


Figure 4 - Allocation Diagram in Portugal

2.5.1.4. Allocation system objectives

▷ The allocation system objectives are:

- To achieve a compromise between equity and fairness to the patients, taking into account the best donor-recipient pair according to the medical and immunogenetic state of the art.
- To take into account specific patient conditions, such as low probability of access to a graft due to genetic characteristics or allosensitization.

2.5.1.5. Allocation Principles

Equity - According to the accepted ethical principles and clinical criteria underlying the unbiased allocation of the available organs.

Efficacy - Clear rules for organ allocation and clinical and laboratorial criteria for the prioritization of the receptor selection.

Logistics - In Portugal there are 5 CPOTs covering 35 harvesting hospitals.

Each office applies the allocation rules and is in charge of the organ delivery to the transplant unit.

Delivery may require the collaboration of the security forces and/or air force for the appropriate and timely arrival of the organ.

2.5.1.6. Allocation Rules Application

▷ The CPOT is provided with adequate information concerning the harvested organ.

The CPOT sends donor blood samples and lymph node to the tissue typing lab and gives information on the anatomical characteristics of the organ, aortic clamping time, preservation solution used and clinical details on the donor such as age, sex, weight, height, cause of death, ICU stay and relevant medical history.

The donor-recipient pair selection is based on clinical and laboratorial criteria for all organs, except for liver transplantation where only clinical criteria apply. The previously defined allocation rules are used to match each organ with potential recipients. The Lusotransplante computerized database, based on a set of algorithms using the clinical and laboratorial of each organ donor and recipient, then generates an ordered list of patients which is used as a guide to propose the organ to the transplantation team in charge of the patient. Each team has the possibility to accept or decline the proposed organ, according to its clinical criteria.

2.5.1.7. Allocation Practices Evaluation

National registry of organ collection and final destination, giving real-time information about each organ's allocation and transplant results as:

Not transplanted

or

Transplanted (one or more receptors).

Regular meetings of the OPT with the CPOT and Transplantation Units in order to assess the efficacy and equity of the allocation system.

Regular update of the allocation criteria.

2.5.1.8. Waiting List registration Procedure

▷ There is national waiting list for kidney transplantation only. Each candidate to a kidney transplantation is registered in one or two transplant units and clinical priority stratification is defined by the published guidelines.

For other organs (liver, heart, lung) each unit has its own waiting list and defines each patient's priority. The OPT is developing a national registry that will provide information concerning the size of the waiting list.

2.5.1.9. Information System

▷ There is a national database for kidney transplantation, which includes all the patients waiting for a transplant. This database is located in the *Lusotransplante* in *Lisboa* and acts as the hub for a network linking all the kidney transplant units. The database is used to administer the national kidney transplant waiting list and contains pre-transplant information on patients and donors.

For other organs there is no information system, although the OPT is now implementing a database.

2.5.2. Allocation system in use: study cases

2.5.2.1. Kidney Allocation

The general allocation guidelines used by LUSOTRANSPLANTE includes:

- previous registration in LT kidney waiting list,
- ABO compatibility,
- Rh compatibility in fertile or presensitised women,
- HLA match (minimum match required is 1 DR+1AB or 2 AB for adults),
- percentage of panel reactive antibodies,
- waiting time,
- age,
- and a negative lymphocyte cross-match (B and T cells) is required.

This algorithm is applied locally to one kidney and regionally to the other kidney.

Selection priority is considered for:

- high urgency status, attributed to patients without vascular access for dialysis (no HLA match is required being only necessary to provide an ABO compatibility and a negative crossmatch),
- highly sensitised patients determined as having a defined reaction frequency against a random panel > or = 85% (HSP); as sera exchange is provided by the three tissue typing centres, a national level is first considered for these patients,
- "full-house" patients,
- paediatric recipients defined as patients aged under 16 years (a minimum match of 2 DR+1AB is required)."

2.5.2.2. Liver Allocation

a. Priority 1 : Extra-urgent

The only patients included in this criterion are those with:

- Acute liver failure (without previous hepatopathy)
- Second transplant within five days of first

Extra-urgent request presupposes:

- Eminent life threat

Has national priority

Is valid for 72 hours

Its prolonging has to be justified

Acceptance or refusal of an offer must be made within 60 minutes

If graft is used in another patient, although request is not overridden, it implies justification with the CPOT that has sent the organ

Commitment to send liver to the issuing unit, by agreement between the two transplantation units.

If several extra-urgent requests coincide:

- paediatric recipients have priority
- selection will be made according to precedence in appeal

b. Priority 2: Paediatric Donors

▷ Livers of donors aged 15 or less will be offered firsthand to Coimbra University Hospitals –HUC (as it is the only paediatric transplantation unit)

c. Priority 3: Urgent

Patients who are in critical condition but who do not qualify for extra-urgent criteria are included in this level of urgency

Eventual satisfaction of these requests is based on an agreement between units in each case

Offer of liver in response to this appeal is conditioned to the sending of liver to the issuing unit.

d. Elective distribution

Will be made according to the following order:

Transplant Unit of Donor Hospital

Note: Non-acceptance of liver by Donor Hospital team, pre- or post-surgery, grants the Office that coordinated collection, the ability to offer it to other transplant Units, respecting the distribution criteria that follow:

Regional Distribution

Non-acceptance at regional level implies the moving of offer to national level.

National Distribution

Rotational

2.5.3. Living Donor and Non-heartbeating donor Organ Allocation

▷ In Portugal, by law living donation may be permitted when the donor and receiver are next of kin up to the third degree.

Currently, non-heartbeating donor retrieval is not allowed in Portugal.

2.5.4. Summary and Perspectives for the current allocation system

▷ In Portugal, the organ allocation system is based on clinical and immunogenetic criteria, with regional preference being given, whenever possible, for kidney transplantation.

Highly sensitised patients (HSP) and those less favoured by genetic reasons (ABO blood group) are given a fair chance of getting an organ through the implementation of a national program for HSP and a selection algorithm in the database, respectively. Children as recipients are also contemplated and given priority at national level whenever a donor is under 18 years of age.

The implementation of national waiting lists for liver and heart recipients would allow for the assessment of patients dying while waiting for a transplant and for a clear picture of possible disparities between the supply and demand of these organs. This should be seen as a goal for the near future.

2.6. Organ Allocation in Spain

2.6.1. Aims, General Principles and Organization

2.6.1.1. Historical and legal context

▷ Spanish transplantation history started in 1965 with the first kidney transplant performed in Madrid and Barcelona. In 1979 we got the transplant law. The transplantation activity was increasing during this years. In the middle of the decade started heart and liver transplant. At the end of the eighties we had a big decrease in the number of donors, then patient associations and professionals claimed for an organization which coordinate all the activities of the process and manage the waiting list. In 1989 the Ministry of Health set up the ONT. Later a Royal Decree regulated the development of the whole donation and transplantation process in 1999.

So, these three laws describe the legal context, in which the donation and transplantation activity is developed:

- Transplant Law (1979)
- Royal Decree for the tissues and cells removal and transplantation (1996)
- Royal Decree for the organ retrieval and transplantation (1999)

2.6.1.2. Dealing with Societal concerns

▷ In Spain was created the Interregional Committee. This Committee was made up by the regional transplant coordinators, members of the Ministry of Health, the National Coordinator and technical personnel of ONT. This Committee established the geographical criteria and designed the transplant zones in which we have divided Spain.

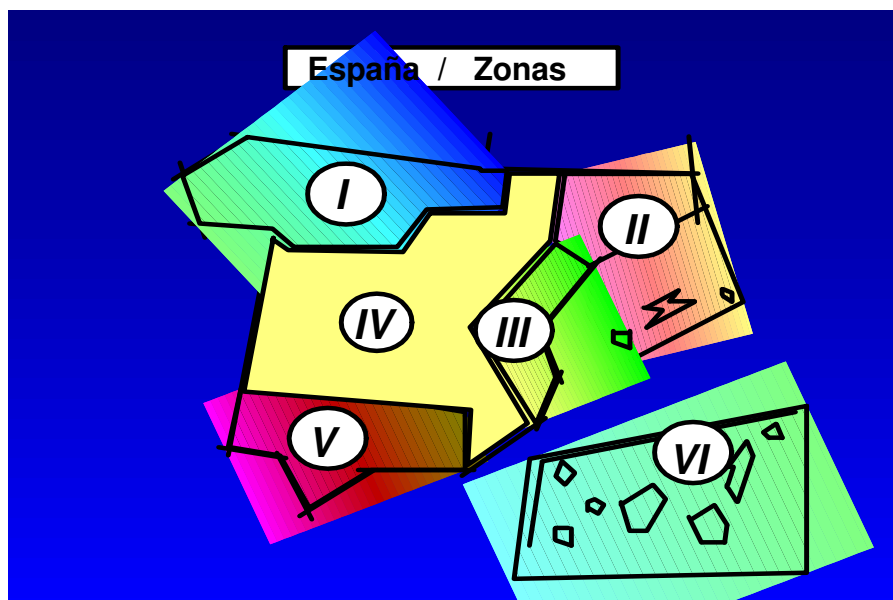


Figure 5 - Organ allocation Zones in Spain

In 1992 a consensus document was created with the general, ethical principles to be respected by the allocation criteria

During an annual meeting, the different transplant teams decide which will be the clinical allocation criteria of each year.

2.6.1.3. Allocation Policy Definition and Improvement

▷ Trying to assure that all the recipients will have the same opportunity for being transplanted, each year a statistical analysis of the waiting list management is presented to the transplant teams and after its study it's decided the changes to be made in the clinical allocation criteria.

2.6.1.4. Allocation system objectives

▷ The allocation system objectives are included in the consensus document created in 1992. The allocation system must respect the justice and equity principles. The allocation criteria must be based in clinical criteria without any racial, economic, and religious discrimination. The allocation criteria must agree with the scientific knowledge that are in force at each moment. The allocation of the organs inside the transplant hospital will be managed by each transplant team.

2.6.1.5. Allocation Principles

▷ Clinical:

- Medical compatibility: blood group identity / size, age and sex match / Ag compatibility / local medical priorities
- Urgency status (Urgency / Priority / Elective)

Urgencies: National priority. (Organs shall be returned in cases of liver and lung transplants)

- Priorities: zone allocation after requesting. (organs shall always be returned)
- Local agreements will be respected and applied

For elective transplants organs will be offered after geographical criteria following compatibility and medical criteria

Following the **geographical criteria** the offers are made after a logical system from the inside to the outside

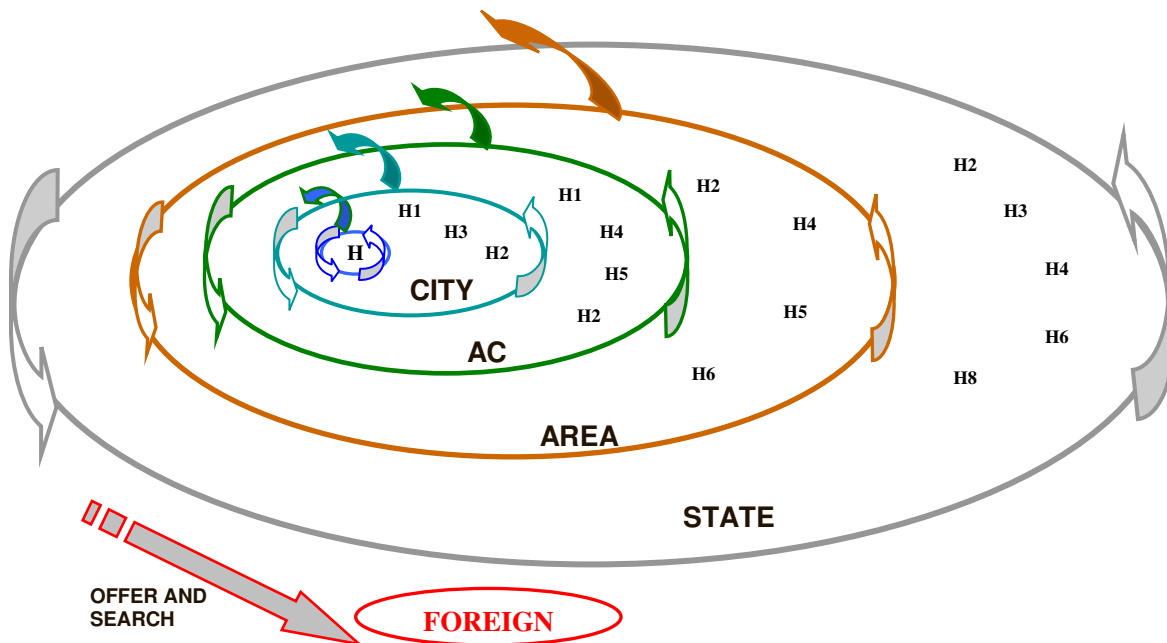


Figure 6 - Geographical Criteria in Spain

In that way Spain is divided into six areas.

These areas born as a consensus among the regional, and national coordinators

2.6.1.6. Allocation Rules Application

The Central Office managed and co-ordinates the donation alarms in those situations, which they beforehand presuppose it could be a multi-organ offer or if it takes place in a hospital that hasn't the capacity to carry out an organ removal, or whenever our collaboration is required.

When a hospital co-ordination team detects the existence of a potential donor, they should inform the central ONT office QUITAR.

We record a donor's data dossier for each case, including a incident sheet used to record all the steps being taken and the time when each of them occurs

We began the search for recipients. This search is made following the allocation criteria looking for the Efficiency, Transparency and Credibility of the system.

Our system exists because everybody, transplant teams, patients and general population are sure of that we apply them strictly.

We also have to follow the two groups of allocation criteria: clinical and geographical

Each organ is evaluated separately with reference to the distribution criteria.

If there is an emergency 0 it becomes a national priority. In the rest of the emergencies we have criteria that we strictly applies.

This criteria are reviewed every year and are established by the transplant teams, an ONT representatives, and as well as the geographical official criteria are established in the bosom of the Interregional Council.

When a transplant team accepts an organ, the decision of who is going to be transplanted is taken by them.

2.6.1.7. Allocation Practices Evaluation

▷ The allocation process is reported in an annual activity report. This report describes:

- Number of transplants performed by region, by hospital, by organ, categories of priority, by blood group, by sex, by age etc..

- Waiting list management: waiting time, deaths in waiting list, number of recipients by organ and by hospital.

2.6.1.8. Waiting List registration Procedure

▷ When a transplant team includes a patient into the waiting list they must inform to the hospital coordinator. This coordinator sends to the ONT the inclusion and we register it in our database. To be registered they must send this information: name and surname, age, sex, region, blood group, weigh, height, primary disease, date of inclusion, type of urgency, and type of transplant.

Once a month each waiting list is checked together the transplant team to be sure that it's updated.

If a recipient is excluded of the waiting list, the procedure is the same, the hospital coordinator send the information to the ONT with the date and the cause of exclusion.

2.6.1.9. Information System

▷ It's used a database called GESONT in which are included all the recipients that has been in a waiting list (except kidney). The register is divided in historical (for death and transplanted or excluded patients) and active (for the patients that are actually in the waiting list).

2.6.2. Allocation system in use: study cases

2.6.2.1. Kidney Allocation

▷ In Spain there are 40 centres that carry out kidney transplant. Each Centre has a waiting list including its own patients and patients who receive treatment in other dialysis Units for which the transplant team is the reference Centre. Kidneys are distributed according to strict local criteria

The ONT collaborates when necessary in exchange agreement providing the infrastructure required. The ONT participate, when it's necessary in the search for recipient for kidneys with special characteristics, usually when a recipient cannot be found on a local waiting list. For example this includes organs with infrequent blood types (B and AB) or with some positive viral markers or low-weight children kidneys

We have also an National Program in which are included hyperimmunized patients and when a typing Unit detect that a kidney may be suitable for one of these patients, then they informs to the ONT that makes the offer and coordinate the transportation for sending it. Also we distribute serum samples exchanges between the Centres included in the National Program

2.6.2.2. Liver Allocation

▷ For liver allocation we follow the procedure described above. It's the same for all the organs except for kidney.

Patients are registered in the centre's waiting list which are recorded at the ONT office. Currently urgent patients have National priority on the waiting list. Liver urgency is defined as a primary graft failure within the first 7 days after the graft or fulminant liver failure of any origin but with a healthy liver prior to the event. In the absence of liver urgencies, livers are offered first locally, then regionally, then to the zone and, if no available recipient can be found, to the rest of the country. Allocation is thus centre oriented, but before the organ is offered it must be stated that there is an available recipient meeting the agreed medical criteria to match donors with recipients (age, size, blood group, etc).

2.6.3. Living Donor and Non-heartbeating donor Organ Allocation

▷ Living donation allocation is managed by the hospitals. They have their own procedures (following the law) and the only thing we manage is that the recipient must be included into the waiting list.

Non-heartbeating donor organ allocation is managed as the heart beating donor allocation. The only difference is that not all the transplant teams accept these organs.

2.6.4. Summary and Perspectives for the current allocation system

▷ The allocation system is always under evaluation. Each year is evaluated and changed. Now some transplant teams are working in a scoring system for hospital liver allocation. There is a pilot experience to design a liver allocation system inside the local waiting list using MELD and time in the waiting list.

2.7. Organ Allocation in UK

2.7.1. Aims, General Principles and Organization

2.7.1.1. *Historical and legal context*

▷ The only Special Health Authority within the National Health Service (NHS) with a UK-wide remit, UK Transplant's key role is to ensure that donated organs are matched and allocated in a fair and unbiased way. UK Transplant are directly accountable to health ministers in Scotland, Wales and Northern Ireland and to Parliament through the department of health in England. The Authority was originally established in 1991 as the UK Transplant Support Service Authority (UKTSSA). In July 2000, UK Transplant was formed with a new, extended remit to increase organ donation rates. With effect from 1 October 2005 the current functions of UK Transplant and the National Blood Service will be taken over by a new organisation NHS Blood and Transplant.

2.7.1.2. *Dealing with Societal concerns*

▷ Public opinion surveys on organ donation in the UK suggest that 90% are in favour of donation. This is not borne out in practice as approximately 40% of relatives approached about organ donation refuse. Some people are not sure whether their religion would prevent them from agreeing to donate their organs after death – yet all the major religions in the UK support the principles of organ donation and transplantation. Various leaflets have been written with the support of religious leaders to promote organ donation.

The Organ Donor Register is a nationwide confidential list of people who are willing to be donors if the time ever comes. The list contains over 12 million names, representing 20% of the UK population.

2.7.1.3. *Allocation Policy Definition and Improvement*

▷ Rules for allocating organs are determined by the medical profession in consultation with other health professionals, the Department of Health and specialist advisory groups.

UK Transplant's organ specific advisory groups propose and agree changes to allocation schemes. Major changes are discussed and agreed by a meeting of all transplant unit Directors, a meeting of the Board of UKT and by the health departments of the relevant countries.

There is a UK Transplant Patient Advisory Group and patient representation on each of UKT's organ specific advisory groups.

2.7.1.4. *Allocation system objectives*

▷ The advisory groups agreed that any changes to the national allocation of organs should be based on rigorous analysis of robust data to determine factors influencing transplant survival in the UK. Further requirements are that allocation schemes should be flexible, easy to understand and apply and should reflect natural justice and common sense.

The main objectives for the kidney allocation scheme are that there should be equity of access to transplant, high priority for patients with extended waiting times, minimisation of cold ischaemia times, HLA matching for patients in whom it is important and inclusion of patient choice.

2.7.1.5. Allocation Principles

▷ The general allocation principles in the UK apply to hearts, lungs, livers, small bowel, kidneys and pancreas and are as follows:

- 1 - Potential recipients must be registered on the national list held by UKT
- 2 - All donors are reported to the UKT Duty Office who manage the offering of organs
- 3 - The Duty Office run the computer allocation algorithms and offer the organs available from each donor to the local transplant team of the selected patients
- 4 - The local transplant team responsible for the selected patients decide whether or not to accept the offer
- 5 - Organs are offered down through the priority order of patients/centres until they are accepted

Note that children and urgent patients are prioritised and that while national allocation schemes operate for all organs, patients local to the donor retrieval are given priority. In addition, kidneys with no nationally identified well-matched recipient may be retained and used according to local allocation procedures.

2.7.1.6. Allocation Rules Application

▷ All donor and patient data are entered and held on an Oracle database. The allocation programs are written in Oracle PL/SQL, following the agreed rule sets. Each program compares the donor's information with that of all patients on the 'active' waiting list (ie excluding those temporarily suspended for personal or medical reasons). The kidney allocation program is patient specific and produces a prioritised list of patients to whom the kidneys should be offered. Liver and cardiothoracic allocation schemes prioritise to a named list of urgent patients and then to a prioritised list of centres for local allocation.

2.7.1.7. Allocation Practices Evaluation

▷ There are regular reports to Advisory Groups evaluating performance of allocation schemes. The schemes are routinely monitored including analysis of waiting times, geographical disparities, HLA matching, survival rates and rate of transplant for HLA-DR homozygous patients, highly sensitised patients and children.

These reports may highlight the need for changes to allocation schemes. Any issues identified are then investigated and proposals for change are subsequently discussed and agreed as appropriate.

2.7.1.8. Waiting List registration Procedure

▷ All patients requiring an organ transplant must be listed with UKT on the national database. Registration details of each patient are completed by the local transplant professionals and sent to UKT (electronically or on paper) to be entered onto the database. The information is stringently validated to ensure that the data are accurate. A patient can only be registered for a particular organ by one centre at any one time.

For kidney patients the registration details include HLA matching requirements for the patient and details of any HLA antigens that are unacceptable to the patient.

2.7.1.9. Information System

▷ The national transplant database held by UK Transplant records details of all actual and potential solid organ donors in the UK, all patients requiring a transplant and all patients who have received a transplant.

There are currently about 6200 patients awaiting a solid organ transplant in the UK and the database also holds information on over 70,000 solid organ transplants dating back to the early 1970's. Follow-up information post-transplant is sought at 3 months and annually after transplant.

All donor and transplant information are entered onto the database by UKT staff based at the office in Bristol. Information relating to patient registration and follow-up may also be sent to UKT on paper for data entry or may be sent electronically over secure NHS links.

The database is relational and contains numerous tables of data. For example, core recipient information is held in a table with associated tables recording information about each transplant the recipient receives and further tables containing follow-up information for each of these transplants etc. Each donor can easily be linked to each of the recipients receiving organs from that donor.

2.7.1.10. Allocation to non residents

▷ In situations where there are no suitable recipients who are entitled to National Health Service (NHS) treatment, that is patients who are not ordinarily resident in the UK, an organ may be allocated may be allocated to a person not entitled to NHS treatment. Typically, these patients will not be ordinarily resident in the UK. In this situation, the transplant procedure would be carried out in the UK, but will be privately funded.

2.7.2. Allocation system in use: study cases

2.7.2.1. Kidney Allocation

The current kidney allocation scheme in the UK operates as follows:

a. Exclusions

▷ Patients are excluded from consideration for a kidney from a particular donor if they:

- Are not on the active kidney transplant waiting list.
- Have a non-identical ABO blood group to the donor. Exceptions –
 - 000 mismatched HSP¹ - blood group compatibility is allowed
 - 000 and favourably matched paediatric patients - O to B, A & B to AB is allowed
 - 000 and favourably matched adult patients – if donor is O, B patients are eligible
- Have unacceptable HLA antigens which are present in the donor.
- Are a paediatric recipient and the donor is over 50 years of age.
- Have a requirement for a particular degree of HLA match that is not achieved.
- Are at a centre where the local criteria for that centre are not met e.g. minimum donor age = 5 years.

¹ HSP – Highly Sensitised Patient (>=85% Panel Reactive Antibodies (PRA)).

Note that Group 2 (ie non NHS entitled) patients are included for consideration after all Group 1 patients.

b. National allocation procedure for adult kidneys

All 000 mismatched kidneys are offered through the national scheme to the most appropriate patients, following the Tier 1 priority order:

Tier 1

Priority is given to HLA-DR homozygous patients only when the donor is HLA-DR homozygous. If the donor is blood group O (ABO-) then priority is given to ABO-O patients then ABO-B patients as shown.

1	paediatric	HSP	HLA-DR homozygous		Local
2	paediatric	HSP	HLA-DR homozygous		national
3	paediatric	HSP	HLA-DR heterozygous		Local
4	paediatric	HSP	HLA-DR heterozygous		national
5	paediatric	non-HSP	HLA-DR homozygous		Local
6	paediatric	non-HSP	HLA-DR homozygous		national
7	paediatric	non-HSP	HLA-DR heterozygous		Local
8	paediatric	non-HSP	HLA-DR heterozygous		national
9	adult	HSP	HLA-DR homozygous		Local
10	adult	HSP	HLA-DR homozygous		national
11	adult	HSP	HLA-DR heterozygous		Local
12	adult	HSP	HLA-DR heterozygous		national
13	adult	non-HSP	HLA-DR homozygous	ABO-O	Local
14	adult	non-HSP	HLA-DR homozygous	ABO-O	national
15	adult	non-HSP	HLA-DR homozygous	ABO-B	Local
16	adult	non-HSP	HLA-DR homozygous	ABO-B	national
17	adult	non-HSP	HLA-DR heterozygous	ABO-O	Local
18	adult	non-HSP	HLA-DR heterozygous	ABO-O	national
19	adult	non-HSP	HLA-DR heterozygous	ABO-B	Local
20	adult	non-HSP	HLA-DR heterozygous	ABO-B	national

Within each of groups 1 to 8, patients are sorted in order of waiting time (high to low).

Within groups 9 to 20, patients are sorted in order of points score (high to low). Points score is described under the heading 'Ties'.

All but four centres are part of a group (or an 'alliance') of two or more geographically close centres sharing a common waiting list of patients. 'Local' patients are those registered at the same centre or within the same alliance as the kidney transplant centre responsible for the donor retrieval.

+Tier 1 Sharing Policy:

When there are 2 '000' mismatched recipients at another unit, both kidneys will be offered to these recipients, provided there are no local '000' mismatched patients at the same or higher priority level.

Remaining favourably matched kidneys (100, 010, 110) will be allocated nationally following the Tier 2 priority order:

Tier 2

Priority is given to HLA-DR homozygous patients only when the donor is HLA-DR homozygous. If the donor is blood group O (ABO-) then priority is given to ABO-O patients then ABO-B patients as shown.

1	paediatric	HLA-DR homozygous		local
2	paediatric	HLA-DR homozygous		national
3	paediatric	HLA-DR heterozygous		local
4	paediatric	HLA-DR heterozygous		national
5	adult	HLA-DR homozygous	ABO-O	local
6	adult	HLA-DR homozygous	ABO-O	national
7	adult	HLA-DR homozygous	ABO-B	local
8	adult	HLA-DR homozygous	ABO-B	national
9	adult	HLA-DR heterozygous	ABO-O	local
10	adult	HLA-DR heterozygous	ABO-O	national
11	adult	HLA-DR heterozygous	ABO-B	local
12	adult	HLA-DR heterozygous	ABO-B	national

Within each of groups 1 to 4, patients are sorted in order of waiting time (high to low).

Within groups 5 to 12, patients are sorted in order of points score (high to low).

+Tier 2 Sharing Policy:

One kidney will be made available for national allocation when there are no patients in either Tier 1 or Tier 2 on the local waiting list.

Tier 3

Non-favourably matched kidneys may be retained for local use according to local policy. Medical emergencies are catered for by local kidney allocation.

+Tier 3 Sharing Policy:

When no favourably matched patients are found nationally or locally, then kidneys may be retained for local use. If the local unit is unable to use one or both kidneys, they should be offered to other centres through UKT to the unit with the highest balance of exchange.

Ties

If two or more equally matched adult patients are found at the same priority level at Tier 1 or Tier 2, the allocation will be in the order of the individuals' points scores based on the following factors:

Factor	Points	Purpose
Recipient age	1 to 10 old to young	To favour younger patients
Donor-recipient age difference	1 to 10 large to small	To avoid large age differences
Waiting time	0.5 to 5 short to long	To favour longest waiting patients
Matchability	1 to 10 large to small	To favour patients with rare HLA types
Sensitisation	0.5 to 3 high to low	To favour low residual sensitisation and avoid positive crossmatches
Balance of Exchange	1 to 10 low to high	To control balance of exchange between centres

c. Allocation procedure for paediatric donor kidneys

Kidneys from paediatric donors are offered in a similar manner. However, priority is given to all paediatric patients before organs are offered to adult patients.

Paediatric patients are defined as either less than 18 years of age or registered as requiring a paediatric organ.

2.7.2.2. Liver Allocation

▷ UK and Republic of Ireland Liver Allocation Scheme

a. Adult donor organs

Adult super-urgent liver patients receive priority in the offering sequence from any blood group compatible donor. Super-urgent patients registered at the local centre take priority, but if there are none, super-urgent patients at other centres are prioritised according to their waiting time. To be registered on the Super-urgent Liver Scheme, the clinical condition of patients should accord with any one of ten indications for registration. If there are no suitable adult super-urgent patients registered, offers are made to blood group compatible adult elective (ie non-super-urgent) patients at the local (retrieving) centre and then to other liver transplant centres in the UK and Republic of Ireland (according to centre 'balance of exchange' - exported livers minus imported livers).

However, blood group O donors for adult elective patients are offered in the following priority order:

- Blood group O or B patients locally
- Blood group O or B patients nationally (according to 'balance of exchange')
- Blood group A or AB patients locally
- Blood group A or AB patients nationally (according to 'balance of exchange').

b. Paediatric donor organs

Paediatric patients are defined as patients aged 16 years or under at the time of registration. In addition, a centre may register a small adult patient weighing 45kgs or less as a paediatric patient at their discretion. Paediatric donor organs are offered to paediatric patients first before being offered to adult patients.

Paediatric super-urgent liver patients receive priority in the offering sequence from all blood group compatible donors. Only patients under the age of 2 years at the time of registration on the super-urgent list can be considered for ABO incompatible livers.

Paediatric elective patients receive priority after super-urgent paediatric patients. Offers are made to blood group compatible elective paediatric patients at the local (retrieving) centre and then to other liver transplant centres in the UK and Republic of Ireland (according to 'balance of exchange') for their elective paediatric patients. For elective paediatric patients, blood group O donors are offered in the same priority order as stated above for elective adult patients.

Lastly, if the paediatric donor organ has not been placed at a paediatric centre, it is then offered to the adult centres.

c. Livers from non-heart beating and domino donors

Livers from non-heartbeating and domino donors are usually retained by the local centre but may be offered direct to another centre.

2.7.3. Living Donor and Non-heartbeating donor Organ Allocation

All transplant centres in the UK perform living donor transplants. Currently, 74% of living donor transplants are from genetically related donors, but increasingly, living unrelated donor transplants are carried out. In the latest year (April 2004 - March 2005), there were 314 related living donor transplants in the UK and 113 unrelated donor transplants.

There is a new Human Tissue Act in the UK, which will give the potential for paired donation from 2006. This will enable living donor transplants to be offered to those pairs who are blood group incompatible or where sensitisation prevents transplantation.

Most UK transplant centres now retrieve organs from non-heartbeating donors. These may be retained by the centre, to minimise cold ischaemia time, to transplant in a patient of their choice. This programme has increased rapidly in the UK in the last few years and in the latest year (April 2004 - March 2005) there were 143 non-heartbeating donor kidney transplants.

2.7.4. Summary and Perspectives for the current allocation system

▷ While the current national kidney allocation scheme for kidneys from heartbeating deceased donors, introduced in 1998, has been successful in increasing the degree of HLA matching achieved, it is now clear that the scheme is associated with some inequity of access to transplantation for patients. Among other factors, this inequity is related to the location of the patient's transplant centre, the patient's blood group and their tissue type. Patients in some centres were found to have a median waiting time to transplant of one year, while patients in other centres waited 3 or 4 years on average. These inequities were shown through regular review of the allocation scheme.

A review of current evidence was therefore undertaken to inform discussion about revisions to the allocation scheme. This involved a rigorous analysis of factors influencing the outcome of transplants performed in 1995-2001. Specific objectives for a revised scheme were agreed after wide discussion. These include optimal HLA matching for patients for whom it is most relevant, reductions in the waiting time for patients who currently wait longest, and greater equity of access to transplantation for all patients. The aim was that these must all be achieved with no change to the current success rates for both patient and graft survival and that abrupt short-term changes to transplant activity within individual transplant units should be minimised.

A large number of alternative allocation schemes were considered, and their likely impact investigated using simulation. A proposed new algorithm is now in discussion. The new scheme will be phased in over a number of years in order to minimise abrupt changes in transplant activity for individual centres. It will give overall priority for 000 HLA-A, B, DR mismatched patients but most patients will be prioritised according to a points score. This score is based on waiting time, age and HLA match (linked), donor-recipient age difference, HLA-B and DR homozygosity and blood group match. There are also additional points for patients in the same geographical area as the donor. The new scheme will be introduced in 2006.

The liver allocation scheme in the UK is also under review.

2.8. Comparative Summary Tables

▷ The first table compares the general characteristics allocations systems in the Alliance-O participating countries.

Two other tables compare allocation criteria in use for kidney allocation (recipient related criteria and donor/recipient matching related criteria).

	France	Germany	Hungary	Italy	Portugal	Spain	UK
Institution	Agence de la biomédecine, former Etablissement français des Greffes (EiG)	Deutsche Stiftung Organtransplantation (DSO)	Hungary Transplant (HT)	Centro Nazionale Trapianti (CNT)	Organizaçao Portuguesa de Transplantaçao (OPT)	Organizacion Nacional de Transplantes (CENATMER)	UK Transplant (UKT)
Law	Bioethical Laws Ministerial Decrees	German transplantation act	Act on Health 1997	Law 91, 04-01-99	Decree-Law 553/76 , Law 12/93, Decree-Law 244/94	Transplant Law (1979) Royal Decrees (1996, 1999)	Human Tissue Act
Societal concerns	Public consultation committee (1995) Patient's association representatives in the agency's Orientation Council No public opinion poll	Legislative Procedure No public opinion poll	Organ Specific Waiting List Committees	through Consulta National, patient associations representatives	Legislative Procedure No public opinion poll	Public Information	Patient representatives on organ specific advisory committees
Allocation system revision	Organ Specific advisory committees Major change implies change in ministerial decree	German Medical Association ET specific committees	Organ Specific Waiting List Committees + Hungarotransplant + Transplantation and Nephrology Society	Regional and Inter-regional agreements	Organ Allocation Advisory Committee for proposal of changes	Except kidney allocation: Interregional Committee Only professionals No public nor patient associations Annual meetings	Organ Specific advisory committees
Allocation documentation	Ministerial decree Allocation procedures guide	German Medical Association Guidelines ET manual	Official guide to be published	Region	OPT Guidelines for kidney and recommendations for other organs	Consensus document (1992) on geographical criteria Inter-professional agreement for clinical criteria	Published 'Oragn sharing principles' agreed by all transplant centers
Objectives	Formally defined by decree Justice, Equity, Medical ethics Improve quality of health Take into account emergency and low access to Tx Optimise graft utilization	Formally defined by law Equality of treatment Patient oriented Transparent Objective medical criteria	Mixture of patient and centre oriented criteria, under revision	No formal definition of objectives Mixture of patient and centre oriented criteria	Compromise between: - equity - efficacy (best donor-recipient matching) - logistics Addressing patients with low probability of access to a graft	Mainly geographical distribution + general donor-recipient matching criteria + urgency + local agreements	Defined by advisory committees. Compromise between equity, efficacy and logistics
Allocation Implementation and Coordination	6 Regional Allocation Offices + 1 national Allocation office	1 supra-national Allocation Office by Eurotransplant (ET)	Nationally, kidneys regionally also	3 interregional Allocation offices	5 Regional Coordination and Procurement Offices for Transplantation Lusotransplant for kidney Regional coordination for other organs	1 national coordination for all organs except kidney 6 allocation areas	UKT co-ordinates national and local allocation schemes
Information system	CRISTAL: - for all organs - donor database - waiting lists - allocation - follow-up	ENIS (ET) + ISYS (DSO) - for all organs - donor database - waiting lists - allocation - no follow up	Only for kidneys at HLA Lab.	For all organs: CIT -donor database - waiting lists - allocation - follow-up	Lusotransplante Database for kidneys only - donor database - kidney waiting list - allocation - no follow-up Database in progress for other organs	GESONT - donor database - all waiting lists except kidney - allocation - follow-up of liver, in progress for lung and heart	UKT national database : - for all organs - donor database - waiting lists - allocation - follow-up
National registration systems	National WL for all organs, single centre registration	National WL for all organs, single centre registration	National WL for all organs, single centre registration	Regional and centre waiting lists multiple centre registration Paediatric National WL	Kidney only, in progress for liver & heart	National WL for all organs except Kidney (centre WL)	All organs
General medical specifications	+	+	+	+ at regional level	+	+	+
Patient oriented Nationwide national and regional priorities	+	+(supranational)	Mixed	+	+	+ for urgency, rare blood groups or sensitised patients with payback	+
Regional or inter centre specific allocation schemes -with payback -without payback	+ + +	-	Without rigid payback rules	+	-	Geographical distribution + payback for prioritised patients	+ implemented within UKT database with payback points in the score
Local Priority in absence of regional and national priority	+ it is the main allocation determinant	-	+	+	+	+ it is the main allocation determinant	+
Geographical Distribution In absence of local or regional candidate	+		exceptional	+	+	unfrequent	One kidney local, One national
Patient based allocation scoring system	In experimentation for kidney Scheduled for liver	+	+	-	+ for kidney	no	+
Evaluation of allocation policies	+	+	By waiting list committees Act on Health 1997	-	For kidney allocation	+ except kidney allocation	+

Kidney

1 - Allocation Criteria related to Recipient's Condition

	Social Status	Ethnicity	Non Residency	Initial Disease & Risk Factors	Urgency	Post-Transplant Prognosis	HLA-Matchability	HLA-Sensitisation	Age	ABO	Dialysis Duration	WL time	Nbr Tx	Other
France	-	-	-	-	+	-	+	+	+	+	-	+/-	-	
Germany	-	-	+	-	+	-	+	+	+	+	+	-	-	
Hungary	-	-	-	-	+	-	+	+	+	+	+	+	-	
Italy at least one region using the criterion all regions are using the criterion	-	-		-	+									
Portugal	-	-	+	-	+	-	-	+	+	+	-	+	+	
Spain				at the appreciation of centres			+	+	-	+		at the appreciation of centres		
UK	-	-	+	-	+ (local)	-	+	+	+	+	-	+	-	

Kidney**2 - Allocation criteria related to Donor/Recipient Matching**

	Age	ABO	Morphology	Risk Factors	HLA	Other
France	+	+	-	-	+	Cross-match negativity not mandatory but widely achieved
Germany	-	+	-	-	+	
Hungary	+	+	+	-	+	CMV
Italy						
Portugal	-	+	-	-	+	Cross-match negativity required
Spain		+	According to center			
UK	+	+	-	-	+	

2.9. Discussion

▷ The first result of this comparative study is that a wide range of allocation systems, procedures, protocols and allocation criteria have been instituted in each country. This diversity may result from variations in cultural and historical contexts. The place given to the "medical decision", to the so-called "local priority", to the geographical distribution of organs, to "organ sharing" and to evidence-based medicine in the government of allocation systems are likely to be the determinants of such variations. The place given to the societal concerns in the development of allocation system is another determinant. Variations are also due to various stages of development in transplantation organization and to the number of transplant centres in each country: when there are few transplant centres, logistical constraints are less important and the allocation decision remains more naturally a medical decision. This is the case for example in Hungary for liver transplantation.

▷ Individual medical decisions plays a central role in Spain for kidney allocation: the waiting lists are managed at centre level; the interference with medical decision is limited to general principles (ABO matching, general ethical statements); there is no national nor regional waiting list; only transplanted patients are registered in the national database. If one considers that the allocation of an organ is the selection of a given patient and the exclusion of the other potential recipients, then the evaluation of organ allocation procedures requires data to be collected on every patient registered on waiting lists. Otherwise, the measure of time spent on the waiting list only for patients that are transplanted is biased; it is not possible to study the problem of the long waiting patients; it is not possible to investigate geographical and social discrepancies in access to transplantation; last, it is not possible to build studies comparing patients remaining on dialysis versus those who are transplanted in terms of individual benefit judged on survival or quality of life. The place of individual patient-doctor medical decision is minimal in Germany and the societal specifications for patient selection is maximal: very precise and operative statements have been defined to drive not only the allocation decision but also the registration on the waiting list: equity is not only a general intention, it is also a specification for the allocation scoring system. The decision that the allocation system must be patient-based is a crucial step in organ allocation. Such an approach permits to widening organ sharing to a supra-national level, provided that a minimal equilibrium in balance of organ exchange is organised.

▷ The place given to the so-called "local" or "geographical" priority also varies from one country to another. In Spain, it is the main and concrete basis of the allocation system. In UK and in France, the kidney allocation systems are aimed at optimising HLA-matching and giving priority for highly sensitised patients. In absence of well-matched patients, the allocation remains local then geographical. In both countries, the emerging issue is that some patients do have poor access to transplantation related to the location of their transplant centre, their blood group, their tissue type and their sensitisation. Two main paths are followed in planning the organ allocation system. It can be patient oriented which is the case for the USA and some European countries, or centre oriented, as in other European countries, including Spain. Both can have advantages and disadvantages []. Furthermore, different strategies to manage the growing waiting lists, mainly for kidneys, are being proposed []. However, one must keep in mind that the first and last steps in the chain, respectively are the acceptance of the patient as a candidate for transplantation and a final decision about using or not using a given organ for a given patient. Both these decisions remain the responsibility of physicians.

▷ In a given country, the balance between the distribution of transplant units, the distribution of patients among the waiting lists and the efficacy of organ procurement can also affect organ allocation policy. In France for example, there are contradictions between the distribution of liver transplant units which is concentrated in Paris, the allocation of retrieved livers which is mainly geographical and the registration on the waiting list which is free, e.g. not related to the regional organ procurement activity.

▷ Organ allocation is usually a matter of consensus between transplant teams, organizational bodies, health authorities, patients associations, etc. Independently of the chosen model, all systems are based on two main categories of factors. In one category one can list medical criteria such as severity of the liver failure, ABO group, HLA matching, primary disease etc. In the other category of non-medical criteria one can list geographic distances or available resources, while some factors such as waiting time or ischemic time can be listed in both categories. The Committee of Ministers of the Council of Europe, in considering that the organ transplantation is severely restricted by the availability of organs for transplantation, underlined the need for setting up a public system with an officially recognized network of transplant centres and officially recognized registers of patients on the waiting list. The Committee also recommended such a system to periodically provide complete information for both health professionals and the general public. This information should include criteria for registration and allocation, figures and flows of registered patients and average waiting time for the different groups of patients. The system must ensure, as far as possible, that no group of patients waits longer than another group [].

▷ The use of a scoring system is an efficient way to implement a patient based allocation system. It is also an efficient way to maintain competition between categories of patients that is not possible with an allocation system applying sequentially ordered priorities. Categories of priority that can be ordered with no overlap are few. Priorities given in France for liver-kidney or pancreas-kidney transplantation for example appeared excessive, as patients were not in competition with kidney and liver transplantation candidates. For a long time and in many countries, a priority is given for patients with a fulminant hepatitis or for patients who require an early re-transplantation. Because such patients have a very short life expectancy without transplantation, this priority has the highest level; it is generally nationwide: this is the case in Italy, Portugal, Spain and the UK. It is a supranational priority for Germany and ET participating countries, and for France and the Swiss who share the same liver "super-urgency" priority. For other patients, the severity of the hepatic insufficiency judged on a severity index such as the MELD score appears now as a relevant criterion to prioritise the sickest patients and classify together liver cirrhosis and liver cancer [].

A scoring system can be used at local level as a decision support system.

▷ Indeed, organ allocation is a set of compromises. Intrinsically, it is a compromise between conflicting objectives: equity, efficacy, justice and logistical feasibility. It is also a compromise between medical knowledge and societal concerns. Extrinsically, its implementation results from a compromise between the conflicting interests of transplant centres that are in competition and public health authorities that are in charge of the allocation system. Any change in the allocation system that results in abrupt and/or huge changes in the activity of transplant centres, even if it significantly improves the overall efficacy and equity, will be difficult. In such a situation, the allocation system may also become a compromise between the public health authority in charge of the revision of the allocation system and the political authorities, thus a compromise between healthcare improvement and social peace. The compromises found about allocation

procedures and the way to implement them, are influenced by the consequences on centre's activity. The complexity of the allocation problem requires close interaction between professionals. The fact that abrupt or significant variations in activities of transplant centres jeopardize the scope of changes that can be expected from consensus based revision process is a complication in the organ allocation revision procedure.

In all countries, the evaluation of results gains a central place within the allocation revision process. Indeed the definition of the objectives of the allocation system should comprise a formal definition of evaluation end-points. In doing this, European countries hope to meet objectives, and use the diversity of allocation systems to find the best organisations. If by chance, the regional disparities in organs retrieved are proportional to the variations in the epidemiology of end stage organ diseases, then national organ allocation is not required to balance regional discrepancies in the purpose of achieving equity, or at least minimizing inequity.

The regionalisation of health care must be taken into consideration. It does not preclude organ sharing. But financial considerations, especially in renal replacement therapies (dialysis versus transplantation), may require changes in allocation systems with a redistribution of dialysis availability.

▷ Categorizing organ allocation decision making:

Organ allocation can be a **“local and extemporaneous” medical decision** when physician decides according to his “personal” knowledge and to his “personal” experience who will receive the retrieved organ among a variety of patients confined to his own waiting list. This personal and local medical decision is generally based on medical science and conform to established medical facts. It remains “personal” because it combines and weights extemporaneously established allocation criteria in different manner and can take into account conjunctural surrogate criteria. Such an approach of allocation decision making has advantages and weaknesses, pros and contras. Clinicians naturally prefer that kind of approach, which is also historically the first step in organ allocation policies. It is flexible, adaptative and clinically sound: the clinician knows his patients. It is likely to be non determinist in the sense that the same waiting list and the same organ can lead to various decision over time. Contras will object that such an approach is not transparent and may be biased with unacceptable surrogate criterion. Such objections can be removed or controlled through an evaluation of allocation practices. Furthermore, the average centre allocation practices can be optimised through evaluation.

Organ allocation can also be a **“local and standardized” medical decision** when clinician applies predefined and published criteria to select among his local waiting list the patient who will be offered the retrieved organ. Such an approach is more determinist, reproducible and transparent. It is an evolution toward standardisation of allocation practices. It can be a computer assisted medical decision but still remaining confined to a local waiting list.

Local decision making approaches are relevant until the optimisation of the allocation of retrieved organs requires to expose limited subgroups of patients spread out various local waiting lists to a wide variety of donors (patients with poor access to transplantation due to short life expectancy or to limited amount of suitable donors).

Such a requirement leads to introduce some **“remote” decision** within the allocation system to deal with predefined prioritized patients categories. For these patients, allocation decision makers are outside the transplant centres. They apply predefined and well-established selection criteria. The registration of prioritised patients on shared public regional, national or supra-national waiting lists becomes necessary, even if prioritised patients are a few. In absence of prioritized patient, the decision is then usually local.

As soon as the optimisation of the allocation of retrieved organs requires to expose a wide variety of patients to a wide variety of donors, the allocation becomes a “**systematized and remote**” **medical decision**.

Such an approach is relevant to optimise donor-recipient multivariate matching or to optimise a “just in time” allocation of vital organs (heart, liver). It has also pros and contras. Its is the only way to get a multivariate and/or temporal optimisation of organ utilization. It is transparent and determinist. Because it is systematized, it has to be evaluated to guarantee there are no bias or unwanted side -effects. Contras will say that it is no more a medical decision but a computer decision.

All European allocation systems started with “local and standardized” decision making. Most of them introduced some “remote” decision to deal with patients requiring a regional or national priority to access to transplantation.

Only countries working with ET allocation system rely organ allocation on a “systematized and remote” medical decision making for all organs.

3. Best Practices for Organ Allocation in Europe

3.1. Introduction

▷ This second part of the document attempts to promote Quality Assurance for organ allocation through a set of statements and proposals for best practices. The difficulty here is that our purpose can't be limited to "write what we do" and "do what we write".

The main purpose is to do things that make sense; this means to have a critical and global view point about our allocations systems and allocation policies. Such a purpose requires a feed back from the results of evaluation studies into the allocation policy making cycle.

An example of critical view point, coming from "intention to treat" or comparative studies [Poynard99, Deng00, Merion05], is that an allocation preference for patients with the best survival after transplantation can lead to transplant the less sickest patients which also are prone to be patients with no or low individual benefit of transplantation. For liver or heart transplantation, the less sickest patients have the best post transplant survival but a higher risk to dye getting a transplantation than remaining on the waiting list. For liver transplantation, Merion [Merion05] showed that the MELD score can be used to predict patients with no individual benefit from transplantation. Below a Meld score of 15, patient have a higher risk of death in being transplanted than remaining on the waiting list. Below this cut off are the "futile transplantations". In the case of liver transplantation, the sickest patients still have an individual benefit to be transplanted: there is no "too late transplantation" regarding this individual benefit criterion. Conversely, for other organ transplantation, one can have a degradation of individual benefit for very sick patients, the covariate adjusted hazard ratio of death defining "too late transplantations" above another cut-off. This result has been shown for heart transplantation by Deng [], although it did not meet acceptance among the heart transplantation community. Between these two cut-offs is the "therapeutic zone" of transplantation (figure 1).

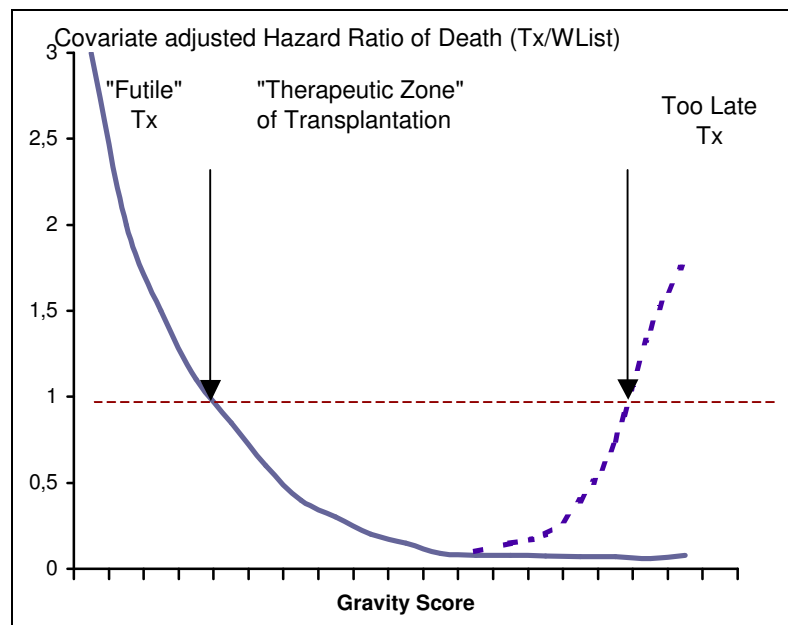


Figure 7 - Individual Benefit Paradigm

An example of global view point is that any changes in kidney allocation that result in abrupt variations in transplant activity in some region can require to redistribute dialysis health offer. Thus a global public health approach is to coordinate kidney allocations changes and dialysis regulation policies if there are huge regional discrepancies in organ retrieval efficacy and/or incidence of renal diseases.

The following section comprises general statements and recommendations for best practices. More detailed allocation processes description will be part of WP4. More detailed allocation evaluation statements will be part of WP5. More detailed statements for living donation and ethical issues will be found in WP7.

3.2. Statements and Recommendations

▷ This section is a proposal for general statements and recommendations that could be shared among European Countries.

3.2.1. Statement 1: Organ Allocation in the Transplantation Process

▷ The definition of a policy for Organ Allocation is initiated by the necessity to supply a retrieved organ to a transplant candidate in a context of organ shortage. Organ Allocation Organisation is thus a concern for Public Health. An Organ allocation occurrence is triggered by the detection of a donor. It takes place before and during organ retrieval; it is achieved by the transplantation of retrieved organs to the selected recipients.

3.2.2. Statement 2: Societal Concerns in Organ Allocation

▷ Decision-making in transplantation medicine cannot rely on the sole doctors for many questions that define societal concern. We study here more specifically those that are related to organ allocation.

The allocation of an organ results in a decision with a positive individual result: the provision of a vital resource to a patient with an end-stage disease. But the selection of a given patient for transplantation means the exclusion of other patients, still awaiting transplantation and thus exposed to the hazards of their end-stage disease. Among transplantation medicine societal concerns (retrieval of organs in cadavers, definition of Brain Death), the scarcity of organs and the discriminating aspect of organ allocation are more specific to the Allocation Process.

3.2.3. Statement 3: *Optimizing individual benefit from transplantation rather than the sole post-transplant results*

▷ One of the prominent objectives is to optimise the use of retrieved organs. An emerging end-point to evaluate this objective is to take into account the individual benefit of transplantation. One pitfall to avoid is to give too much importance to the sole post-transplantation results.

3.2.4. Recommendation 1: Defining objectives with valuable end-points

▷ Organ allocation policies occupy a central place between the need and supply, requiring transparency, guarantee in term of justice, equity and efficiency. National authorities in charge of organ allocation among EU countries should carefully organise the definition of allocation objectives, the definition of allocation methods and the definition of allocation evaluation. They should set up relevant groups of designers tacking into account the multiple stakes involved and organize interactions between designers groups. General Objectives should be associated with relevant valuable end-points and evaluation procedures.

3.2.5. Recommendation 2: Method Specification and Implementation

▷ National authorities in charge of organ allocation among EU countries should implement Organ Allocation within a transparent, objective, fair and efficient allocation system. Detailed Functional and Methodological Specifications should be elaborated according to the general allocation Objectives.

3.2.6. Recommendation 3: Sharing Methods

▷ The definition of allocation objectives at national levels do not preclude the use of Allocation Methods shared among European countries. National Institutions in charge of Organ allocation in EU should organize a continuous collaboration to formalize a common readable description of their allocation procedures, examine and compare their results, the specificity of their allocation organizations. Allocation Methods realizations are performed through information systems. European Institutions in charge of Organ Allocation should collaborate at European level to promote interoperability and standardization of their allocation systems.

3.2.7. Recommendation 4: Organ Allocation evaluation

▷ National Authorities in EU should carefully organise the evaluation of their allocation systems.

▷ This point will be developed in WP5.

3.2.8. Recommendation 5: Quality Assurance

▷ National Authorities in EU should organise the quality assurance of their allocation systems. This point will be developed in WP4

3.2.9. Recommendation 6: Changing Allocation Policies

▷ According to evaluation results and new medical science facts, organ allocation systems must be improved and adapted through the time. To facilitate this work and the interactions with professionals, scientific survey and simulation tools are recommended.