



Alliance-O Work Package 3 - Deliverable #2

# **Specification of a Common Simulation Tool for Organ Allocation**



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# 1. Introduction

## ▷ Organ allocation - a moving and open issue:

Progress in surgical procedures and immunosuppressive therapies brought about an increased need for organs to transplant [1]. Despite efforts and improvements in many countries, organ retrieval still fails to cover an always-increasing demand [2]. In such a context, organ allocation systems are an essential interface between the supply and the demand [3]. According to medical science, organ allocation systems conform to general immunological and morphological matching principles [4]. They also usually take into account specific conditions related to the recipient such as emergency or low access to Transplantation [5]. They usually strike an empirical compromise between equity, justice, efficacy, practicability, quality of post-transplant results and technical constraints related to organ retrieval and preservation [6].

The survey of allocation systems among Alliance-O partners [WP3-Deliverable #1] showed us that this compromise led to the implementation of a wide range of allocation systems from a country to another. 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. Individual medical decision plays a central role in some countries: the waiting lists are managed at centre level; the interference with medical decision is limited to general principles (ABO matching, general ethical statements). The place of individual medical decision is minimal other countries where very precise and operative statements have been defined to drive the allocation decision and the registration on the waiting list. The evolution toward a patient-based allocation system is a crucial step in organ allocation. In most countries, allocation system is a mixture of nationwide allocation priorities and general donor-recipient matching principles, combined to regional allocation procedures and local allocation practices that represent the foremost - and transplant teams favourite - allocation modality.

Thus, organ allocation has no unique or definitive solution: it remains an open and moving issue. More issues will arise in the future, as medical science, the needs of population and its demographics change [7].

▷ **The need for simulation:**

Organ allocation is poorly accessible to prospective experimental study: for ethical and practical reasons, it is difficult to randomize patients between allocation regimens. In countries which register data on the donors, on the recipients and on the allocation process, the allocation policy is usually evaluated through cyclic observational studies. Such studies are prone to motivate changes in allocation policies when results demonstrate odds results or adverse side effects. Observational studies can indeed motivate changes, but they are of limited help to bring about deep modifications in allocation policies due to the fear of unpredicted adverse consequences.

Another trigger for changes in Allocation policies is the publication of new bioclinical facts [8] or the emergence of a new allocation paradigm that matter for organ allocation, for example: the shift from best post transplant results to best individual benefit as utilitarian allocation criterion [9, 10].

Simulation is a relevant mean in such a situation to compare various allocation schemes and to forecast the behaviour of the new system according to the tuning of its parameters. It is an alternative to experimentation because this latter is not available in our context.

Last, organ allocation systems define complex socio-technical systems and are in many aspects a matter for social economy: they have to deal with conflicting interests and contradictory objectives. Due to the scarcity of organs for transplantation and to the competition between transplantation centres to provide the best organs for their patients, any change in organ allocation policy remains a sensitive issue in public health decision-making [11]. Simulation in such a context has the interest to introduce a more distant and abstract approach of the allocation problematic. An interactive design of the new allocation scheme with professionals and patients representatives also facilitate discussions and thus the integration of contradictory points of view.

Simulation implies to formalise allocation process and sub-processes and to define evaluation end-points. It permits to compare and to evaluate the impact of various allocation schemes and their acceptability prior to the implementation of a new system. Thus, it is likely to promote an evidence-based debate [12].

## 2. General Functional Specifications

▷ National Institutions in charge of Organ allocation in EU have periodically to promote changes in their allocation schemes. Such changes can be triggered by the results of the evaluation of allocation procedures. They are sometimes motivated by new law, new biomedical facts or by changes in organisation. Simulation in the context of organ allocation has been shown to be a useful mean to promote evidence-based changes. It is an alternative to experimentation that is not available in this context. The building of a common simulation tool shared by National Institutions in charge of Organ allocation in EU gives the opportunity to capitalise knowledge and experience around organ allocation. The aim of this paper is to provide functional specifications that might lead to the implementation of a European Organ Allocation Simulation Tools (EO-AST). In a first step, it will help to coordinate national initiatives.

A simulation tool for organ allocation is wanted as a mean to build interactively flexible and parametric allocation schemes, to compare various allocation schemes, including actual ones, according to a set of predefined allocation end-points and to forecast the behaviour of new allocation schemes before their implementation.

Such a tool is required to provide at least manual tuning facilities enabling to reach stepwise and empirically targeted allocation end-points, at best algorithms enabling to automatically optimise allocation scheme parameters according to a predefined "cost-function" derived from the set of targeted allocation end-points.

Tuning and Reporting functionalities are required to facilitate interactions with end-users and deciders. The incremental elaboration of a new allocation scheme has to be interactive with transplant professionals and specific advisory groups that might comprise patients and society representatives.

Relevant statistical and modelling libraries are required.

Such a shared Simulation Tool is required to be disseminated among Institutions in charge of Organ allocation. Thus, standardization of Input and Output files and libraries is needed. The possible use of existing open-source development environment (such as Eclipse), database servers (such as MySQL) and statistical resources (such as R) will be considered prior to any implementation.

The Simulation tool is required to be generic enough to deal with various organs and allocation approaches. It will comprise a set of components described in the next section.

## 3. Simulation Tool Components

▷ The process of organ allocation itself is related to other processes that are to integrate in a comprehensive simulation model (registration, outcomes and movements on waiting lists, donor selection, organ acceptance, post transplant outcome).

The comprehensive allocation simulation model and its components are summarized in Figure 1. It comprises a Donor Component, a Recipient Component, an Allocation Component and a Post-transplant Outcome Component. The Simulation Tool is also associated to an Evaluation Module.

Dependencies between components can be single-way: the output of a component is the input or part of the input to a next component. Dependencies between components can be more complex when feed-back from latter components are taken into account in a previous component: for example, transplanted patients which are the output of the Allocation Component and patients re-listed for graft loss which are one of the output of the Post-transplant Outcome Component can be taken into account by the Recipient Component. A comprehensive simulation model could also integrate a feed back from the regional transplant activity level - an output of the Allocation Component, onto the Donor Component.

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### 3.1. The Donor Component:

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A comprehensive Donor Component is due to mimic the sub-processes leading to the proposition of a Donor for organ retrieval. The donor component is required to provide facilities:

- to integrate historical actual data describing donors retrieved during a specified period of time in a specified geographical area, according to a standard file format;
- to generate notional donors (a n-uple of donors characteristics) using Monte-Carlo and re-sampling techniques (including re-ordering of historical data), according to epidemiological/demographic specifications provided inter-actively by the expert-user;
- to integrate pre-established models predicting trends in crucial donors characteristics (aging, extended pool of marginal donors).

Functions and models used for simulations will be organised in re-usable libraries.

A chronicle of donors proposed for organ retrieval based on Historical Data or based on generated Data is the heart the Donor Component that acts as a timer synchronizing the Allocation Component and the Recipient Component on each step of time  $t$  where a donor is virtually proposed for Organ Retrieval.

The output of the Donor Component is an individual donor proposed for retrieval at time  $t$ . It provides a first input to the Allocation Component. The cohort of donor proposed for organ retrieval will be an input to the Evaluation Module.

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### 3.2. The Recipient Component:

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The recipient component provides the second input to the Allocation Component. It is required provide facilities:

- to integrate historical actual data describing the waiting list at the beginning of a user-specified period of time in a geographical area (file 1) and the patients registered on the waiting list during the same period of time in the same area (file 2), according to standard file formats,
- to generate notional recipients (a  $n$ -uple of patients characteristics) using Monte-Carlo and re-sampling techniques (including re-ordering of historical data), according to epidemiological/demographic specifications provided inter-actively by the expert-user,
- to update the Waiting List each time  $t$  where a Donor is virtually proposed for organ retrieval, according to Waiting List Updater subcomponent tacking into account waiting list removals, death on the waiting list, transplanted patients (an output of the Allocation Component) and re-listing of patients who experienced a graft loss (an output of the Post-Transplant Outcome Component).

The Waiting List Updater is a complex and crucial sub-component, especially when one simulate the allocation of vital organs. In this later context, deaths on the waiting list and removals of patients that are too sick to benefit from a transplantation are likely to be used as important end-points to evaluate the expected properties of a new allocation scheme. The Waiting List Updater is thus required to offer facilities:

- to simulate patients removal and death on the waiting list according to (simplified and robust) survival models provided by the expert-user, simulating individual survival with Monte-Carlo techniques;
- to simulate patients characteristics evolution on the waiting list, especially for individual characteristics that are taken into account for Organ Allocation; discrete-event simulation models have been shown to be relevant in such a context; for example, one can have to simulate the evolution of Serum Creatinin, Bilirubin and INR if the MELD score is taken into account for Liver Allocation;

When historical data are used for Kidney Allocation, one can avoid to simulate patients removal and death on the waiting list and use instead historical movements on the waiting list, admitting that patients remain alive in dialysis. When historical data are used for Vital Organs Allocation, one have at least to simulate the survival of patients who where actually transplanted and who are de-allocated using the new scheme.

Functions and models used for generation and simulations will also be organised in re-usable libraries.

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### 3.3. Allocation Component:

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The Allocation Component is due to support the targeted Allocation Schemes. It is required to provide functionalities:

- to build interactively flexible and parametric allocation schemes,
  - to perform the fine tuning of the allocation scheme parameters:
    - . according to, at least, user-driven specifications intending to reach stepwise and empirically targeted allocation end-points,
    - . according to, at best, a relevant optimisation algorithm if an optimisation function derived from the set of targeted allocation end-points can be defined and if the optimisation of the targeted simulation model is tractable (depending on the linearity and the complexity of the simulation model).
- The input of the Allocation component is a sequence of pairs associating a donor proposed for organ retrieval at a given time  $t$  to the set of patients on the waiting list at time  $t$ .
- The allocation process can be split in two sub-processes. The first sub-process mimics the organ offer. Its output is a subset of patients on the waiting list at time  $t$  to which the studied organ is virtually offered. In a score-based patient-oriented allocation scheme, the subset of patients is ordered according to the rank of the scoring function that supports the allocation scheme. In a region-based centre-oriented allocation scheme, the subset of patients is ordered by transplant centre according to the geographical model that governs allocation. The second sub-process is due to mimic the "acceptance" of the organ for a given patient: including Cross match results, logistical hazards and medical decision to accept or not an organ proposed to a given patient or given group of patients. If one have to examine the influence of logistical constraints on multi-organ retrieval, one might have to build a more comprehensive and complex allocation simulation model including the interactions with the allocation of other organs .
- The final output is a cohort of patients transplanted with a given organ.

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### 3.4. Post-transplant Outcome Component

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The Post-transplant Component is due to simulate the outcome of virtually transplanted patients after their transplantation. This component is required to provide functionalities:

- to compute the individual patient life duration using Monte-Carlo and survival models provided by expert-user;
- to compute the graft function duration using Monte-Carlo and survival models provided by expert-user;
- to provide robustness and sensitivity tests able to give an idea of the influence of survival simulation models used on the evaluation end-points.

The output is a cohort of transplanted patients that are still alive with a functioning graft at the end of the evaluation period, a group of patients that virtually died after their virtual transplantation, a group of patients who virtually lost their graft and are to re-transplant. This latter group can be used as an input to the Recipient Component.

It can be very interesting do add this feed-back if one want to study allocation strategies that aim to preserve at long term the "immune capital" of young patients requiring a kidney transplantation.

Adding such a feed-back renders the allocation simulation model more realistic but it has the disadvantage to introduce a higher degree of complexity for computation and optimisation.

Notice that it is possible to evaluate the impact of an allocation scheme on graft and patient survival without simulating individual survival according to the method proposed in WP5.

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## 3.5. Evaluation Module

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The evaluation module gets as an input the output of the Donor, Recipient, Allocation and Post-transplant Components.

It has to comprise reporting functionalities providing predefined descriptive statistics, controls and sensitivity tests able to give an idea of the influence of survival/evolution models used on the evaluation end-points.

The evaluation module will describe:

- the characteristics of donors and recipients involved in the simulations,
- the characteristics of recipients,
- the impact of allocations schemes on evaluation end-points provided by expert end-users.

Detailed functional specifications of the evaluation module will take into account the results from the experimental study described in the next chapter.

Figure 1 - The Allocation Simulation Components

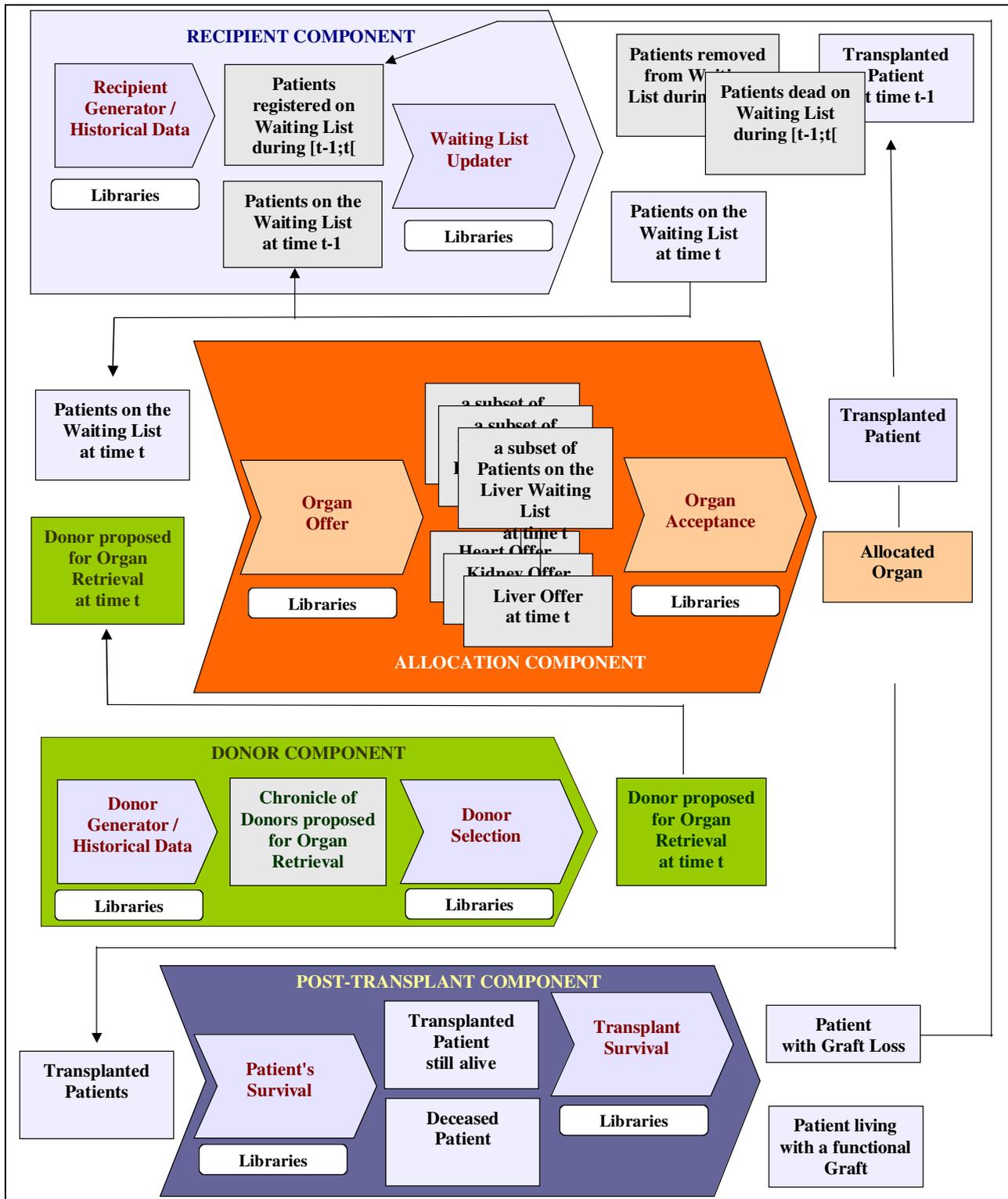
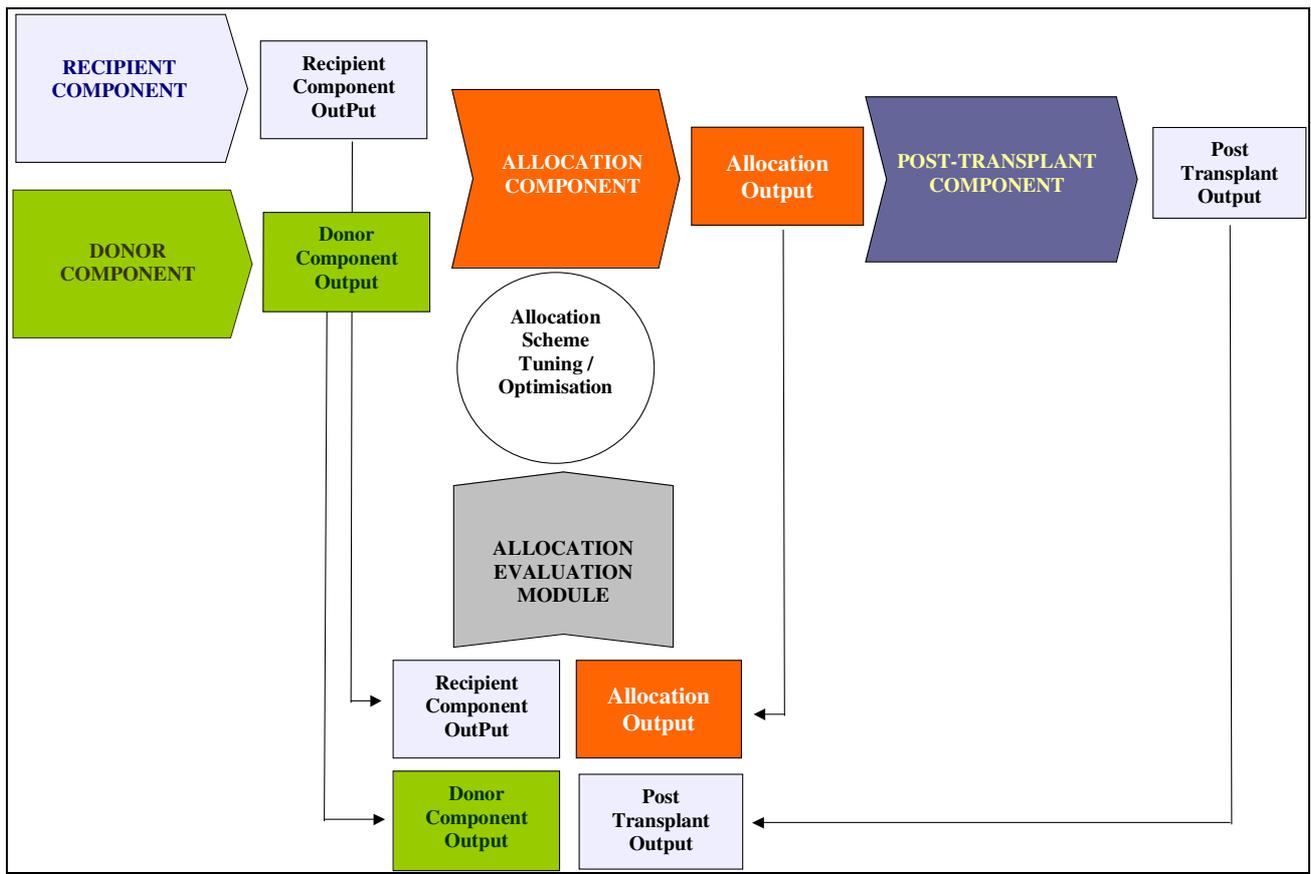


Figure 2 - The Allocation Simulation Evaluation Component



## 4. Experimental Study

The specification of a Common Simulation Tool that will be used by a consortium of European Organ Exchange Organisations is an interesting mean to capitalize expertise and to share knowledge about organ allocation among our institutions. Due to the limited impact of small intestine pilot action and the emergence of simulations as a crucial need for our institutions, a consistent proposal was to build a pilot study of allocation simulations using an existing prototype as a demonstrator. This experimental study has been decided to constitute the pilot action of WP3. It is a pilot action by the promotion of standardized data exchange format, by the fact we try to define objectives and discuss results outside of our national contexts and by the acceptance of an external and distant advice on the sensitive issue that organ allocation usually is.

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### 4.1. The study Protocol

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▷ The aim of the experimental study was to illustrate the main functionalities of an Organ Allocation Simulation Tool using a prototype provided by Abm.

The selected study case was related to Kidney allocation, using data coming from Alliance-O partners that have an information system providing the required data. The study compared observed allocation according to actual allocation scheme over a past period [01/01/2001-01/12/2005] to a simulated allocation over the same period according to a test-bed of modified allocation schemes.

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## 4.2. Material and Methods:

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### 4.2.1. Data:

▷ The actual allocation schemes were either national or supra-national scoring system or a composition of allocation priorities working at local, regional or national level. Actual allocation schemes have not been imitated. Only allocation actual result (a given kidney from donor x transplanted to patient y) have be taken into account together with the allocation modality (priority #1, #2).

▷ Modified allocation schemes considered for simulation have been 2 scenarios using a scoring function: the second scenario was tuned according to results obtained with the first scenario.

Alliance-O partners participating to the study provided 3 files according to the Data Interchange Format previously specified by Abm :

- a file describing the waiting list at the beginning of the selected period of time (file 1),
- a file with the patients registered on the waiting list during the period of time (file 2),
- a file with donors retrieved during the observation period of time (file 3).

No nominative data have been used. Actual donors and recipients Ids could be replaced by another Id provided that the actual link between the recipient and the donor be preserved. Dates of birth were not required, only the age at registration for recipients and age at death for donors were provided.

Centre and Region were not nominative (Centre01..., Region 01...).

Alliance-O partners with an existing information system were asked to provide the required files.

Data from UKT and Abm have been obtained.

### 4.2.2. Simulations:

Simulations were realized according to a simple determinist historical data-based model simulating the control of the allocation process according to a scoring function. Various functions were available and could be combined in different manner with variations on weights to build relevant allocation schemes. The outcome of patients that where actually transplanted has not been simulated. They were supposed to remain alive on dialysis. The outcome of transplantation has been simulated. According to post transplant survival models provided by WP5, the outcome of patients after transplantation has be simulated. Donor generation, recipient generation and recipient characteristics evolution have not been simulated in this experimental study, as they are no yet provided by the Abm prototype.

The input of the allocation model comprises: (i) an historical chronicle of donors compiled during a given period of time where at least one kidney was transplanted to a patient in a given allocation region; (ii) all the patients waiting for a kidney at the beginning of the period and all patients actually registered on the WL by one of the Tx team of the allocation region during the observation period. The output is a chronicle of pairs of recipient and allocated kidney. The chronicle of donors triggers the simulation loop. The WL is actualized according to real WL registrations and withdrawals since the last donor retrieval.

### 4.2.3. Analysis of results:

Description of results were provided for transplanted patients and for patients remaining on the waiting list according to a set of evaluation end-points: waiting time, PRA, recipients matched donor potential (MDP), and for transplanted patients: age and HLA matching.

#### a. Computing Matched Donors Potential for Tx Candidates

We compute for each recipient the number of donors:

- (1) matching his blood group,
- (2) retrieved during the past years (usually 5) within a relevant allocation area (region/nation),
- (3) with less than 3 HLA A, B and DR mismatches and
- (4) without unacceptable HLA.

This metric, referred to as Matched Donors Potential (MDP), is especially relevant to identify patients with a low Transplant accessibility. Because MDP takes into account the frequencies of HLA phenotypes and blood groups within the real allocation area, together with the impact of registered unacceptable antigens, it is a more accurate measure than the panel reactive antibody (PRA) rate.

Patients that have a high level of PRA, but a very frequent HLA phenotype with unacceptable antigens that are not frequent among donors, can have a good access to transplantation whereas patients with rare HLA or frequent unacceptable antigens may have low PRA, but a poor access to Transplantation.

#### b. Transplantation Access Rates (TAR)

We define the Transplantation Access Rate (TAR) as the Number of Patients Transplanted during a given period of time divided by the Number of Transplant Candidates during the same period:

$$\text{TAR} = \frac{\text{Nb of Patients Transplanted during a given period of time}}{\text{Nb of Transplant Candidates during the same period}}$$

Where:

Nb of Transplant Candidates during a given period of time =

$$\begin{aligned} & \text{Nb of Patients on the WL at the beginning of the period} \\ & + \text{Nb of Patients registered on the WL during the period} \end{aligned}$$

Specific Transplantation Access rates can be computed according to region, centres, HLA Mismatches and ranges of waiting time, PRA, MDP and age.

For example, one will compute the specific TAR of patients with PRA  $\geq 80\%$ :

$$\text{TAR}_{\text{PRA} \geq 80\%} = \frac{\text{Nb of Patients Transplanted during a given period of time with PRA} \geq 80\%}{\text{Nb of Transplant Candidates during the same period with PRA} \geq 80\%}$$

Evaluation results, especially Specific TAR, are used to tune empirically the parameters of the allocation scheme, moving from a scenario 1 to a scenario 2.

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## 4.3. Results

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### 4.3.1. Changing Kidney Allocation in France

This section describes the real use of the allocation simulation prototype to promote in-depth changes in Kidney Allocation in France from 2004. They have been published in [13].

#### 4.3.1.1. *The historical kidney allocation scheme:*

Allocation in France falls under the responsibility of the Agence de la biomédecine (Abm). Allocation policy includes general principles such as: donor-recipient ABO blood group identity, unique and mandatory registration on the national waiting list (WL) and definition of some organ specific nation-wide allocation priorities.

For each kidney recipient, minimal HLA matching and forbidden antigens can be specified. Paediatric recipients get a priority for paediatric donors. Kidneys are proposed by order of priority (1) to urgent patients, (2) to patients with panel reactive antibodies level  $\geq 80\%$  included in a specific acceptable antigen protocol or  $\leq 1$  HLA mismatch (MM) with the donor, (3) to zero MM patients and (4) to patients with limited Transplant accessibility. Abm's coordination offices make the organ offer. When a retrieved kidney triggers no allocation priority, it is proposed at the local Transplant centre.

The French kidney allocation system at this time was a mixture of nationwide patient-based allocation priorities combined with centre-based allocation procedures, that represent the main - and transplant physicians' favourite allocation modality. Its evaluation demonstrated inter-region and inter-centre discrepancies in terms of Transplant accessibility and waiting time. HLA matching was pin-pointed as too much prominent in many regional and local allocation procedures, leading to the exclusion of rare HLA patients awaiting a kidney. In a context of significant increase of organ donation in France (1629 Kidney Tx in 1997 vs. 2572 in 2005), these results prompt Abm to study the feasibility and the impact of a new policy for kidney allocation with the introduction of a scoring function whose capability to improve simultaneously efficiency through donor-recipient matching in HLA and age, equity through waiting time and matched donors potential has been previously reported [5-7].

The need to compare various allocation schemes, to evaluate the impact of scoring function tuning and to assess the acceptability of a patient-based scoring system prior to its implementation prompt us to build a simulation tool. This section describes the core functions used in the allocation model, reports on some evaluation end-points and discusses the value of a simulation in such a context.

#### 4.3.1.2. *The new allocation scheme*

The simulation model (SM) combines a Distribution Model (DM) and an Allocation Model (AM). The SM preserves existing allocation priorities. It also preserves general allocation principles: blood group identity, absence of forbidden antigens. In the absence of prioritized patient, various distribution models can be simulated. The two kidneys can be first proposed to local recipients and next, when there is no suitable local recipient, to other regional recipients. One kidney can be allocated within the local WL and the other within the regional WL, resulting in a local-regional distribution model, which may or may not lead to double Tx in the same centre. Last, both kidneys can be distributed at the regional level.

The SM is implemented in Visual Basic. The SM is limited to allocation-reallocation of kidneys.

When a potential donor is detected, an allocation score is computed for each patient waiting for a kidney. Recipients are then ranked according to the score value. Kidneys are offered to the patients with the highest score. To facilitate discussion with transplant teams, we use a scoring system that is a weighted sum of parametric functions  $f_i$  that vary between 0 and 1. Each function can take donor and/or recipient characteristic as variables. We propose below a generic definition of a simple linear allocation score. The possible use of more sophisticated allocation score including interactions and non linear functions is to counterbalance with its readability and appropriation by transplant centres.

**Score**( $R_t ; D_t$ )=  $\sum [w_i \cdot f_i(R_{Ci}; D_{Ci}; P_{ik})]$  where:

- $R_t$  a recipient on the WL at time  $t$ ,
- $D_t$  a retrieved donor at time  $t$ ,
- $w_i$  : weight given to function  $f_i$  ,
- $f_i$  : discrete or continuous function on  $[0 ; 1]$
- $R_{Ci}$ : recipient characteristic considered in  $f_i$
- $D_{Ci}$ : donor characteristic considered in  $f_i$
- $P_{ik}$  : the  $k$  parameters of function  $f_i$

Each function  $f_i$  has a particular objective, a practical definition and a computational specification. For kidney allocation, we proposed five functions. The functions  $f_1$  and  $f_2$  are donor independent (no  $D_{Ci}$ ).

• **Recipient time on the waiting list: function  $f_1$**

Function  $f_1$  aims at avoiding the selection of long waiting patients in giving an increasing amount of points to patients according to their time on the waiting list WL ( $T_{WL}$ ):  $R_{C1} = T_{WL}$ .  $f_1$  has two parameters  $P_{11}$  and  $P_{12}$ , which are durations (months). From a practical point of view, a patient with  $T_{WL} < P_{11}$  is assigned 0% of the points  $w_1$  given to the function; a patient with  $T_{WL} > P_{12}$  receives 100% of  $w_1$ . Between  $P_{11}$  and  $P_{12}$ , patients get a linear increasing percentage of the points (Figure 3).

$f_1(T_{WL}; P_{11}; P_{12})$ :

$$\begin{aligned} T_{WL} \in [0, P_{11}[ &\rightarrow f_1(T_{WL}) = 0, \\ T_{WL} \in [P_{11}, P_{12}] &\rightarrow f_1(T_{WL}) = (T_{WL} - P_{11}) / (P_{12} - P_{11}), \\ T_{WL} \in ]P_{12}, +\infty] &\rightarrow f_1(T_{WL}) = 1 \end{aligned}$$

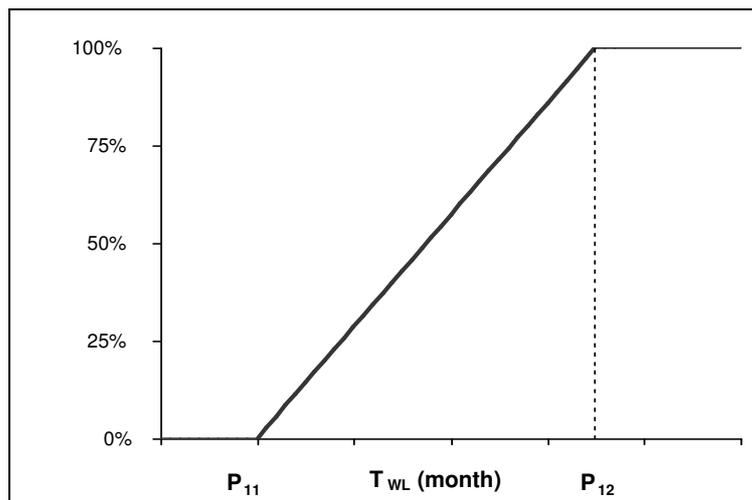


Figure 3 - Function of  $T_{WL}$  with inflection points at  $P_{11}$  and  $P_{12}$ . If  $P_{11}=6$  months, patients won't get extra-points until they meet 6 months on the Waiting List. If  $P_{12}=126$  months, a patient that waited for more than 126 months will get 100% of the points  $w_1$  given to this function. A given patient A who waited  $T_{w1}=66$  months at the time a potential donor is retrieved will get 50% of the  $w_1$  points given to  $f_1$ . If  $w_1 = 500$ , this patient gets 250 points due to his waiting time.

• **Recipient's well-Matched Donors Potential (MDP): function  $f_2$**

Function  $f_2$  aims at improving *Transplantation Accessibility* for patients with low potential for a well-matched donors. This function balances points given to the quality of Donor-Recipient HLA-matching as in function  $f_3$  below. Using an appropriate weight factor, such a function should provide improved matched kidneys and reduced waiting times to those difficult patients.

Function  $f_2$  considers the recipient's Potential of Matched Donors:  $RC_2 = MDP_{(donors \leq 3MM.5years)}$ .  $f_2$  has one parameter  $P_{21}$  which is the highest MDP among the recipients with an identical blood group:  $\max(\{MDP_i\})$ . From a practical point of view, a patient with no donor less than 3 MM receives 100% of the points  $w_2$  given to the function; the patient with the highest MDP receives 0% of the points  $w_2$ . Between 0 and  $P_{21}$ , patients get a linear decreasing percentage of points (Figure 4).

$f_2(MDP; P_{21})$ :

$$MDP \in [0, P_{21}] \rightarrow f_2(MDP; P_{21}) = 1 - (MDP/P_{21})$$

$$P_{21} = \max_i(\{MDP_i\})$$

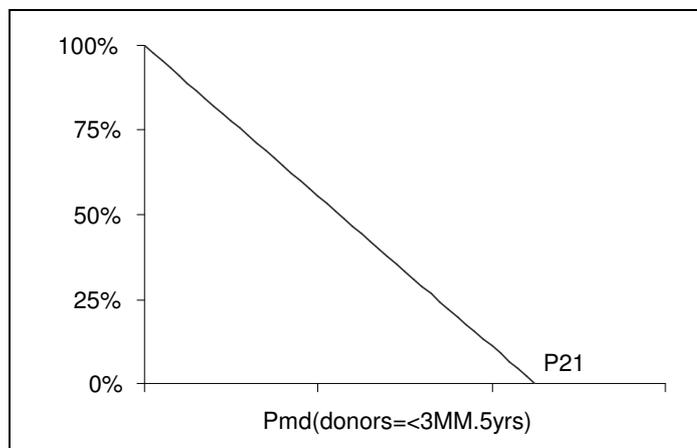


Figure 4 - Recipient's matched Donors Potential function. If the highest MDP on the waiting list for blood group A is 500, patients with the highest access to well matched donors ( $MDP=500$ ) won't get any extra-point; conversely, patients with  $MDP=0$  will get 100% of  $w_2$  points affected to this function. Our patient A with  $MDP=250$  donors  $\leq 3$  Mismatches over 5 years will get 50% of the  $w_2$  points due to the linear decreasing shape of  $f_2$ . If  $w_2=300$ , he will get 150 points due to his medium MDP to sum with the 250 points due to his waiting time. Due to the dynamic computation of MDP, changes in organ retrieval and/or in the allocation area the recipient is affiliated to can result in changes of patients MDP through the time.

• **Donor-Recipient HLA Matching:  $f_3$**

Function  $f_3$  aims at improving post-transplant results by favouring a good HLA A, B, DR matching. It is a discrete decreasing function giving a percentage of  $w_3$  depending on the number of HLA MM. For a given donor, recipients with 0-MM will get  $P_{31}=100\%$  of  $w_3$  whereas 6-MM recipients get  $P_{37} = 0\%$  of  $w_3$ .

The 5 other parameters  $P_{32}$  to  $P_{36}$  (Figure 5) are scaled according to the relative risk of graft loss calculated in a multivariate analysis.

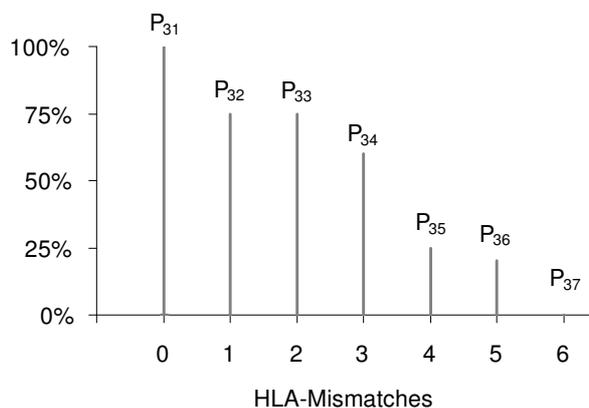


Figure 5 - Donor-Recipient HLA mismatches function. If  $P_{35}=P_{36}=25\%$ , patient having 4 or 5 mismatches with a given donor B will get 25% of the points  $w_3$ , say 300 points, given to  $f_3$ . This is the case of our patient A that will get only 75 points due to his poor matching with this particular donor, partially compensated by the  $250+150=400$  points he already got due to his waiting time and his medium MDP.

• **Donor-Recipient age matching:  $f_4$**

Function  $f_4$  aims at improving post-Tx results in dealing with nephronic reduction. It favors an appropriate donor-recipient age matching. The solution we show here is a function giving a percentage of points  $w_4$  decreasing with an increasing differential of age classes (Figure 6). Classes and their related values are the parameters of  $f_4$ .

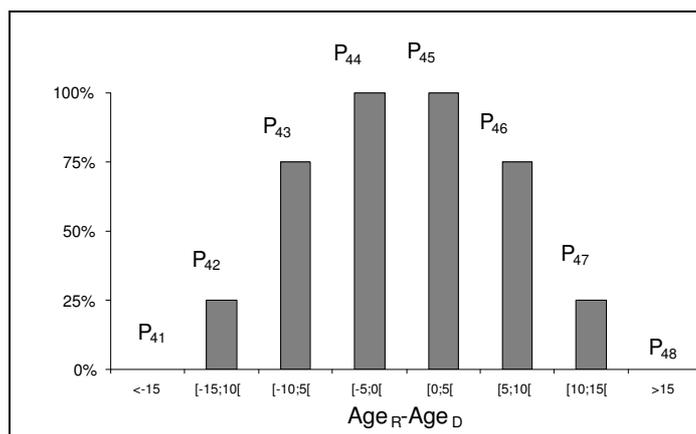


Figure 6 - Donor-Recipient age matching function. If  $w_4=800$  points because one considers that age matching is the major allocation criterion; if  $P_{47}=0.10$  because one wants to avoid the allocation of kidneys to recipients 10 to 15 yrs older than the donor, and if it is the case for our patient A for the given donor B, then patient A gets 80 points due to HLA matching, thus a total of  $475+80=555$  points. This individual score computed each recipient on the waiting list will be used to order patients by rank and select the 2 patients with the highest score as the patients to whom one kidney is to offer.

**4.3.1.3. Results**

To illustrate our approach, we present here some results obtained in one of our 6 allocation districts. During the selected evaluation period, 2,956 new patients were added to the 568 patients registered on the Waiting List at the beginning of the period; 2,421 Kidney Transplantations were performed. Patients' characteristics are in table 1.

In the studied region, the former allocation system was based on a dual-local distribution model (LLDM). One challenge was to implement a cultural change by introducing a local-regional distribution model (LRDM). National allocation priorities were kept unchanged in both models, accounting for 18% of kidney Transplantations during the period of virtual evaluation. In the observed LLDM, Transplantations were performed at the local level in 61% and at regional level in 21% versus 48% and 35%, respectively, with the simulated LRDM.

	Patients on WL on 01/01/1998	Registered patients 1998-2003	Transplanted 1998-2003	Patients on WL on 1/01/2003
<b>n</b>	568	2956	2461	770
<b>Sex</b>				
<i>male</i>	342 60%	1846 62%	1573 64%	473 61%
<i>female</i>	226 40%	1110 38%	888 36%	297 39%
<b>Blood Group</b>				
<i>A</i>	191 34%	1274 43%	1100 45%	233 30%
<i>AB</i>	29 5%	106 4%	93 4%	16 2%
<i>B</i>	33 6%	303 10%	199 8%	106 14%
<i>O</i>	315 55%	1273 43%	1069 43%	415 54%
<b>Age</b>				
<i>years (m±ds)</i>	44,6 ±13,1	45,8 ±14,2	46,0 ±14,4	48,4 ±13,0
<b>PRA</b>				
<i>≥80%</i>	128 99%	175 6%	162 7%	92 12%
<i>≥5%</i>	183 32%	475 16%	394 16%	198 26%
<i>&lt;5%</i>	257 45%	2306 78%	1905 77%	480 62%

Table 1 - Patients characteristics

*c. Evaluation end-points 1: Characteristics of transplanted patients*

The simulated allocation model significantly increases the number of transplantations for long-waiting patients (Figure 7) and for patients with low MDP (Figure 8) during the 3 first years and after reaches a steady state.

In the observed situation, the median MDP was around 105 donors $\leq$  3MM (Fig.6); in contrast, patients remaining on the WL had median MDP around 80 donors $\leq$ 3MM (Fig.9).

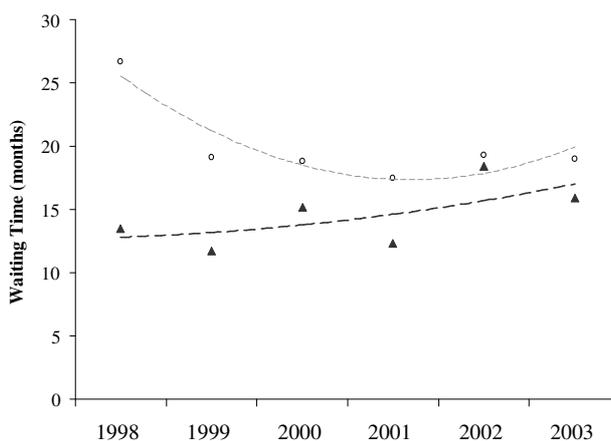


Figure 7 - Median Waiting Time at Transplantation in transplanted Patients

With the simulated allocation model, the median MDP in Transplanted patients at steady state (Figure 8) becomes similar to the median MDP in the WL (Fig.9), suggesting that there is no more segregation of patients, excluded from Transplantation due to a rare HLA phenotype.

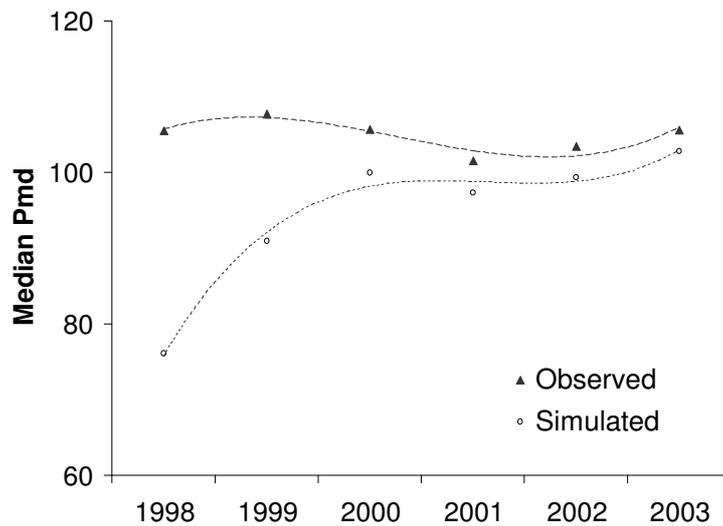


Figure 8 - Median MDP in transplanted patients

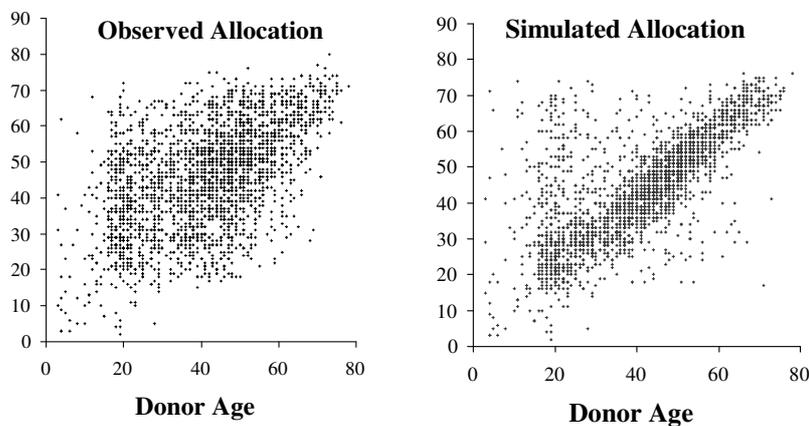


Figure 9 - Donor-Recipient age matching in transplanted patients

In the observed situation, kidneys retrieved in young donors were frequently allocated to old recipients, and kidneys retrieved in old donors were frequently allocated to young recipients. The switch to a LRDM and the use of a scoring function significantly improves the age matching between donor and recipients (Figure 9). The regional distribution indeed enlarges the diversity of recipients screened for a given donor. The simulated scheme minimizes 5 and 6 MM Tx that were a side effect of the local distribution (Figure 10).

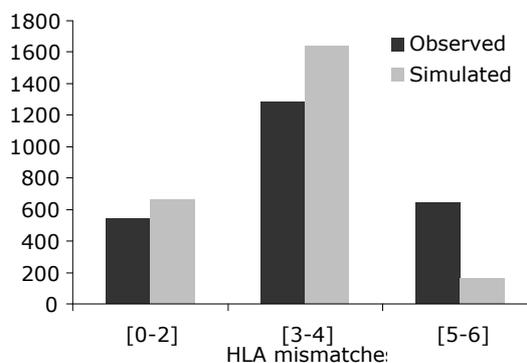


Figure 10 - Donor-Recipient HLA matching

d. *Evaluation end-points 2: Characteristics of patients remaining on the waiting list for a kidney transplantation*

The simulated allocation model significantly changes the content of the WL in terms of median MDP as shown in Figure 9. The same holds for median waiting time.

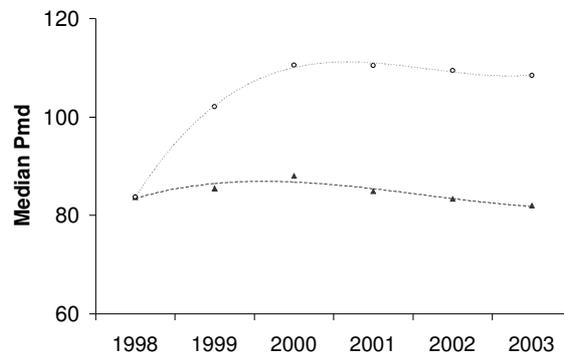


Figure 11 - Median MDP among patients on WL at each 1st of January

e. *Specific Transplantation Access Rates*

Transplantation access rate is defined by the number of transplanted patients among the total number of Tx candidates for a given period. One can examine specific Tx access rates according to various patients characteristics: blood group, Tx centers, age or MDP as shown in Figure 12, which suggests an over-correction of Tx access rate for patients with lowest MDP in the simulated model. Tuning  $w_3$  resulted in a more equitable allocation scheme.

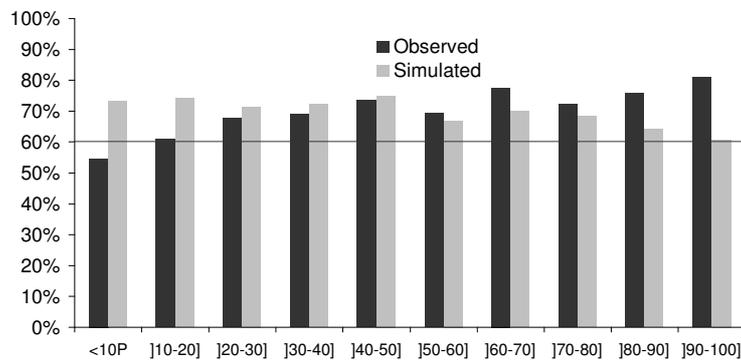


Figure 12 -Specific Transplant Access rates per MDP deciles

Results obtained indicated that the objective to improve both equity and efficacy was feasible. The expected improvements in terms of the clearance of long waiting patients from the WL (Figure 7), age (Figure 9) and HLA matching (Figure 10) and the scalability of the scoring system appeared promising. The simulated allocation model also minimizes differences in Centre Specific Transplant Access Rates, improving the equity between patients and centers at the price of slight - but highly sensitive variations in Transplantation activities for some centres. The magnitude of expected results facilitated the switch from local centre-based to regional patient-based distribution in regions that required such a change. The new scoring system has been implemented first in Paris allocation area in April 2004. It has been generalized to other allocation regions during years 2005 and 2006. Simulations have been widely used to interact with Transplant

physicians and patients associations to promote evidence-based allocation [8] and to customize the allocation model to the regional specificity.

#### 4.3.2. Experimenting Abm's Simulation Prototype with data from UKT

##### 4.3.2.1. The historical Allocation Scheme

▷ During the historical period of the simulation study, kidney allocation in UK was driven by HLA matching. A national priority referred to as "Tier 1" was given to recipients having no HLA A, B and DR mismatch with the donor. If 2 such recipients were identified, the two kidneys were involved by the allocation priority tier 1. A national priority referred to as "Tier 2" was given for one kidney only to recipients with no DR mismatch with the donor. The other kidney was allocated according the local centre scheme. For non favourably matched kidneys (Tier 3) were allocated according to local schemes.

##### 4.3.2.2. Study-Case Allocation Models

▷ Two scenarios have been studied: the first virtual allocation scheme (simulation 1), roughly build as a starter independently of UKT, reallocated tier 3 kidneys according to a nationwide allocation score. It was improved and tuned to build a the second allocation scheme (simulation 2) that met more accurate UKT specifications and reallocated tier 2 and tier 3 kidneys according to a nationwide allocation score. Patients with forbidden antigens against a potential donor were not considered for allocation in both historical and simulated allocation schemes. In simulation 1, the score used to order recipients (R) took into account their time on the waiting list (WT) and their Matched Donors Potential (MDP). These two first components of the scoring system are referred as to "fix" components because they are independent from the donor; they only depend on recipient characteristics and can be computed prior to any organ allocation to compare for example centre waiting lists. The allocation score also takes into account HLA and Age matching with the donor. These last components depend on donors characteristics, are referred as to "random" components.

$$\begin{aligned} \text{Score UKT V1} = & 600 * f_1(WT_R) \\ & + 200 * f_2(MDP_R) \\ & + 300 * f_3(\text{HLA A,B Matching}_{R-D}) \\ & + 300 * f'_3(\text{HLA DR Matching}_{R-D}) \\ & + 300 * f_4(\text{AGE Matching}_{R-D}) \\ & + 300 * f_5(\text{AGE}_R | \text{Age}_D) \end{aligned}$$

In simulation 2, a second version of the score was used, in addition to the changes in the "distribution model" (reallocation of tier 2 + Tier 3 kidneys):

$$\begin{aligned} \text{Score UKT V2} = & 800 * f_1(WT_R) \\ & + 200 * f_2(MDP_R) \\ & + 300 * f_3(\text{HLA A,B Matching}_{R-D}) \\ & + 500 * f'_3(\text{HLA DR Matching}_{R-D}) \\ & + 150 * f_4(\text{AGE Matching}_{R-D}) \\ & + 300 * f_5(\text{AGE}_R | \text{Age}_D) \end{aligned}$$

Functions  $f_1$ ,  $f_2$  and  $f_4$  were the same as the one used in France (see previous chapter). In contrast with the allocation score used in France, HLA A+B matching and HLA DR matching DR are taken into account separately [Figure 13]. These functions were thus added to the library of functions of the simulation tool. They are likely to be used also in a next future in France because they indeed realize an interesting

refinement. A fifth component  $f_5$  was also created to introduce a priority for young recipients with constraints on the age of the donor.

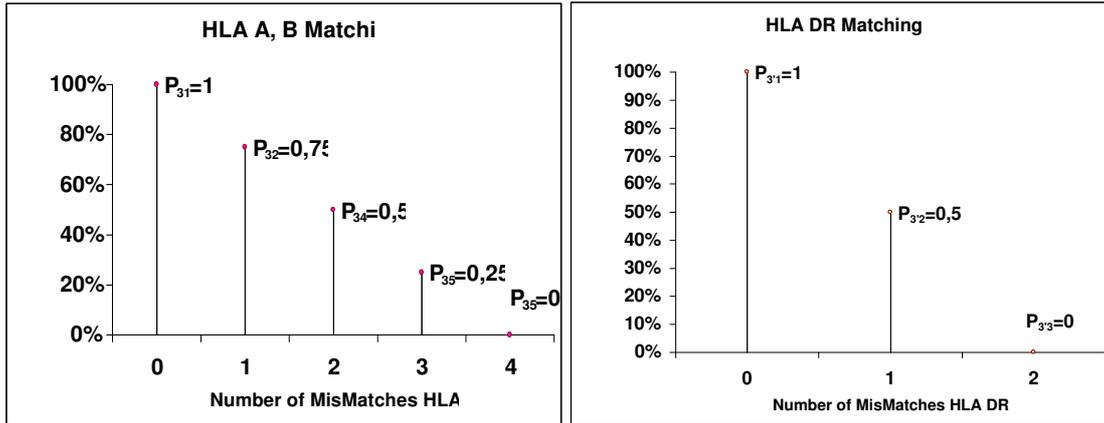


Figure 13 - Refined HLA matching Functions introduced in the Allocation Component Library

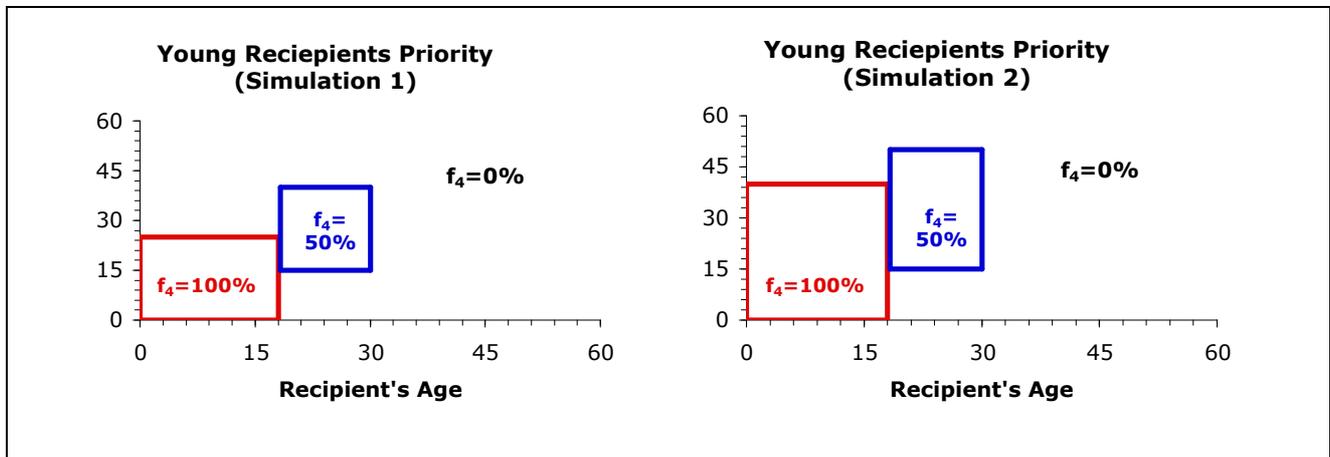


Figure 14 - Another Parametric Function added to the Allocation Component Library to offer a extra points to Young Recipients

Allocation simulations were based on historical data: 2379 kidneys retrieved from brain dead Donors transplanted in UK from the 1 Jan 01 to the 31 Dec 02, 4756 patients on the waiting list as of the 1 Jan 01 and 4468 patients joining the waiting list during the study period. In simulation 1, 792 kidneys allocated according to tier 3 local allocation schemes were re-allocated according to Score UKT v1. In simulation 2, 1996 kidneys allocated according to tier 2 and 3 schemes were re-allocated according to Score UKT v1 [Figure 15].

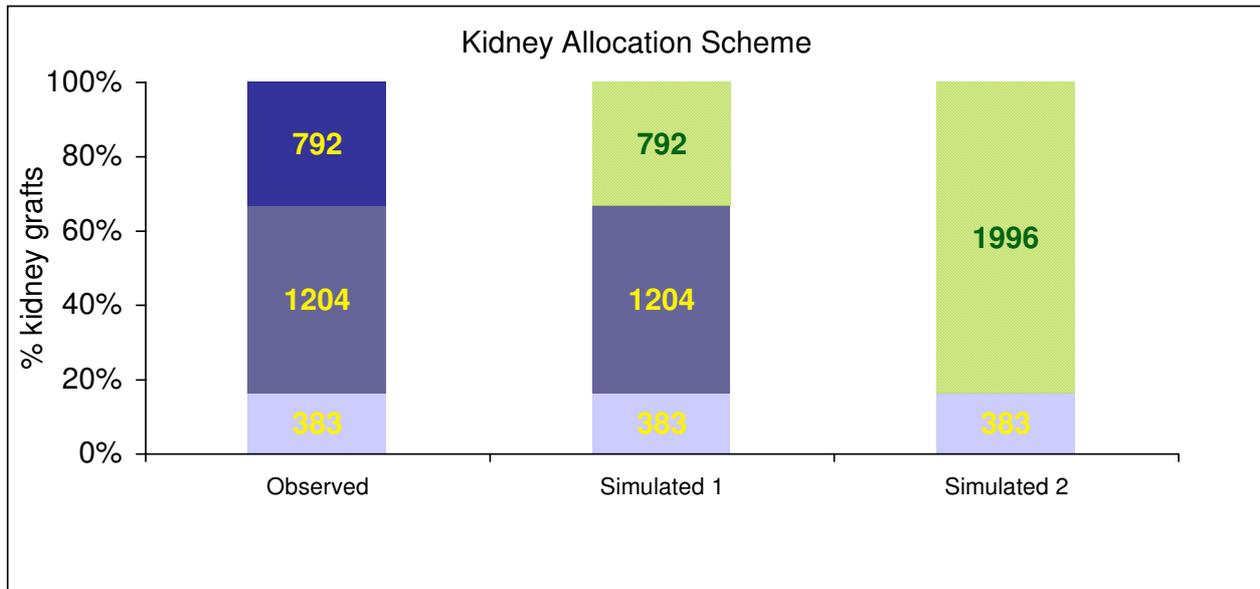


Figure 15 - Reallocation of kidneys in the two simulated Scenarios

#### 4.3.2.3. Results

##### a. Evaluation end-points 1: Characteristics of transplanted patients

- **Waiting Time (WT) in transplanted Patients:** The distribution of WT can be used to evaluate the efficiency of the new allocation scheme to reach one of its targets: the clearance of long waiting patients from kidney waiting list. The new allocation scheme in Simulation 1 is related to an increase in the number of transplantation performed for long waiting patients [Figure 16]. In simulation 2, the phenomenon is enhanced, due to an extended sharing of organs and an increased weight given to  $f_1$ . With the later scheme, a limited number of patients are transplanted before one year of time on the waiting list.

- **Matched Donors Potential (MDP) in transplanted Patients:** The distribution of MDP [Figure 17] can be used to evaluate the efficiency of new allocation schemes to improve the number of transplantation for patients that have a limited potential to get a well matched kidney. The new virtual allocation scheme in Simulation 1 is related to an increase in the number of transplantation performed for low MDP patients. Because the risk of a positive cross-match is not simulated in Abm's prototype, such a result wont probably be observed at this level if the scheme were implemented. In Simulation 2, results suggest an excessive number of transplantations for patients with a poor access to matched donors and an artificial excessive diminution of transplantations for patients with common HLA phenotypes and/or with no or limited sensitisation.

- **Panel Reactive Antibodies level (PRA) in transplanted Patients:** Although not directly taken into account in the score, the number of patients with  $PRA \geq 85\%$  is increased in the two virtual allocation schemes [Figure 18]. This result is related to MDP and WT. Again, because the risk of a positive cross-match is not simulated in Abm's prototype, such a result wont also be observed at this level if the scheme were implemented.

- **Distribution of Age in transplanted Patients:** Simulated allocation schemes lead to the same distribution of age in transplanted patients as the observed past allocation system [Figure 19].

### *b. Evaluation end-points 2: Donor-Recipient Matching*

- **Age Matching:** the introduction of a function that favours age matching together with an increased number of organ shared at national level result in a better matching in age with simulation 2 [Figure 20].
- **HLA Matching:** Compared to the historical allocation scheme, simulation 1 results in an increased number of patients transplanted with 2 DR mismatches [Figure 21]. Tuning up the weight given to function  $f_3'$  from 300 to 500 fixed this weakness. Nevertheless, one get less patients transplanted with 0 DR mismatch and 2 mismatches A or B. Such result is consistent with the fact that offering a better access to transplantation for patients with poor MDP and for long waiting patients might be feasible with limited adverse effects on HLA matching.

### *c. Evaluation end-points 3: Specific Transplantation Access Rates*

Specific TARs provide interesting metrics that take into account together the characteristics of Transplanted Patients and the Characteristics of patients on the Waiting list. They give an idea of the "equity" of a new allocation scheme and facilitates fine tuning of the scoring functions. Specific TAR can be computed for many relevant recipient characteristics. We illustrate below the use of TAR according to MDP and blood group.

- **Transplantation Access Rate according to MDP ( $TAR_{|MDP}$ ):** The historical allocation scheme gave importance to HLA matching without consideration to rare HLA phenotypes and/or to the consequence of forbidden antigens. The result was a 15% TAR for patients whose MDP was below the first quartile, in contrast with a 39% TAR for patients having MDP greater than the 4th quartile [Figure 22]. In simulation 1, we obtain more balanced TAR from a quartile to another.

In simulation 2,  $TAR_{|MDP}$  decreases from 32% in patients with MDP below the first quartile to 21% in patients with MDP greater than the 4th quartile. TAR demonstrates more clearly the overcompensation of the access to transplantation in patients with low MDP than the distribution of MDP in transplanted patients [Figure 17].

- **Transplantation Access Rate according to Blood Group ( $TAR_{|ABO}$ ):** Transplantations according to blood-group compatibility were performed in the historical allocation scheme. We artificially imposed identical blood groups for donor and recipient for reallocated kidneys (792 in simulation 1 vs 1996 in simulation 2). The result is a 34% TAR for AB recipients and a 21% TAR for B recipients with the historical scheme, versus a 29% TAR and a 24% TAR in A and O blood group patients. We observe that allocation schemes that increase transplantation with identical blood group result in more balanced TAR except for blood group B patients [Figure 23].

### *d. Simulating post-transplant outcome*

Patient and Graft survival are crucial evaluation end-points. Patient and Graft survival are crucial evaluation end-points. Indeed, an improved allocation scheme should provide improved access rates to long waiting patients and to patients with poor access to transplantation together with good post-transplant results. During this pilot action, two methods have been assessed in parallel using UKT data. **Method 1:** One can evaluate the impact of an allocation scheme on post-transplant survival in computing the individual risk score of death

(or graft loss), the median of risk for the entire cohort of actually and virtually transplanted patients and last the expected 1-year and 5-years survival according to the method described in WP5. Such a method is likely to be implemented in the Evaluation Component of the Simulation Tool. **Method 2:** One can use individual risk function to simulate survival for each transplanted patient using Monte-Carlo. Survival curves can then be drawn according to Kaplan-Meier method. Such an approach implies to build a Post-Transplant Outcome Component. It is particularly relevant if one want to build a more comprehensive and realistic simulation model that take into account the re-listing of patients with a graft loss, that simulate their return to dialysis or that simulate the evolution of patient characteristics after transplantation.

Such computations rely on a relevant survival model (usually a Cox Model) whose parameters have been previously estimated on an actual and historical cohort of transplanted patients. A relevant survival model must be statistically adapted to the data (e.g: checking proportional hazards hypothesis for Cox model). Its predictive value must be checked: one can for example use ROC curves AUC to qualify the ability of the survival model to predict one-year and five-year survival. It must also be robust to the data because the cohort of patients virtually transplanted might differ from the actual cohort used to estimate model parameters. As a consequence, the robustness of the model used to predict post transplant events should ideally be checked on other cohorts of patients. Last, variables predicting survival must be available in the Simulation Model: it might lead to simplify the set of predictive variables entered onto the model.

Survival must be simulated for both actually and virtually transplanted patients; we show in [Figure 24] simulated transplant survival in actually and virtually transplanted patients. The magnitude of variations that can be observed from a survival simulation to another for the same transplanted patients has to be checked with various pseudo-random samples and can be used as a sensitivity test. The observed transplant survival curve can be used as a control [Figure 25]. Method 1 can also be used as a control [Figure 26]. According to sensitivity tests, one will carefully conclude that change or no change are to be expected in patients and/or transplant survivals.

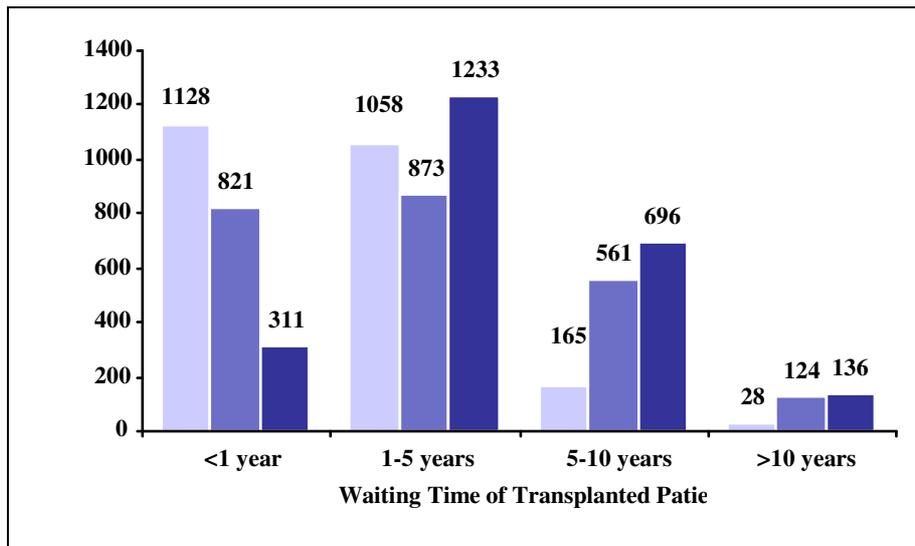


Figure 16 - Waiting Time in Transplanted Patients shows a significant increase of transplantations performed for long waiting patients

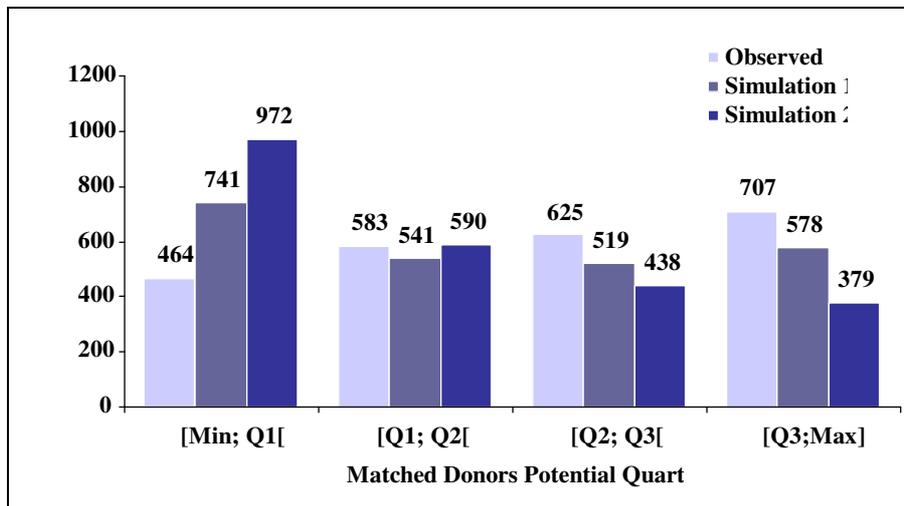


Figure 17 - Matched Donors Potential in Transplanted Patients

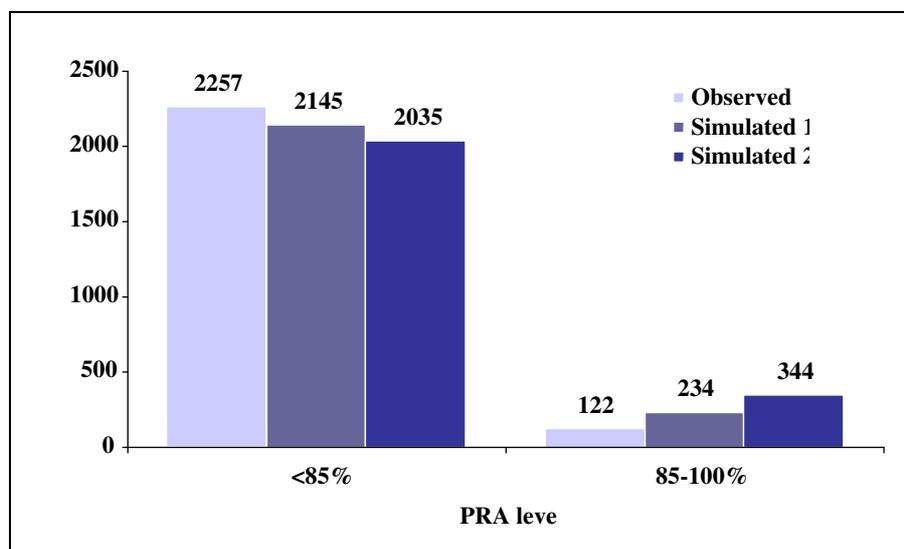


Figure 18 - PRA level in Transplanted Patients

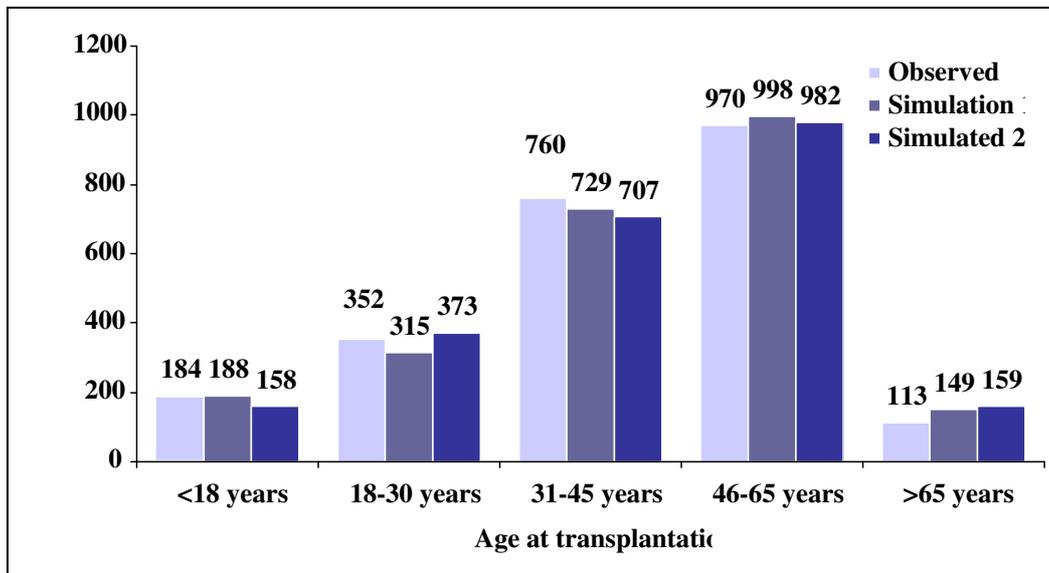


Figure 19 - Age of transplanted patients

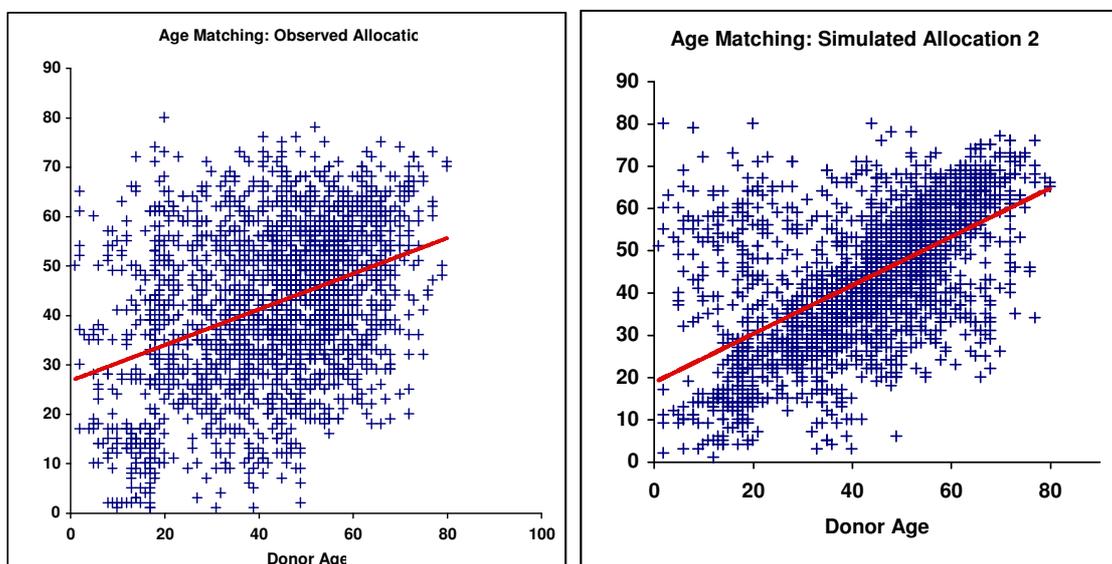


Figure 20 - Donor-Recipient age matching

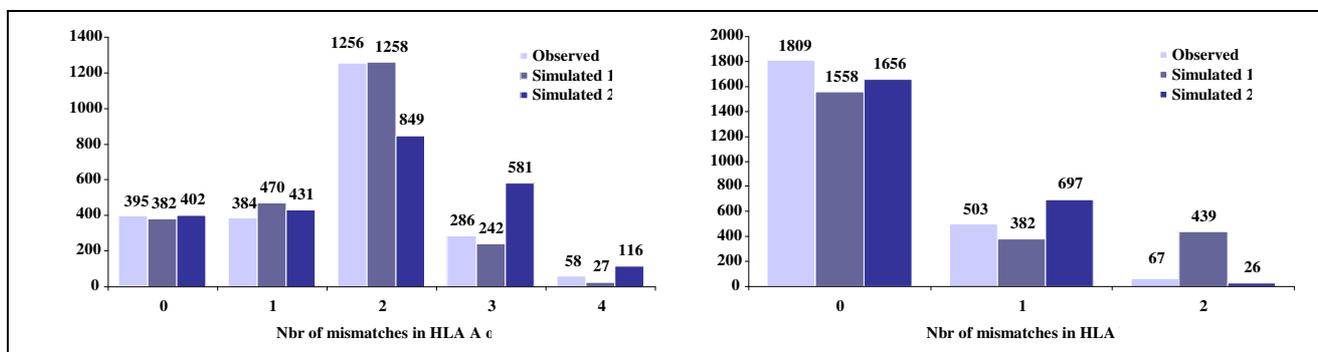


Figure 21 - Donor-Recipient HLA matching

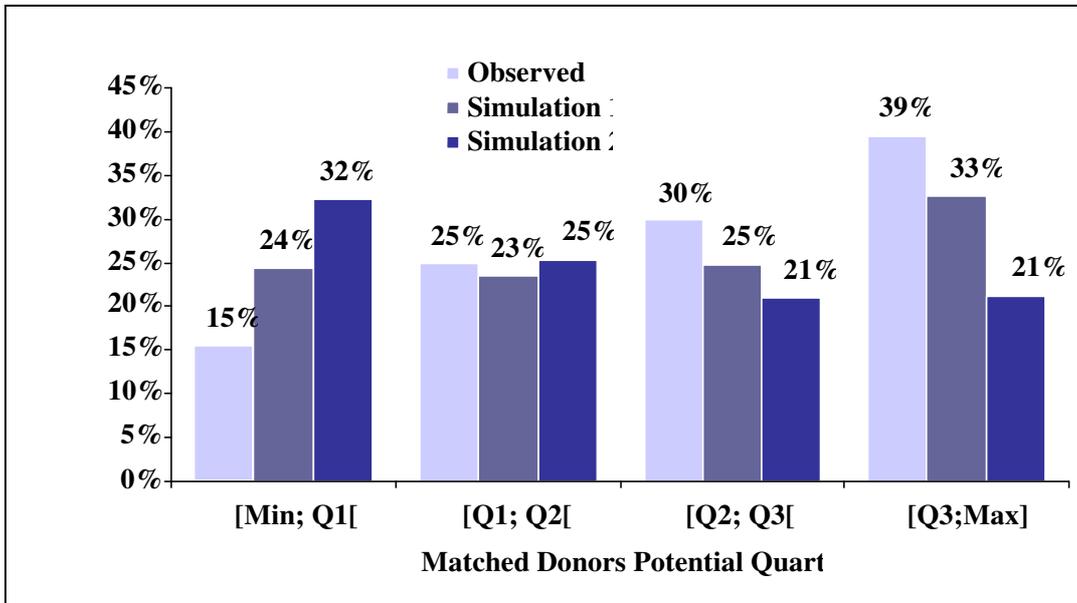


Figure 22 - Transplantation Access Rates by MDP quartiles

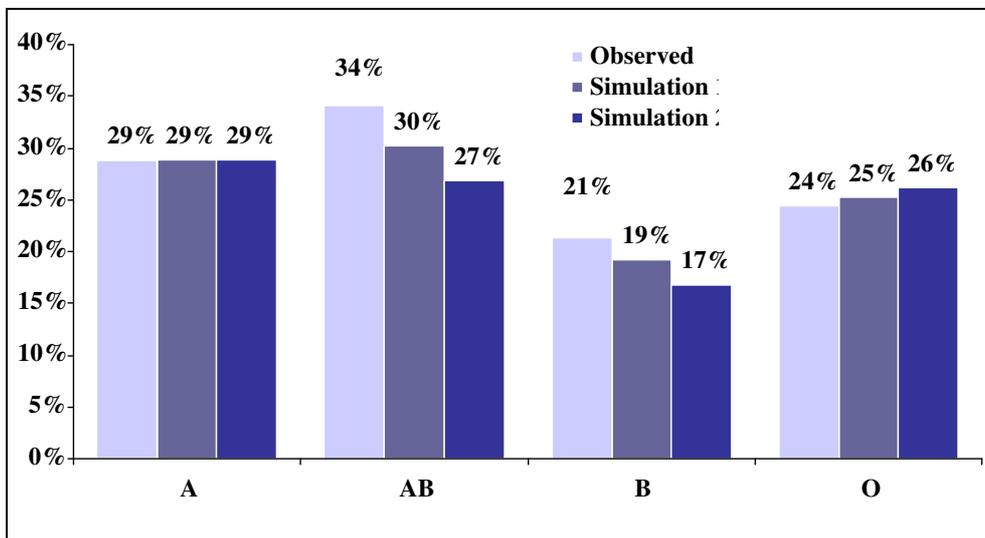


Figure 23 - Transplantation Access Rates by Blood Group

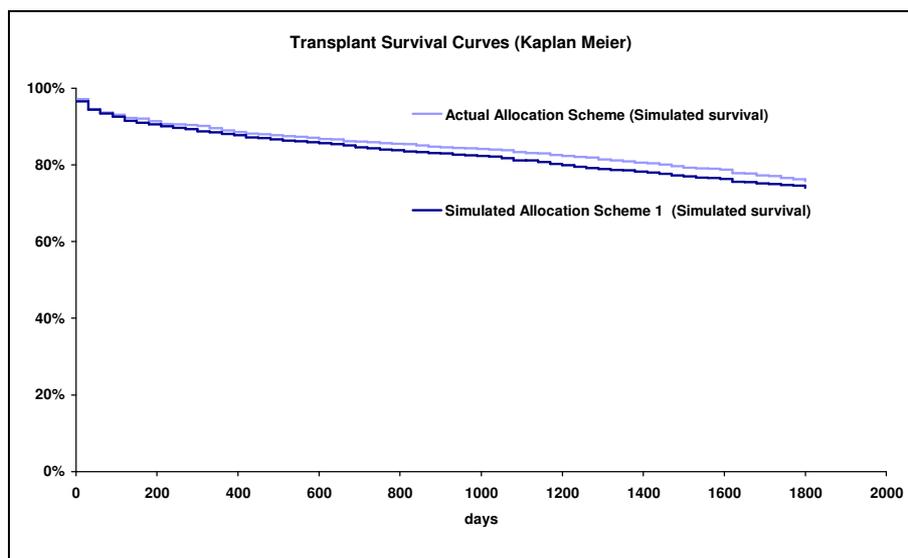


Figure 24 - Simulating individual Transplant Survival using Monte-Carlo

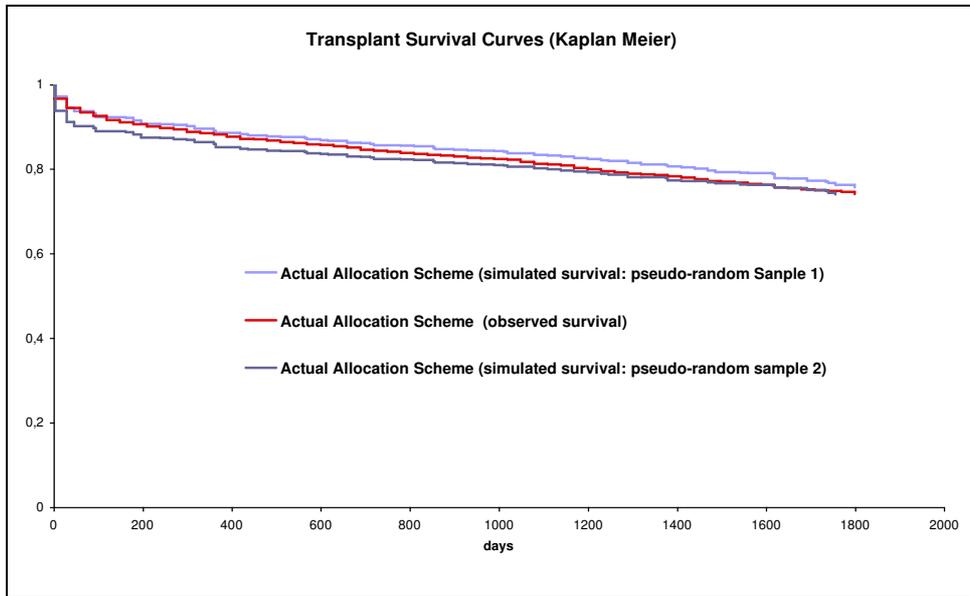


Figure 25 - Using the Observed Survival Curve as a control of the Survival Simulation Model (here with two pseudo-random samples)

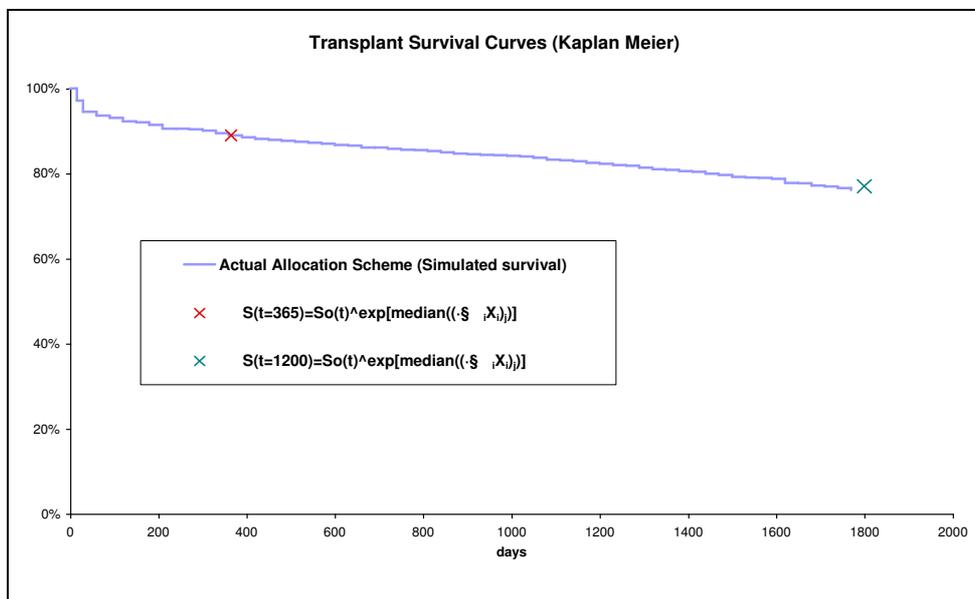


Figure 26 - Using 1 and 5 yr survival rates computed with the median risk of the Tx patients as controls

## 5. Discussion - Conclusion

### ▷ The use of historical data and the use of a Scoring function

Simulating the redistribution of organs according to new allocation schemes using historical data instead of generated ones has interesting advantages: computation is simple, it makes few assumptions and thus it is more credible for the transplant community.

The use of a scoring function has many advantages: tuning of its parameters makes the simulation tool very flexible. Various allocation schemes depending on the setting of the score function and on the distribution model have easily been assessed as demonstrated through the experimental study.

Comparing the results actually observed during a past period of time to results obtained by simulation also facilitated the debates. The question is not "is it the best?" but "is it better?". An important step was to define major allocation evaluation end-points, a key for an evidence-based debate; maybe the beginning of an answer to the absence of well-agreed optimization criteria. Simulation thus permits to tackle the allocation optimization issue that remains a research topic.

Simulation tools have been previously used to change allocation systems [6, 7, 13]. A comprehensive simulation model must include the simulation of the outcome of patients on the WL or after Tx. The use of Monte-Carlo is relevant in this context [7]. It can also comprise the generation of donors or recipients when one need to assess the impact of future changes in donors or recipients populations.

The relevance of simulation is due to the fact that organ allocation is poorly accessible to experimental study. Observational studies permits to evaluate allocation policies. But they are of limited help to bring about deep changes in allocation policies due to the fear of adverse effects. Simulation facilitates the design of new allocation schemes and their acceptability among the Transplant community as it focuses discussions on objective factors and gives an idea of expected results before the implementation of the new policy.

This work illustrates the interest of Information Technologies to deal with ethical and social issues. It underlines the value of simulation in the context of organ allocation that is in many aspects a matter for social economy.

▷ **The importance of Survival and Post-transplant outcome simulation:**

One lesson learnt working with UKT data, and a prominent result of this pilot action, is that the use of Monte-Carlo technique to simulate individual post-transplant outcome (method 1) gives results that are consistent with results obtain with method 2 assessing post-transplant outcome on the entire cohort of transplanted patients. The two methods can be used as controls as shown in figure 26.

The simulation of post or pre-transplant events at individual level using Monte-Carlo technique (method 2) is relevant method when one need to simulate the survival on the waiting list of patients whose actual graft is virtually used for another patient: this is a crucial for vital organs allocation. Method 2 is also relevant to deal with Graft loss and re-listing of patients at individual level. Method 1 cant help in such contexts.

▷ **The interest and expected added-value of a shared simulation tool:**

For the majority of European transplant organisations, Organ Allocation represents with Organ Retrieval a major responsibility. Some organisations recording data and evaluating their organ allocation policy have already performed simulations studies (ET, UK, France, Italy). Ad-hoc methods have been used, not always published. No generic and reusable tool has been built.

Building a common generic simulation tool will supply to a need. The use of a shared virtual lab to experiment allocation schemes is also a good opportunity to capitalise knowledge and experience around organ allocation among European Transplant Organisations.

The simulation of allocation by an external trans-organisational group of specialists is likely to promote the formalisation and the standardisation of allocation procedures. It might reduce the complexity and improve the readability of detailed allocation procedures presently available. It provides a mean for experimental research on organ allocation. It will introduce a shared debate on the allocation end-points to relate to each allocation objectives. It will produce step by step a comprehensive and realistic model of the entire allocation process within the entire transplantation process. The capability of the simulation tool to accurately predict the behaviour and the results of a new allocation scheme can be assessed a posteriori by the comparison of observed and predicted results.

The robustness results from an organisation to another can also be assessed through the time. The robustness and the accuracy of simulations will consolidate step by step the confidence in this shared infrastructure.

At present time, it is very difficult to take lessons from the diversity of the various existing allocation systems because the "compromises" realised in terms of objectives and methods are numerous. Building and using a shared simulation tool in such a context is likely to be a first step to reach benchmarking in the complex field of organ allocation.

The prominent result of this joint activity was to prove that a simulation tool has the potential to provide a significant help in the definition and the implementation of improved allocation schemes.

Prerequisite to simulation imply data on patients and donors be available, consistent with recommendations of deliverable 3.1.

**Recommendation for future works:**

Alliance O consortium strongly recommend:

**a) the development of a shared and generic Organ Allocation Simulation Tool (OAST):**

- to be disseminated among our institutions,
- to support changes in Allocation Schemes according to results of scientific survey and new medical science facts,
- to facilitate interactions with professionals and patients associations,
- to promote evidence-based changes in Organ Allocation Schemes, with the definition of accurate and comprehensive evaluation end-points
- to help in the definition of improved allocation schemes,
- to deal with Organ Allocation optimization.

**b) the formation of a common task force:**

- to share expertise and capitalize knowledge around Organ Allocation Simulations,
- to contribute to the detailed specifications and to the follow-up of IT engineering works,
- to facilitate training of users and dissemination of OAST.

**c) to find the required funding.**

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