

ALLIANCE-0

**EUROPEAN GROUP FOR COORDINATION OF NATIONAL RESEARCH
PROGRAMMES ON ORGAN DONATION AND TRANSPLANTATION
2004-2007**

ERA-NET SCHEME
COORDINATION ACTION
Contract EC 0011853

EXECUTIVE SUMMARY

ALLIANCE-O ERA-NET Coordination Action: description and objectives

The severe shortage of donors across all organ categories remains a major public health issue the Member States of the European Union are faced with, at the same level as the other countries worldwide. The ALLIANCE-O consortium is built on an already existing collaboration. Indeed, the partners are also involved in different groups working on organ transplantation (OT) issues, including within the Council of Europe. The group then decided to focus on the organ transplantation policies and planned to apply for an ERA-NET.

The ERA-NET ALLIANCE-O coordination action has been established to coordinate the efforts of countries on organ transplantation, each of them having different approaches and programmes to tackle OT issues. The project is coordinated by the Agence de la biomédecine, France, and involves partners from six other countries: Germany, Hungary, Italy, Portugal, Spain and United Kingdom. They are represented by national public bodies involved in the organisation of OT.

ALLIANCE-O project lasted three years and was granted € 2 million by the European Commission.

The objective was to identify existing organisations and programmes and propose strategies for improving coordination including joint activities between several countries with a national public body in charge of organ transplantation. Research programmes for improving OT efficiency concern many activities from donor to the follow-up of the patient. They are described in our workpackages.

Results of ALLIANCE-O

The six technical workpackages (WP) allowed us to go into details on each step of the organ transplantation process, from donation, allocation, safety and quality to methods for the evaluation of results, fundamental research programmes and ethical concerns. Each partner country participated in each WP: the proposals reflect a consensus between all of them. The “State of the Art” analysis generally reveals big differences and discrepancies among partner countries. Some are due to the size of the country or the number of transplantation teams, but many of the differences cannot easily be explained.

Our observations allowed us to make proposals or recommendations to strengthen the activity

- Some of those proposals involve the national or regional funding (obviously a priority factor) required to optimise the organisation of organ transplantation and organ retrieval activities, including training, quality and safety management, information systems, evaluation of results and organ allocation procedures.

The huge amount of money spent to provide dialysis for patients with end-stage renal disease in all of our countries, must be considered *per se* as the strongest incentive to organise organ retrieval with the most relevant efficacy, kidney transplantation being the most cost-effectiveness treatment.

- Many of the proposals imply collaboration between member states. The goal is not to obtain a unique uniform system, but to allow more powerful strategies:

- ⊖ common definition of terms is mandatory to share experience and results
- ⊖ common approach in tools used for organisation, training, education, allocation, safety, quality and evaluation, could avoid duplication of work and save time.

Many of these already existing tools that have been developed by one or the other countries must be now better translated and disseminated. Their improvement could also be shared to increase their pertinence and decrease the need for investments in each country.

These proposals concern all steps of activity for heart beating and non-heart beating and living donors. Some of them are immediately applicable; some others require additional implementation work.

Organ transplantation is a success story but organ shortage leaves people dying in all countries, with an important discrepancy between national rates.

The different state of the art studies carried out proved that we generally knew what direction should be taken, and allowed us to make practical recommendations. It is also clear we already have tools to improve the activity, the results and monitoring. However, the first step in any country is the sufficient funding of hospitals and a dedicated organisation for creating or reinforcing the human and technical resources.

Future perspectives for ALLIANCE-O efforts

The consortium is now eager to implement the actions after this first step of coordination, analysis and proposals.

Finally, the consortium examined the proposed actions for each WP in order to define what kind of actions should be pursued at the ALLIANCE-O group level, avoiding actions already taken in charge by other organisations. The main goal remains to avoid the duplication of work. In this purpose we will exclude actions already undertaken by organisations such as the Council of Europe: (*Ethics, Guide on safety and Quality*), the European Union (*Proposal on cooperation and safety directive, cooperation with new or future member states*), or EOEO* (*logistical cooperation*).

a) Future directions:

Our proposal is to pursue the work initiated by most of our workpackages. Each organisation member would participate in one of the working groups, to make proposals and recommendations of the ALLIANCE-O project on a voluntary basis. The overall objective is to share expertise and capitalize knowledge about Organ Transplantation by setting up technical groups for relevant topics.

b) Proposed actions:

- For Expanding Donor Pool (WP2), most of the proposals are already covered by DOPKI or ETPOD projects. All ALLIANCE-O participants being also part of these projects, we will not duplicate this work.

- For Allocation (WP 3), two actions were validated:
 - ⊗ common simulation tool for allocation rules appliance
 - ⊗ development of allocation rules based on transplantation results
- For Safety, Quality (WP 4):
 - ⊗ Concerning safety, many proposals (rare diseases, knowledge database and patients database, expanded criteria donor database) are already covered in DOPKI and do not need additional work from our group. With regard to recommendations, all ALLIANCE-O participants are also members of the Council of Europe “Group on Transplantation” and involved in the preparation of the guide on safety and quality. Furthermore, the European Union intends to initiate a brainstorming on this topic.
 - ⊗ Concerning quality, all members are interested in pursuing the work towards common indicators and methodology for hospital coordination certification and for transplantation teams auditing. Brainstorming about the use of a European donor form is also planned.
- For Evaluation methods and tools (WP 5), the fruitful collaboration leading to shared methodologies between France, Italy and UK must continue and focus on:
 - ⊗ Common definition of terms and dataset
 - ⊗ Development, dissemination of statistics models
 - ⊗ Data Base Quality standards
 - ⊗ Centre Monitoring: Common methodology for transplant result analysis
 - ⊗ Methodology of data exchange for specific evaluation
- For Fundamental Research (WP6), the group decided not to pursue in this direction beyond the work already done. The project called TRIE focuses on these research aspects.
- For Ethical and legal issues (WP 7), the subjects should not overlap with the Council of Europe or WHO work, but databases or tools should be developed to take specific questions into account in this field:
 - ⊗ Children common data base
 - ⊗ Non-residents
 - ⊗ Minorities data
 - ⊗ Tourism, trafficking survey
 - ⊗ Double listing of patients

Concerning these various issues, the standardisation of the definitions of terms and of methods and the interoperability of information systems could become a transversal topic for the traceability, the evaluation of results, the allocation of organs and the simulation of new allocation schemes. Information technologies can also be used to support expertise and knowledge management.

Organisation and enlargement of the future ALLIANCE-O

Each group will work on voluntary bases, reporting to a common annual meeting.

The technical groups will be opened to any European, national or international organisation officially involved in procurement, allocation or transplantation.

As many EOEO* members have expressed their interest in joining our project, we will organise the next ALLIANCE-O meeting at the same time as the 2008 EOEO meeting.

New developments at the European Commission level concerning their proposal for coordinated actions in the field of organ transplantation could change these plans.

In the name of the whole consortium, the Agence de la biomédecine would like to thank the European Commission for its financial support. The Agence de la biomédecine thank all the medical and administrative staff from all the partner organisations which participated in ALLIANCE-O and made this project a success in a very pleasant and convivial working atmosphere.

*EOEO: European Organ Exchange Organisation.

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I. GENERAL INTRODUCTION

1. Organ transplantation: a success story but a recurrent shortage

Since the first successful kidney transplant in 1954, organ transplantation has progressively become a health care practice of unequivocal importance. Human organ transplantation is defined as the therapeutic use of human organs as a substitute for one that is non-functional. Kidney transplantation represents the best therapeutic option for patients with end stage renal disease, providing best outcomes in terms of survival, quality of life and cost-effectiveness than other renal replacement therapies. Transplantation represents an almost unique therapeutic alternative for patients with end stage liver, heart and lung failure, although liver transplantation has been also applied to the treatment of specific pathologies not causing end stage liver failure. Pancreas transplantation, in its different modalities, has become a solution to re-establish insulin secretion in selected diabetic patients aiming to improve patient survival and quality of life. Small bowel transplantation usually performed as a part of a multi-organ transplant, is still a relatively rare procedure but aimed to solve life-threatening conditions.

Transplantation in general has higher measurable quality indicators than other replacement therapies such as dialysis. Results of organ transplantation are progressively improving over time, according to the figures provided by national and international registries. This improvement is due to the advance in the surgical techniques, the availability of new and more specific immunosuppressive drugs, and the experience acquired by the transplant surgical and medical teams.

The reduction of health cost due to kidney transplantation is huge, as dialysis costs 5-6 times more than transplantation. Currently more than 40,000 patients are waiting for an organ transplant in Western Europe. Mortality rate on the waiting list ranges from 5% to 30% depending on the country and the type of organ. Improving organ transplantation organization through borders, sharing practices and programmes to improve organ donation as well as transplantation efficiency certainly has a huge socio-economic impact in terms of health cost, working days and quality of life of patients. Such figures are quite difficult to establish precisely and further work on this aspect is desirable. In fact, organ transplantation not only provides the possibility of saving lives but also yields the best results in terms of quality of life for patients and the reduction of long-term health care costs.

Success of transplantation depends on several factors, related in part to recipient health conditions, in part to donor characteristics. The organ may come from a deceased or a living donor. Today this procedure is used throughout the European Union. Each donated organ should have an acceptable quality and should not expose the recipient to unacceptable risks. The evaluation of donors suitability is largely influenced by the limited availability of organs, the balance between risks and expected benefits for the recipient and time constraints due to ischemia of organs. Despite these limitations and taking into account the risk of transmission of infectious or neoplastic diseases, it is of first importance to establish a consensus about common basic guidelines and methodologies. It could be then matter of choice at a more local or national level to take more stringent measures if required, but keeping in mind the balance between benefit and

risk of not being grafted for a patient. Expanding the limits of criteria for older or other donors should also take this aspect into account. Increased patient mortality in order to avoid tolerable risk would be undesirable.

Organ shortage remains a major obstacle, preventing the full development of transplantation services, and sets a severe limit on the number of patients who benefit from this therapy. Although organ transplantation has saved thousands of lives and transformed the quality of life of thousands more, many people will not have that opportunity, as demand for organs is never met. The main problem in the area of transplantation lies in the shortage of donated organs. In fact, organ transplantation is in practice confronted to the lack of available grafts, but also the possible failure of the transplantation including chronic rejection. The demand is increasing continuously owing to greater experience, better results and increasing indication while the number of deceased donors remains stable

Large differences in organ donation and transplantation rates exist within the European Union (EU), with a procurement rate ranging from 34.6 donors per million people in Spain to less than 14 in many countries and nearly none in some others. These huge disparities have multiple factors and some organizational patterns clearly work better than others. Sufficient human and technical resources for donor detection, procurement, transplantation and follow-up are a prerequisite and funding is crucial. Scarceness of organ also impacts on transplantation resources and activity. Also, the shortage of legally donated organs can, unfortunately, encourage illegal human organ trafficking; which creates both serious ethical problems and health dangers.

2. Intergovernmental Context

During the 20th century biomedical research enabled dramatic progresses in the field of health, especially in the domain of organ transplantation. This progress has had repercussions on the perception of such values as the individual, family, health, private life, human rights and human dignity. Organ transplantation is such a sensitive field to many aspects such as ethics, regulations and the medical benefit for the patient, that many institutions have produced different kind of reports and recommendation since several decades in support to policies.

2.1. The Council of Europe

In order to facilitate organ and tissue transplantation in Europe in the interest of the patients, necessity emerged to see to the respect of individual rights and liberties and to prevent the commercialisation of parts of the human body during the procurement, exchange and allocation of organs and tissues.

Indeed, the Council of Europe adopted the first Resolution (78) 29 of May, 11, 1978, with the aim of establishing harmonious legislation for a better protection of donators and recipients while favouring progresses in science and medical therapy.

In 1987, the Council of Europe set up the Select Committee of Experts on the organisational aspects of cooperation in organ transplantation (SP-CTO). This group prepared many recommendations for the Committee of Minister (see Annexes). The Expert Group is now changed into a Steering Committee on Transplantation and will continue its work on the ethical and organisational aspects.

A new step was reached with the Oviedo Convention adopted in 1997 by the Council of Europe since its influence is more significant than a simple recommendation or resolution. The aim of the Convention is, as defined in article 1, to protect the human being in his/her dignity and identity, and to guarantee anybody without discrimination the respect of his/her integrity and other fundamental rights and liberties concerning the application of biology and medicine. This convention has an annex: Additional Protocol relating to human organ and tissue transplantation dated January 24, 2002. The article 21 bans any financial aspect in this domain.

The Council of Europe also set up the group of specialists on quality assurance for organs, tissues and cells and drew up a *“Guide to Safety and Quality Assurance for Organs, Tissues and Cells”* in February 2002, updated in 2006 and 2007.

2.2. The World Health Organization

The resolution WHA 44.25 adopted by the WHO in 1991 recommend the member States that they take “guiding principles” into account as regards organs and tissues, aiming at condemning the sale and purchase of human organs.

The WHO has been working on the revision of the 1991 Guiding Principles on Human Organ Transplantation. In 2004, the World Health Assembly adopted a resolution requesting the Director General to continue examining and collecting global data on the practices, safety, quality, efficacy and epidemiology of allogenic transplantation and on ethical issues, including living donation, in order to update *“the Guiding Principles on Human Organ Transplantation”*. In response, the Secretariat has examined relevant issues through consultations with experts and representatives of health authorities and of scientific and professional societies within a working group *“Global forum on transplantation”*. Also, with technical and financial support from the Spanish Government, the Global Knowledge base on Transplantation was launched in 2006 as a tool to monitor activities and practices in transplantation and to foster transparency at a global level.

2.3. The European Union

a) The Commission, under article 152 of the Amsterdam Treaty (1997), considers the need to identify, monitor and control the factors influencing the quality and safety of organs used for transplantation at the European Union level. From 1997 on, this article has enabled the European Parliament and Council to adopt health measures setting high standards of quality and safety of blood, blood components, organs and substances of human origin used in medical treatment. In order to improve the quality and safety of the products stemming from the human body the EU adopted directives concerning blood, tissues and cells such as the Directive 2004/23/CE of the European Parliament and Council dated March 31, 2004, relating to the set up of quality and safety standards for donation, procurement, control, transformation, storage and distribution of human cells and tissues. However the Community role is subsidiary and mainly involves supporting the efforts of the Member States and helping them formulate and implement coordinated objectives and strategies.

b) Recently several initiatives have been undertaken by the European Commission in various fields of transplantation organization in order to ensure a better coordination of the actions carried out by the Member States through the exchange of their experience.

- *Organ transplantation organisations survey*: at the beginning of year 2003 the European Commission conducted a survey¹ on requirements related to organ transplant in the 25 EU Member States as well as in Bulgaria, Norway, Romania and Turkey. The survey was intended to collect information on the legal framework related to ethical, organisational and technical aspects of organ transplant.

- *European funded projects (see Table in Annexe 3)*:

The Information Society Directorate General did support the creation of a European registry on organs, cells and tissues through the EURODONOR and EURO CET projects (European Registry on Organs, Cells and Tissues). This last project is a database and internet portal covering aspects of organs, tissues and cells donation in Europe.

The Health and Consumer Protection Directorate General did or is currently funding projects on transplantation:

- ⊕ EQSTB project is an analysis of the factors influencing the final tissue quality and security;
- ⊕ EUSTITE project targets the harmonisation of tissue establishment inspection and accreditation systems;
- ⊕ ETPOD consists in the adaptation/improvement for training programs on organ donation (TPM);
- ⊕ POSEIDON project aims at improving safety of unrelated haematopoietic stem cell transplantation and at promoting more egalitarian access to this therapy.

The Research Directorate General in the framework of the FP6 is also funding several projects besides ALLIANCE-O. Two of them have been conceived and funded as an action of Support to Policy (FP6, 3rd block), and another one is an Integrated Project funded in the frame of the “life sciences” thematic priority (See annex 3).

- ⊕ DOPKI project focuses on the improvement of the potential of organ donation, such as promoting cooperation and sharing information and best practices among certain European countries,
- ⊕ Riset project consists in research on “*Reprogramming the Immune System for Establishment of Tolerance of transplanted organs*”.
- ⊕ TRIE is a recently started Specific Support Action which aims at trying to improve the coordination in the scientific and biomedical research domains relevant to transplantation and tolerance at a supra national level.

ALLIANCE-O partners are also involved in one or more of these different projects.

¹ http://ec.europa.eu/health/ph_threats/human_substance/documents/organ_survey.pdf.

Indeed by funding these different initiatives over a period of several years and setting up different coordination meetings such as the Inter-DG workshop held in Brussels in December 2005, the Commission showed its strong willingness to support coordination in the field of organ transplantation.

- c) One of the most important aims of European Union policies is that all inhabitants should have the same duties and rights. This obviously applies to health care provision and hence transplantation medicine. The provision of harmonized health standards and guidelines is of the upmost interest. It is also very important to study the different problems likely to affect each national system and try to harmonize common ways to face and solve these problems.

As an annex to its recent communication (May 30th 2007) the Commission provided a comprehensive impact assessment, which identifies the major policy challenges with respect to organ donation and transplantation. These include ensuring quality and safety for human organs, increasing organ availability, and enhancing the efficiency and accessibility of transplantation systems in the EU Member States. The Commission intends to act in response to these challenges in the areas where there is a clear added value for EU initiatives. The communication entails two mechanisms of action: an action plan for strengthened coordination between Member States and an EU legal instrument on quality and safety of organ donation and transplantation. The results of an open consultation launched by the Commission demonstrated the wide support for the coordination measures and contradictory positions about the need for a safety directive. Non UE countries should also been taken into consideration.

2.4. European Organ Exchange Organization (EOEO)

EOEO is an informal group of transplant agencies which started having yearly meetings in order to discuss very operational issues such as exchange of organs among countries and common procedures and policies.

Today the group is composed of national agencies as well as international foundations such as Eurotransplant and Scandiatransplant. It has elaborated a chart aimed at harmonising procedures of organ exchanges between countries, and taking into account the waiting time of patients moving from one country to the other within the European region.

The aim of this group is to keep a flexible and operational organisation that does not overlap with institutional groups such as Council of Europe or European commission but rather to be complementary.

2.5. The transnational cooperation

There are several scientific societies or professional associations in the field or sub-domains of transplantation and **there is a high risk of duplicate work**. The work done in different contexts is sometimes difficult to compare and coordinate due to unnecessary methodological variations. The organisation of work in a common frame and the harmonization of analysis and implementation practices are hence of great interest with the benefit for patient and citizen kept in mind. The development of a uniform and comprehensive set of standards or suggestion programs will be the basis for a better care in this field within the scope of the European countries.

3. ALLIANCE-O

3.1. From collaboration to European coordination: ALLIANCE-O turned to ERANET

The ALLIANCE-O consortium is built on an already existing collaboration. Indeed, a bilateral initiative between France and Germany (meeting with Health Ministers, Strasbourg 2002) led to the Symposium of Frankfurt (2003) in which the respective agencies of several European countries concerned with organ transplantation took part together with representatives of the different Ministries of Health. Since then Portugal joined this group, with the participation of Organização Portuguesa de Transplantação. ALLIANCE-O partners are also involved in different groups working on issues of organ transplantation (OT) including within the Council of Europe.

The Frankfurt meeting (Sept 16th 2003), was the opportunity on the occasion of the European Forum “Alliance for Organ Donation” of a Joint Declaration of Governments and Procurement Organizations from France, Germany, Hungary, Italy and Spain and the United Kingdom. The group then decided to focus on the organ transplantation policies and planned to apply for an ERA-NET coordination action.

The ERA-NET scheme was a new instrument of the FP6 which aims at promoting collaboration and coordination of research activities undertaken at national or regional level in Member States and associates, by supporting a network of research programmes and mutual collaboration in these programmes.

3.2. ALLIANCE-O ERA-NET Coordination Action: description and objectives

The severe shortage of donors across all organ categories remains a major public health issue the Member States of the European Union are faced with together with the other countries in the world. Cooperation between the Member States should focus on identifying the most efficient systems, sharing experience and promoting best practice as well as supporting Member States whose transplantation systems are not yet sufficiently developed.

The ERA-NET ALLIANCE-O project has been established to coordinate the research efforts of countries on organ transplantation, each of them having different approaches and programmes to tackle the issues of organ transplantation.

The project is coordinated by the French partner, Agence de la biomédecine, and involves partners from six other countries: Germany, Hungary, Italy, Portugal, Spain and United Kingdom.

These seven partners are represented by national public bodies involved in the organisation of OT:

- ⊙ Agence de la biomédecine in France,
- ⊙ Deutsche Stiftung Organtransplantation (DSO) in Germany,
- ⊙ Hungarotransplant (Hu-T) in Hungary,
- ⊙ Centro Nazionale Trapianti (CNT) in Italy,
- ⊙ Organização Portuguesa de Transplantação (OPT) in Portugal,

- ⊗ Organizacion Nacional de Trasplantes (ONT) in Spain,
- ⊗ UK Transplant (UKT) in the United Kingdom.

ALLIANCE-O project lasted three years and was granted 2 million Euros by the European Commission.

The overall objectives of ALLIANCE-O are to set up cooperation and coordination of national and regional research activities through networking of programmes in the field of OT.

Knowing that several countries have a national public body in charge of organ transplantation, the aim is to identify existing programmes and to propose strategies for better coordination and cooperation including joint activities. Research programmes for improving OT efficiency concern many activities but can be categorised on a step-by-step basis as follows:

- ⊗ Expanding donor pool (heart beating, non heart beating donors, living donors)
- ⊗ Improving allocation rules
- ⊗ Improving safety and quality of OT
- ⊗ Improving evaluation methodology
- ⊗ Improving fundamental research
- ⊗ Improving coordination on ethical and legal issues raised in the field of OT

Three specific objectives were considered:

a) The activities of the Consortium have addressed, for each step, questions at the coordination level of Research programmes. The identification and comparison of the respective national/regional programmes, their methodologies (aims, organization, evaluation, funding, benchmarking) and their results will be performed.

The aim of this **benchmarking** is:

- to improve, set up and coordinate the exchange of information, good practices and results of research programmes led by the different members among partners;
- to enhance research relevance and validity, and maximise research utility by avoiding duplication;
- to develop, in a coordinated way, an **applicable common methodology** that could be used (through joint actions) to improve the potential for organ donation, the allocation, quality and safety of organs, and the evaluation of OT.

b) From these different benchmarking analysis, relevant **recommendations** and position papers where discussed.

c) For some of these programmes, **joint pilot actions** focused on specific questions for which some of the partners are already involved in identified comparable objectives and for which joint activity is already obviously desirable.

3.3. Results of ALLIANCE-O

The work progressed well during these three years, with an excellent collaboration between the members. The “state of the art” of each work package (WP) led to a great deal of work involving questionnaires, survey analysis and synthesis. All the tasks of all WP have been performed in a quite consensual manner. The last step of work on recommendations or proposals led us to fruitful brainstorming and strategies sharing.

The ALLIANCE-O White Paper summarizes the findings and proposals of each work package expressed by the respective leaders. It is composed as follows:

- ⊕ WP1: Coordination activities, management and Dissemination (ABM, France)
- ⊕ WP2: Expanding donor pool (ONT, Spain)
- ⊕ WP3: Comparison of Allocation rules & their impact on equity & efficiency (ABM, France)
- ⊕ WP4: Coordinated methodology in increasing safety and quality of organ transplantation (CNT, Italy)
- ⊕ WP5: Coordination of evaluation methods of transplantation performance (UKT, United-Kingdom)
- ⊕ WP6: Fundamental research activities (DSO, Germany)
- ⊕ WP7: Comparative analysis of Ethical and legal aspects (DSO, Germany)

II. SUMMARY OF RESULTS AND RECOMMENDATIONS

Expanding donor pool (WP2)

I. Introduction

Work package 2 (WP2) in ALLIANCE-O project deals with the problem of organ shortage, trying to explore the ways to expand the donor pool and increase the opportunities of transplantation in the European countries. Severe organ shortage remains the main challenge to be faced by member states in the European Union in the field of transplantation. As a result of organ shortage, there is an important gap between the number of patients waiting for a transplant and the number of patients who are indeed transplanted. Besides, while the number of patients being included in the waiting list increases over time, the rate of organ donation and the number of organs available for transplantation does not increase or improves at a slower rate.

II. State of the Art in expanding the donor pool and donor pool estimation

- **Wide differences exist in organ donation and transplantation activities among the European countries and when compared to other countries outside Europe.**

The analysis of harmonized data from the year 2004, recorded for 39 countries, made apparent to ALLIANCE-O consortium this high degree of variation. A population of nearly 600 million people was covered by this analysis. However, there was a very high diversity, both in geographic extension and population. Six countries have over 40 million inhabitants and accounted for 60% of the population (370 million people) and 23 countries have fewer than 10 million inhabitants. Deceased donation rates ranged from 0.5 up to 34.6 donors pmp (median 14.25) and corresponding transplantation activities ranged from 1.6 to 57.6 pmp (median 30.69) for kidney and 0.8 to 24 pmp (median 10.2) for the liver. Heart and lung transplantation activities were obviously lower and also variable, ranging from 0.13 to 6.8 procedures pmp (median 3.4) for the heart and from 0.1 to 5 procedures pmp (median 1.2) for the lung.

- **Important differences were also noticed among the evaluated countries with regards to living donation activity.**

The percentage of kidney transplants performed with living donors was as variable as 0% to 100%, with three countries not registering any living kidney transplantation activity. Therefore, while living donation was very frequent in some countries, it still remained an anecdotal procedure in some others.

The same variability applied to non-heart beating donation (NHBD), which was present in only 10 of the analyzed countries. The recorded activity was low in every case, ranging from 0.01 to 6.8 donors pmp (median 0.42). Nine of these countries reported kidney transplantation activities with NHBD and only five described liver procedures with organs obtained from this source.

It also appears from this analysis that the **same important variation applies to the size of the waiting lists**, as well as to the admittance rates and the mortality while in the waiting list. The ALLIANCE-O consortium agreed that these differences are probably not only the consequence of variations in the incidence and prevalence of specific diseases, susceptible of being treated through organ transplantation. Therefore, this heterogeneity should be a matter of further and deeper analysis.

- **In order to understand the differences in donation and transplantation activities, a comparison on the basic characteristics and frameworks of the countries seemed mandatory.**

Therefore, a comprehensive picture of the socio-demographic, economic, health-care and mortality data, as well as the legal, organizational and technical background on donation and transplantation issues for every European country was established in WP2, so facilitating the comparisons of the countries.

The association between variations of sociodemographic, economic, health-care and mortality (general mortality and by specific causes potentially leading to brain death) data and among countries was also explored. Notably, no significant relations between any of the previously mentioned factors and deceased donation rates were observed, relations that could have served as a basis to generate country-based indicators to estimate the potential of donation. The consortium understands that other factors, mainly of organizational and structural nature, may explain many of the differences in the donation activity among the countries.

- **To evaluate the state of the art in expanding the donor pool, the consortium analyzed the already running programmes aimed at expanding organ donation and retrieval in ALLIANCE-O countries.**

Circulation and discussion of a specifically designed questionnaire ensured a detailed exchange of experiences. Common approaches to increase the donor pool, but also substantial differences were noticed with regards to the legal, technical, organizational, training, educational, promotional and financial initiatives developed, as well as the human resources used across ALLIANCE-O countries. These differences applied to heart beating and living donors, but especially to non heart beating donor (NHBD), its use not being even legally admitted in two of the seven ALLIANCE-O countries (Germany and Hungary).

From the **organizational point of view, differences were quite small among** the countries, with the exception of the profile of the hospital figure of the so-called key donation person in hospitals. However, **from the technical perspective, important differences** were noticed. For instance, the use of expanded criteria donors (ECD) was highly variable across the countries, with the greatest use of old and very old donors described in Italy and Spain (in the year 2003, respectively 17.5% and 16.5% of organ donors were over the age of 70). The same variation applies to the use of donors with specific conditions. While organs from this type of donors are allocated in some countries under very specific circumstances to ensure safety, these same conditions represent absolute contraindications to donate in others (this is for instance the case for donors with a positive serology for HCV and/or HBV).

The use of **special techniques**, such as split or domino liver transplantation (this last technique highly dependent on the prevalence of specific pathologies, as familial amyloidotic polyneuropathy) and double kidney transplantation with kidneys from ECD also varies among ALLIANCE-O countries, which suggests a scenario with a potential to increase organ donation and transplantation in Europe. Also in the technical dimension, initiatives for the study of the potential of donation have only been developed in some European countries, some of them with the added value of analyzing the performance, identifying weak areas that are able to be improved through the implementation of specifically tailored corrective measures in the complex and delicate process of donation.

Finally, after a detailed description **of educational and promotional activities across ALLIANCE-O countries** found that similar approaches have been developed to face the common

problem of the refusal to donate. These activities are targeted to the general population, specific social groups (e.g. mass media) and health-care professionals. It should however be emphasised that in most of the countries there is no strategic plan to reduce refusals to donate, based on the planning and integration, of not only educational and promotional activities, but also of training programmes, specifically those targeted to the approach to the donor's family.

III. Position of the group on expanding the donor pool

The usefulness of all the previously analyzed expansion of the donor pool initiatives was discussed among the partners (except for legal and ethical issues, which were discussed within WP7). Unfortunately, in the field of organ donation we all agreed that establishing the position of the group with an evidence-based approach is not always possible. In spite of this important limitation, the consortium reached a common position concerning a different set of initiatives and programmes targeted to expanding the donor pool on heart beating donation (HBD), NHBD and living donation. The set of statements summarizes the group's position.

1. Brain death donors (heart beating donors, HBD)

• Organizational initiatives

- a) **Every hospital with intensive care facilities** should be available **to detect brain death and activate the donation process**. Policies should be developed which encourage hospitals to actively engage in organ donation.
- b) A sufficient number of qualified personnel and an adequate structure should exist at any procurement hospital in order to effectively develop the activities of donation.
- c) **A key donation person** with the main responsibility of developing a **proactive donor detection programme** should be appointed at every acute care hospital.
- d) **A network of transplant procurement hospitals** should be developed, where small hospitals are progressively incorporated.
- e) To optimise organ donation, there is need for a **supra hospital transplant organisation**, appropriate in size and structure to the local situation, with specific responsibilities for the whole process of organ procurement.
- f) The **most effective organisational approach** balances the requirements for effective organ procurement (small/local) with those for organ allocation (large, national/ multinational). The aim should be to optimise organ procurement whilst ensuring the most clinically effective allocation of organs and tissues.
- g) **A donor process evaluation program** should be developed in order to estimate the potential of donation within a hospital and to identify areas of improvement in the process of donation, providing the basis to introduce corrective measures. Strategies to evaluate the **cost-effectiveness** of these programmes should also be developed.
- h) **A quality management** approach of the process of donation/transplantation should be developed which establishes standardized protocols, evaluates performance and introduces measures to improve. Participation of hospitals in the donation process should be considered a quality issue.

- **Human resources**

- a) **The number of persons** involved in the process of donation at every procurement hospital should be sufficient to efficiently cover all the steps of the process.
- b) The presence of the **key donation person** at every hospital with intensive care facilities, with a principal responsibility for developing a proactive donor detection programme represents the most important human element in the optimisation of organ donation.
- c) Other roles to support specific activities in the process of donation should be taken into consideration.
- d) A well-organized **suprahospital team** should exist, with enough sufficiently trained members to enforce and develop strategies to support all the process of organ donation.

- **Technical initiatives**

- a) The use of **special techniques** such as split and domino liver transplantation or double kidney transplantation with kidneys from **expanded criteria donors** (ECD) may be considered as areas that could contribute to the expansion of the donor pool, provided an adequate evaluation of results obtained by using these organs is ensured.
- b) The consortium agrees on giving a general **definition of ECD**, as those potentially related to worse results in the recipients when compared to recipients receiving their organs from classical or more ideal donors. According to this definition we would include: extreme ages of life, transmissible diseases (infections and neoplasias) and other pathologies. When allocated in specific conditions, the use of organs from ECD may give very acceptable results. Pilot studies should be carefully and properly evaluated.
- c) The **safety limits in the use of organs obtained from ECD** should be properly evaluated through the development of registries, collecting information on the outcome of the corresponding recipients. Consensus Documents and Guidelines on the adequate use of organs from ECD should be created if not available and properly updated with an evidence based approach.

- **Training initiatives**

- a) Training should properly **cover all the steps of the donation process**: brain death diagnosis, brain death referral, and evaluation of the donor, maintenance of the donor, the approach to the family and organ retrieval.
- b) Training in the context of a properly **planned, harmonized and accredited national programme** would be the ideal approach.
- c) A system to continuously evaluate the efficacy of the training program should be developed.

- **Financial initiatives**

- a) **Hospitals should be sufficiently resourced** to efficiently develop all the activities related to donation and transplantation. Donation should never be a disincentive activity for procurement hospitals.
- b) To develop their specific functions related to increase the donor pool, the supra hospital transplant organizations should also be sufficiently resourced.

- c) European and national programmes and activities aimed at expanding the donor pool whilst ensuring quality should be properly funded: donor process evaluation, quality management, training, and organ registries, among others.

2. Non-heart beating donors (NHBD)

- a) NHBD may be considered to be **a real alternative source of organs faced with donor shortage**, so provisions should exist in the countries in order to allow this kind of programmes to be drawn up. NHBD should always be considered as a complementary activity to HBD. **Maastricht category type 1 NHBD (dead on arrival)** offers with no doubt a large potential to increase deceased donation activity, although experience with this type of donors is still very limited.
- b) Non kidney transplants from NHBD should be properly explored and evaluated. Research should be promoted to ensure that results with specific types of organs (e.g. livers) are susceptible to improvement.
- c) NHBD should be approached under the scope of **pilot studies** laid by **highly motivated teams** and ensuring that a **continuous sharing of experience** takes place.
- d) NHBD programmes should take into consideration the need for a **highly trained hospital team**, available 24 hours a day. A high qualification with regards to preservation techniques to guarantee the quality of the organs retrieved should be mandatory. It would be highly advisable that this team is led by or well coordinated with the so-called key donation person, ensuring a close link between NHBD and HBD programmes. Hospital facilities (e.g. emergency room) should be available to ensure that preservation manoeuvres start at the right time.
- e) **Specifically and highly trained extra-hospital emergency care teams** are a necessary human resource in order to implement any programme with type 1 Maastricht category NHBD.
- f) **Development of specific** consensus documents, protocols and, guidelines should be encouraged, up-dated on an evidence based approach, to ensure the quality of the organs obtained from this source and the improvement of results over time. Registration and continuous evaluation of results obtained with organs from NHBD seem mandatory through local, national or international registries.
- g) **Research should be promoted** to ensure that quality of organs obtained from these donors progressively increases and provides increasingly better results. **Preservation techniques** represent an area where research should be highly supported.
- h) **Continuous training** of teams with ongoing activity and teams developing new programmes should be ensured. Specific attention should be paid to the continuous training of extra-hospital emergency care teams in the case of Maastricht type 1 NHBD, to ensure a proper detection and maintenance of the potential donor.
- i) **A specific budget** for hospitals developing NHBD programmes should be ensured, covering human and material resources, as well as training and research. A **cost-effectiveness evaluation** of NHBD is needed.

3. Living donation

- a) Living donation is **a real alternative to improve the availability of organs** for transplantation. However, it is necessary to develop living donor programmes in a way that is complementary to

the deceased donation ones, never in competition. A negative correlation between the living and the deceased transplantation activity should not exist.

- b) Morbidity and mortality related to living donation differs according to the type of donated organ. While **referring to living donation, an explicit differentiation between kidney and liver donation must be clearly distinguished**, because of the different risks related to nephrectomy and partial hepatectomy, even in a healthy person. Living liver donation (especially right lobe) should be considered with caution.
- c) **Adequate tools** should be developed to ensure that **information about the medical, psychological, financial and social complications related to living donation in the short and the long term is properly collected**. This information should help to develop evidence based guidelines and consensus documents, addressing the selection, evaluation and follow-up of the living donors.
- d) **The development of new surgical alternatives** and any other type of initiative in living donation and transplantation, aiming to increase the donor's safety, facilitate the recovery of the donors and return to an active and normal life and to improve recipient's outcome should be highly encouraged and research should be promoted in this field.
- e) **The possibility of living donation should be offered to any patient accessing the waiting lists, always on the basis of individual circumstances**. Adequate and complete information should be provided to the patients and their relatives. The appointment of specific professionals in charge of providing this kind of information could be considered in hospitals with an important living donor transplantation activity. In the case of living kidney transplantation, this post could even be considered for large dialysis units or sets of small ones.
- f) **Living donation should receive adequate resources**, especially keeping in mind the benefit not only for the recipient, but also for the entire community, since it allows a person to leave the waiting list at a moment when deceased organ donation is insufficient to fulfil the demand of organs for transplantation. Living donation should never be a disincentive for hospitals.
- g) **Authorities should ensure the health-care coverage of the living donor** before, during and after the procedure, ensuring the long-term access of the living donor to the health care system. Social benefits for living donors should be explored, as well as ensuring that health/life insurances do not penalize the living donor.
- h) **Continuous training** of professionals in charge of an ongoing or new living donation programmes should be guaranteed. The exchange of experiences among medical and surgical teams should be encouraged.
- i) While many ethical and technical aspects still need to be solved, **paired kidney donation (cross over kidney donation)** represents a valuable approach to increase the kidney donor pool and the possibilities of transplantation. Provisions may exist so this kind of specific programmes may be drawn up on the basis of local circumstances.

IV. Position of the group on promotion of organ donation and transplantation

- a) The main objectives of **promotion of organ** donation and transplantation are **increasing referral of brain deaths** to be considered as potential organ donors and **decreasing refusals** to donate.

- b) Surveys** targeted to the general population **and/or specific groups** in the population to explore a set of issues on the field of organ donation and transplantation have been carried out at an international and a national level. Although these surveys are not considered in themselves to be promotional activities, the collected information may guide the design of specific promotional actions and provide useful tools to improve the techniques of approaching the family and the request of organ donation.
- c) Students, teenagers and young adults** are usually more favourable to organ donation than other age groups and they may facilitate the development of discussions about organ donation within the family context. The development of specifically tailored efficient educational and informative tools targeting this group should be encouraged.
- d) Minorities, religious and ethnic groups** have been recognized in general terms as being more reluctant to organ donation. Based on local circumstances and needs, the development of specific informative tools targeting these groups could be considered.
- e) Direct publicity campaigns** on donation and transplantation are not expected to have a deep impact on the donation rates. On the contrary, there is a growing feeling that their practical effects are close to nil. However, **efficient information** on donation and transplantation should be easily available to ensure that society at large is aware of the efficiency of transplantation and the need for organ donation. For countries where registers of people consenting to and/or refusing donation are available, it should always be ensured that any recorded decision is made on the basis of full and accurate donation.
- f) Donor cards** are widely used among the countries and they may indeed facilitate the communication with the family at the moment of bereavement. It should be emphasised that in countries with presumed consent, the donor card should not be an official document.
- g) The mass media** may be considered a very specific target that deserves special attention, since it represents the most adequate channel to reach the public opinion. A constant, fluent and easy relationship of the transplant organizations with the mass media should be ensured and cultivated.
- h) Health-care professionals**, whether directly involved or not involved in the process of organ donation must be aware of the fact that it is necessary to conform to a reliable and homogeneous system of information on organ donation and transplantation in which the public can have full confidence. Since they are responsible for identifying potential donors, approaching the grieving families and/or providing general information on the process health-care professionals deserve special support.
- i) Promotion of organ donation is something which is needed, but it is not enough to ensure the success of the organ procurement and transplantation system.** To efficiently decrease refusals to donate, promotion should be complemented by the **specific training of those professionals** involved in the process of donation and transplantation. Training on the technique of approaching the family should be encouraged and supported. In the context of a positive climate towards donation and transplantation, an appropriate technique during the family interview to request organ donation can make a major difference in obtaining a positive or a negative answer to proceed with organ donation.
- j) Promotional activities**, integrated with specific training programmes for those health-care professionals involved in the process of donation and transplantation, should be implemented as a **national strategic plan**. The informational and educational needs of the general population, specific groups and health-care professionals, whether involved or not in the process of dona-

tion should be explored. A clear definition of the objectives of these global strategies should be established. Specifically tailored promotional, educational and training activities should be developed accordingly.

k) A general consensus of all those involved in the process of organ donation and transplantation is essential to transmit a clear, consistent and uniform information to generate a positive climate concerning donation and transplantation, not only at a national, but also at a European and even a global level.

V. The ALLIANCE-O proposal of common methods and indicators for donor pool estimation

The consortium agrees that **programmes based on the review of clinical charts of patients dying at the intensive care units** of procurement hospitals are the best approach to estimate the potential of organ donation. Keeping in mind local structural and organizational factors and limitations, the development of this kind of programmes is highly recommended, not only to evaluate the potential of organ donation, but also to progressively improve the performance in the donation process.

Self-reporting of data from organ procurement hospitals to the organ procurement organizations could represent the basis of these programmes. **External audits** based on the re-review of the medical charts of patients dying at the **intensive care units** by independent reviewers should also be considered. These audits would potentially give a more objective evaluation of the donation potential and lead to a better performance in the donation process, by analyzing the causes of organ or donor losses that are potentially avoidable. It should be outlined that review of the medical records should rely on **highly trained staff**, whether for self-reporting or for external audits. Finally, strategies aimed to analyse the **cost-effectiveness** of these programmes should also be developed.

A **set of indicators** to estimate the donation potential, but also to evaluate the outcome in the donation process and the global effectiveness of the system have been proposed by the consortium.

Both the methodology and the common indicators have been proposed in agreement with another on-going European project, DOPKI (Increasing Knowledge and Practices in Organ Donation). As a pilot action, DOPKI (www.dopki.es) intends the practical application of this methodology in selected European hospitals. The experience gained will contribute to better facing the problem of organ shortage, not only in Europe, but in the whole world.

Organ allocation in Europe (WP3)

The general objective of WP3 was to compare allocation rules in European countries and their impact on equity and efficacy. It aimed at providing a conceptual toolbox for public health policy makers and institutions involved in organ allocation in European Countries and to build a proposal for a common simulation tool for Allocation Policies, including a joint action using a simulation tool prototype with data from the Agence de la biomédecine and from UKT.

I. Some key points to promote evidence-based organ allocation policies

Organ allocation is **a crucial and complex process linking organ retrieval and transplantation**. Most transplantation candidates have life-threatening organ failure. The allocation of an organ results in the selection of one patient and the exclusion of other patients. Due to these societal and ethical issues, **organ allocation requires transparency and guarantee in terms of justice, equity and efficiency**.

The allocation process is **triggered by the identification of a donor. It involves the distribution of all retrieved organs and tissues to a set of recipients**. The process must take into account issues of logistics and communications related to the management of propositions to transplant teams. **Feasibility, simplicity, rapidity and robustness of allocation procedures are also crucial issues**. For the transplantation medical staff, two points are particularly essential: the place of the medical decision within the allocation process and the consequences of organ allocation schemes on the transplantation activity of their centre.

Due to the scarcity of organs and to the competition between transplantation centres to obtain the best organs for their patients, any change in organ allocation policy remains a sensitive issue in public health decision-making. Moreover, it is difficult to run prospective studies in organ allocation and observational studies on only a low limited comparison of allocation policies.

II. State of the art & Position Paper on Best Practices for Organ Allocation in Europe

II.1.1. “State of the art” of the current situation in the ALLIANCE-O participating countries

This first part of Deliverable 3.1 led to a summary of the allocation process and a comparative analysis section (see annexes).

Two study cases have been selected to illustrate the variations of liver and kidney allocation procedures in each country. The main results are summarized below.

- **A wide range of allocation systems**

A main result of this comparative study is to pinpoint the **wide range of allocation systems, procedures, protocols and allocation criteria that have been implemented in the different countries**. This diversity results 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 also the determinants of such variations. Variations are also due to the level of development of transplantation and especially to the number of transplant centres in each country.

- **The importance of medical decision varies from a country to another:**

In centre-based allocation systems, waiting lists are managed at the centre level; the interference with medical decision is limited to general principles (ABO matching, general ethical statements) that transplant physicians conform to: organ allocation is a distributed (intra-centre) decision.

Conversely, **in patient-based allocation systems**, the place of medical decision is minimal, and organ allocation is a centralised (supra-centre) decision in line with very precise and operative statements. In many countries, allocation systems combine general donor-recipient matching principles, nationwide and/or regional patient-based allocation priorities, and local centre-based allocation practices that represent the major and transplant teams’ favourite allocation modality.

- **Organ allocation: an empirical and political compromise**

Organ allocation is usually a matter of consensus between transplant teams, organizational bodies, and health authorities and patients associations. According to medical science and to ethics, general allocation principles have been defined. One can list medical criteria such as severity of the liver failure, ABO group, HLA matching, primary disease or expected ischemic time and non-medical allocation criteria such as waiting time, geographic distances or available resources. Organ allocation systems **usually strike an empirical compromise between contradictory objectives and a political compromise between the interests of transplantation centres** which are in competition to obtain the best organs for their patients and to reach optimal activity level and scientific excellence.

- **The interest of allocation scoring systems**

The use of a scoring system has been shown to be an efficient way to implement a patient-based allocation system. It also permits the maintenance of competition between categories of patients that is not possible with an allocation system applying sequentially ordered priorities. There are few categories of priority that can be ordered with no overlap. A scoring system can also be used at a local level as a decision support system. Thus a scoring system, usually associated to centralized allocation systems, can also give place to local and shared decision.

- **The evaluation of results**

In all countries, **the scientific survey of allocation schemes gains a central place within the allocation revision process for allocation is not a static but a dynamic 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.

Organ allocation remains an evolutive topic:

In many aspects, there is a balance between equity and efficacy, which does not have for the moment a unique evidence-based solution.

The emergence of new paradigms such as the survival benefit from transplantation as a modern and more comprehensive allocation criteria and results of scientific surveys motivate changes in allocation schemes.

Thus, organ allocation remains an open and moving issue, implying anticipation and reactivity for Organ Exchange Organisation in EU.

II.1.2. Proposition of a set of statements and general recommendations for best practices

Organ allocation policies occupy a central place between the need and supply, requiring transparency, guarantee in term of justice, equity and efficiency.

- **Statement 1 defines 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.

- **Statement 2 addresses the Societal Concerns in Organ Allocation policy making**

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. 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 to associate changes in allocation systems with a redistribution of dialysis availability.

- **Statement 3 pinpoints that organ allocation has to optimize individual benefit from transplantation and not only the sole post-transplant results**

Recent studies [Poynard99, Deng00, Merion05] indicated that an allocation preference for patients with the best survival after transplantation can lead to the transplantation of the less sick

patients who also are likely to be patients with no or low individual benefit from transplantation. For liver or heart transplantation, the less sick patients have the best post-transplant survival but have a higher risk of dying if they receive a transplant than if they remain 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, patients have a higher risk of death in being transplanted than remaining on the waiting list. Below this threshold are the “futile transplantations”. In the case of liver transplantation, the sickest patients benefit individually from transplantation: “transplantation cannot be too late” in terms of individual benefit. On the other hand, for other organs, transplantation can reduce individual benefit for very sick patients, the covariate adjusted hazard ratio of death defining “too late transplantations” above another threshold. 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. Thus, the Individual Benefit from transplantation is likely to become a very important indicator for Organ Allocation.

- **Recommendation 1: Defining objectives with related valid end-points**

National relevant authorities should carefully organise the definition of allocation objectives, of allocation methods and of allocation evaluation with relevant objectives and relevant valid end-points and evaluation procedures across EU countries. Coordinated interactions between stakeholders of the different steps of the process, according to their objectives should be set up in these aims.

To ensure that Organ Allocation Results conform to predefined Allocation General Principles, the definition of Organ Allocation objectives must be related to precise and comprehensive valid metrics.

For example:

- *Specific Transplantation Access Rates can be used to assess Equity*
- *Individual Benefit from transplantation can be used to assess Efficiency*
- *Matched Donor Potential can be used to identify patients with low assess to transplantation*
- *Duration of Allocation Realizations* can be used to assess Practicability*

**[Time of final acceptance - Time of first offer] + Duration of Shipment.*

- **Recommendation 2: Method Specification and Implementation**

National authorities in charge of organ allocation 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.

• **Recommendation 3: Organ Allocation Evaluation and Quality Assurance**

Relevant Authorities should carefully organise the evaluation of their allocation systems. Recommendations for supporting this have been established in WP5.

They should ensure the quality assurance of their allocation systems.

To ensure transparency, objectivity, fairness and efficiency that allocation systems intend to reach, to support scientific survey and evaluation of results, the use of Information Technologies is required, comprising:

- *the registration of all candidates on Waiting Lists,*
- *their follow-up before and after Transplantation,*
- *the registration of all donors,*
- *the implementation of allocations schemes,*
- *their use as an operational decisional support system for allocation,*
- *and the traceability of allocation realizations.*

• **Recommendation 4: Sharing Methods**

The definition of allocation objectives at national levels do not preclude the use of Allocation Methods shared among European countries.

Organisation in charge of Organ allocation in EU should establish a continuous collaboration to formalize a common readable description of their allocation procedures, to compare the specificity of their allocation system, and their results, and to promote interoperability and standardization of their allocation systems.

• **Recommendation 5: 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.

The definition of health care policies at regional or national level among EU countries must not preclude to Share organs on larger areas (supraregional or supranational) when significant benefits in terms of efficacy and equity can be expected for patients according to results from simulations studies, especially when there is no or limited adverse effects in terms of practicability, acceptability and organ donation.

III. Specification of a common simulation tool

III.1.1. Motivation and rationale

- **Simulation tool: a mean to support anticipation and reactivity in Allocation policies**

The survey of organ allocation among ALLIANCE-O partners [WP3-Deliverable #1] showed us that Allocation Systems usually strike an empirical compromise between equity, justice, efficacy, practicability, quality of post-transplant results and technical constraints related to organ retrieval, preservation and organ shipment.

They also realize a political compromise between competition interest of transplantation centres to obtain the best organs for their patients and to reach optimal activity level and scientific excellence.

The absence of unique evidence-based solution, the emergence of new paradigms such as the survival benefit from transplantation as modern and more comprehensive allocation end-points and the results of scientific surveys motivate **changes in allocation schemes that imply anticipation and reactivity capabilities for Organ Exchange Organisation**. The optimization of organ allocation remains a difficult and forthcoming issue. A Simulation tool is a mean to deal with such issues.

- **The need for and relevance of simulation**

The relevance of simulation is due to the fact that organ allocation is poorly accessible to experimental study. Observational studies performed to evaluate allocation policies only note the past situation. They can motivate changes but they are of limited help to bring about deep modifications in allocation policies due to the fear of unpredicted adverse consequences. Last, 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.

Simulation in such a context has the interest to **introduce a more distant and abstract approach of the allocation issues**. The interactive design of new allocation schemes with professionals and patient 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.**

III.2.2. General Functional Specifications

The building of a common simulation tool shared by National Institutions in charge of Organ allocation in EU will give the opportunity to capitalise knowledge and experience around organ allocation.

Such a tool is required to offer functionalities to build and compare interactively various flexible allocation schemes, according to a set of predefined allocation end-points and to forecast the behaviour of new allocation schemes before their implementation.

Tuning and Reporting functionalities will 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.

III.2.3. Simulation Tool Components

A comprehensive allocation simulation model will comprise a Donor Component, a Recipient Component, an Allocation Component, a Post-transplant Outcome Component and an Evaluation Module.

The Donor Component is due to mimic the sub-processes leading to the proposition of a Donor for organ retrieval. It is required to provide facilities to integrate historical data describing actual donors, to generate notional donors according to demographic specifications provided by the expert-users and to integrate pre-established models predicting trends in crucial donor's characteristics (aging, extended pool of marginal donors).

The Recipient Component will provide facilities to integrate historical data describing the actual waiting list, to generate notional recipients, to update the Waiting List each time a Donor is virtually proposed for organ retrieval. This implies to simulate individual survival on the waiting list according to robust survival models provided by the expert-user and to simulate patient's characteristics evolution on the waiting list, especially for individual characteristics that are taken into account for Organ Allocation.

The Allocation Component is due to support the targeted Allocation Schemes. It is required to provide functionalities to build interactively flexible allocation schemes, to tune allocation schemes according to: (i) at least, user-driven specifications intending to reach stepwise and empirically targeted allocation end-points; (ii) at best, a relevant optimisation algorithm if an optimisation function can be defined.

The input of the Allocation component is a sequence of pairs associating a donor proposed for organ retrieval at a given time point to the set of patients on the waiting list. The final output is a cohort of patients transplanted with a given organ.

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 and graft function using survival models provided by expert-user. 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.

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.

III.2.4. Joint Action: A pilot Study using the Organ Allocation Simulation Prototype developed by the Agence de la biomédecine (Deliverable 3.3)

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 the Agence de la biomédecine prototype. The aim of this experimental pilot study was to illustrate the main functionalities of a simulation tool. The study case was related to Kidney allocation, using data provided by the Agence de la biomédecine and UKT. The study compared results of actual allocation scheme to various simulated allocation schemes over a past period. Methods and results are detailed in Deliverable 3.2.

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.

- **Prerequisites to simulation comprise** data on patients and donors must be available, consistent with recommendation.
- **Simulating the distribution** 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 discussions. An important step was to define major allocation evaluation end-points, a key for an evidence-based debate.
- **Interest and expected added-value:** 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, and Italy). Ad-hoc simulation models 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 laboratory 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 technical** group of specialists is likely to promote the formalisation and the standardisation of allocation procedures. It could 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.

• **The capability of the simulation tool to accurately predict** the effects 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. 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.

ALLIANCE-O consortium strongly recommends for future works in allocation:

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 held 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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Coordinated Methodology in increasing Safety and Quality of Organ Transplantation (WP4)

This chapter encompasses two studies, first Safety (A) and then Quality (B) and will be divided accordingly.

A.I. Safety: Introduction

Success of transplantation depends on several factors, partially related to recipient health conditions, partially to donor characteristics. The process of donor suitability evaluation is largely influenced by organ shortage as well as by the risk-benefit balance for the recipient and time constraints due to ischemia of organs that may preclude performing some screening procedures. Despite such limitations and the fact that the risk of transmission of infectious or neoplastic diseases can never be completely ruled out even if approved guidelines are correctly applied, each retrieved organ should have an acceptable quality and should not expose the recipient to unacceptable risks.

A.II. Safety: Methodology

In this project, a state-of-the-art survey was conducted to overview and compare which tests were performed in different European countries, mainly focusing on the transmission of transmittable disease between deceased donor and recipient.

In order to make the inventory of existing national guidelines on safety rules, we conceived a questionnaire that aimed at collecting information on the process of evaluation of the cadaveric donor suitability running in the partners countries and on the tools utilised to collect the information related to donors and recipients in transplants at risk for infectious or neoplastic disease transmission. The evaluation of organ suitability has the goal of ensuring that any organ retrieved for a transplant has a high level of safety and it does not expose the recipient to unacceptable risks. It also allows not to lose donors with identified risks for recipients having a positive benefit / risk balance.

The questionnaire was circulated among partners in December 2004, results were presented and discussed during a Consensus meeting, and further analyses were later performed with a validation of results (deliverable 4.1).

All countries collect a high level of information related to the donor medical history. Only CNT and ONT collect all information detailed in the questionnaire (see Table 1), whereas all other organizations do not collect a few categories of information, (familiar history of malignancies, recent PSA value, menstrual dysfunction, history of recent miscarriages, autoimmune disorders, dislipidemia, exanthematic disease (paediatric donors).

Table 1: kind of information collected from medical history for donor evaluation

- Available Anamnestic information
- Risk factors for HIV/hepatitis
- Previous Infectious Diseases
- Illicit substance abuse
- Neoplastic Diseases
- Familiar history of malignancies
- Recent PSA value available for patients with >50 years)
- Surgical interventions
- Menstrual dysfunction
- Pregnancy status
- History of recent miscarriages
- Cardiovascular diseases
- Pneumopathies
- Liver diseases
- Renal disorders
- Diabetes
- Autoimmune disorders
- Hypertension
- History of chronic drug use
- Dislipidemia
- Alcohol consumption
- Smoking status
- Diseases of unknown etiology

The fact that all countries gathered most of the information is important, allows a comparable donor evaluation and helps to have a clear picture of his recent and past conditions.

As concerns the part of the questionnaire on serological tests, it has to be highlighted that all countries require the following fundamental tests:

- Anti HIV,
- Anti HCV,
- HBsAg,
- Syphilis (TPHA/VDRL),
- Anti CMV (IgG and IgM)

On the basis of these results, a consensus document was then worked out (Deliverable 4.2) where a proposal of guidelines for establishing common criteria for evaluation of donor was depicted.

The guidelines foresaw the adoption of risk levels defined as follows:

- 1. Unacceptable risk** (absolute contraindication). It includes all cases listed in the next paragraph (B). In these cases the donor is not suitable for transplantation.
- 2. Increased but acceptable risk.** It includes cases where transmissible organisms or diseases are identified during the evaluation process of the donor, but organ utilization is justified by the recipient specific health situation or by the severity of his/her clinical conditions.
- 3. Calculated Risk** (criteria referring to protocols for elective transplants). It includes all cases where, even in presence of transmissible diseases, transplantation is allowed for recipient with the same disease or with a protective serologic status independently from the severity of his

health conditions. Donors with meningitis who started targeted antibiotic therapy from a minimum duration (ranging from 24 to 48 hours) and those with documented bacteraemia who started targeted antibiotic therapy are included in this category of risk.

4. Not assessable risk: It includes cases where the evaluation process does not allow an appropriate risk assessment for transmittable diseases.

5. Standard Risk: It includes cases where the evaluation process did not identify any transmittable disease. Experts could be consulted if any doubt arises (second opinion).

The final decision of organ suitability should be taken by the clinician caring for the potential recipient. A patient that is a potential recipient of an organ with increased or calculated risk (categories 2 and 3) must receive adequate information on the specific risks from transplant team members. Informed consent form should always be obtained at the moment of his/her wait listing

Each Organization identifies the coordinating structure to which all intensive care units as well as local coordinators refer during the reporting procedures of the potential donor. Intensive care operators as well as local coordinators must notify to the national reference centre all individuals undergoing the brain death diagnosis process, being ventilated in intensive care units. The process of organ suitability evaluation is a complex and multiphase event. It relies on multiple parties working together towards common goals.

The suitability of the potential donor, who will undergo the process of organ removal, must be evaluated by the intensive care operators as well as by local coordinators and clinicians responsible for the transplant of the specific organ jointly to their reference centres according with the procedures presented in the adopted safety guidelines.

The evaluation of the suitability of the donor has to be based on: medical history; physical examination; instrumental as well as laboratory tests; the laboratory tests should be conducted on a sample collected before procedures which required haemodilution; histological examination and/or *post-mortem* examination with the aim to clarify those issues emerged during the previous evaluation steps or still to be investigated. The gathering of all this information is finalised to the best treatment of the patient. After having certified the brain death, further useful information will be collected. In accordance with current knowledge the following conditions, if present, are usually considered as absolute contraindications for the donor suitability:

- *HIV 1 or 2 seropositivity (but in specific cases of recipient seropositivity exceptions can be considered);*
- *HbsAg and HDV contemporaneous seropositivity;*
- *Current neoplastic conditions (for exceptions see Deliv.4.2);*
- *Systemic infections caused by agents for which treatments are not feasible;*
- *Documented prion diseases;*

The cause of brain death must always be thoroughly investigated.

All potential donors should be referred to the donor transplant co-ordinator for assessment Benefit and risk assessment could allow the use of organs at risk for transmissible disease and the final decision of organ suitability rests with the transplanting team.

A.III. Safety: Recommendations

The group shared some common views that were adopted as basis for both the survey and the drafting of the final document (Deliverable 4.2) and that can be summarized in the following recommendations:

Safety Recommendations

- **A better utilization of all available organs from deceased donors, including donors at risk of infectious or neoplastic disease transmission should be supported as a prompt tool for expanding the existing donor pool;**
- **As a consequence the establishment of some minimum safety standards at European level would be of high value and should be fixed, also taking into account the Guide to Safety and Quality assurance for organs, tissues and cells published by the Council of Europe;**
- **Registries for collection of data on risk evaluation of donors and follow up of their recipients should be set up;**
- **A definition of harmonized European measures for such risk evaluation is needed, for which proposed guidelines could be basis to be supported by already published and further literature data.**

B.I. Increasing Quality: Introduction

Organ transplantation is the only health care service that “starts from the citizens to get to the citizens”. A patient on waiting list may be transplanted only if there is an organ available thanks to the choice made by another person to donate his organs after death.

Organ transplantation is the output of a process (“*The process is a set of correlated activities, which convert an input into an output by generating an added value [UNI EN ISO 9000:2000]*”). In terms of health care, the objective of the processes is therefore to improve the health status of both the single person and the community. In the transplantation field, this is a round process, where the input is the citizen-donor and the output is the citizen-patient.

The scope of WP4 – Task 4.2 “State of the art of quality systems” was to develop a coordinated approach on Quality Management Systems (QMS) to achieve through the following major objectives:

- A. Drawing up of an inventory and analysis of existing quality systems;
- B. Elaborating common best practices, standard operating procedures, for organ transplantation quality systems

B.II. Increasing Quality: Methodology and Results

The analysis of quality systems was not meant to check the existence of quality programmes according to ISO rules or other international standards, while it focused on the approach applied by each organization in the donation to transplantation process. The same for the position paper on common best practices that was designed to recommend the application of a number of practices to ensure the quality of the services for all transplant organizations. Tissue laboratories standards were not taken into account in the present work.

Objective A of the task produced a survey on the quality systems applied in different phases of the transplantation process. The scope of this sub-task was to identify the basic components of a quality system and not to define what a quality system should be. The inventory was performed thanks to a questionnaire distributed to all partners to collect as much information as possible on their quality systems. Assuming that four main sub-processes (donation, allocation, transplantation, follow-up and quality of life) make the donation to transplantation process, we looked into each sub-process in order to gather information on the existing quality programmes. The quality of the process was therefore the main topic, which was also analysed in relation to the organizational structure.

The analysis showed that the coordination of the sub-processes and, therefore, the organization of the respective phases, are in some countries similar, while in some others completely different. This is due to the organization of the donation-retrieval-transplantation process as a whole, from local to national level.

A short summary of the survey results is presented here below:

Donation Sub-process: in the majority of the countries, the local hospital is responsible for the phases of the donation sub-process, apart from some direct responsibility of the regional coordination or of the national organization. Moreover, the responsible unit is usually supported in the development of the activities by either the regional coordination or the national centre. All countries declared the presence of a quality programme made of trainings, procedures, guidelines and audits. Audits are deeply developed in France, Spain and UK, whereas the other countries developed a programme only for the phase of identification of a potential donor.

Allocation Sub-process: in this case most of the countries reported that the regional or the national organizations are responsible for the management of the phases belonging to the allocation sub-process. Laboratories and transplant centres usually cooperates with them for the development of some activities. All countries reported the presence of quality programmes as trainings, procedures, guidelines and audits. France, Hungary, Italy and Spain manage full procedure, guideline and auditing programmes either at a national level and/or at a local one.

Transplantation Sub-process: transplant centres are the responsible units for the transplantation sub-process phases. In some countries transplant centres are supported by regional coordination, while in a few countries are supported by the national transplant centre. Italy, Spain and UK have a national auditing programme, while Germany, Hungary, Italy and UK apply procedures and guidelines to all phases, even though they are produced at different levels.

Follow-up and quality of life sub-process: transplant centres are responsible for the phases of the sub-process. In some specific cases, it is also foreseen the cooperation of the regional or national coordinating centre, this is the case of France, Germany, Italy and Spain. Quality programmes in this phase are not frequent: only Italy and Spain have an auditing programme in place, whereas Germany, Hungary and Italy developed procedures and guidelines regulating the phases of the sub-processes.

The intermediate results of this activity that were essential to define the common best practices are:

- The definition of the transplantation process as a process made of four sub-processes not necessarily subsequent, but in some cases concurrent: donation, allocation, transplantation, follow-up and quality of life;
- The definition of the objectives of the sub-processes, the identification of the phases for each sub-process and their quality requisites;
- The selection of the main quality tools: training, auditing, procedures, protocols, guidelines and quality indicators;
- An overview of the quality programmes running in the different countries at national, regional or local level.

The above mentioned information was necessary to get to the minimum and common practices that should be present in the transplant system of a Country. During the analysis it was decided to keep two requisites out of the sub-processes: “information system” and “standards for safety criteria”. The consortium realized that the two requisites have an impact in each phase; therefore it was preferred to treat them as requisites of the Process as a whole.

The “**Common Best Practices for a Quality Management System in the Transplantation Process**” agreed by the consortium are reported in Annex 4.1 of this **White Paper**. It is important to highlight that these are not best practices in terms of selection of the best ones among others, while they are the results of a mix of good points taken from the actions of the different countries and put together. The best practice of a given requisite is the result of a combination of different aspects pertaining to one or more Countries. To the view of the consortium this was the most effective and fruitful way to achieve the final objective. As a result, the best practices were agreed for each requisite with the following approach: the selection of the common elements applied in each country; the selection of innovative and outstanding elements applied in one or more countries; the ideal components that should be applied in each country, but that are still missing everywhere.

The selection of common minimum practices revealed that most of the tools were already known and applied by the majority of the countries, although with slightly different methods. Through this work it was possible to highlight the most important aspects that could be shared at a European level and agreed by the different countries.

B.III. Increasing Quality: Recommendations

The common best practices document represents a minimum agreed set of practices that should be implemented in the transplant sector of all countries, starting from those of the ALLIANCE-O group. It is thus recommended that every country applies the missing action or improves the weak ones.

The activities developed and the issues introduced here represent a preliminary work plan for launching future actions shared by the European Countries. Following a detailed analysis of the practices laid out in D4.4, the members of the working group highlighted the actions with priority to be carried out in the near future in terms of sharing common practices to apply in all countries.

The main suitable actions agreed by the consortium are the following:

Increasing Quality: Recommendations

- 1. Standards for a continuous education on donation and transplantation and standards for the certification of the education;**
- 2. Standardization of the donation form;**
- 3. Transversal auditing model defining the auditing procedures (certification of the procurement centres);**
- 4. Transversal auditing model defining the auditing procedures (certification of the transplant centres);**
- 5. Definition of transparency and communication principles of the allocation criteria;**
- 6. Methods and criteria for the evaluation of results (Alliance-WP5);**
- 7. Bio-vigilance model: a system to report, investigate, register and transmit information about serious adverse events and reactions (See Eustite project);**
- 8. Ensuring safety standards throughout the process from donation to follow-up;**
- 9. Cooperation among the information system for data exchange (see Eurocet project).**

The consortium decided to develop one of the above mentioned actions during this project, to be considered as a pilot action for the future work.

The group worked on a single European donation form that would include the same data set all over Europe. It was decided to produce a first draft of the donation form with the minimum data recorded by the majority of the organizations (see Annex 4.2). This initiative put in evidence that the seven countries already utilize similar donation forms, in other words they collect, for the majority of the categories, the same data set. As a result, 114 out of 174 data items provided by the partners were identified as minimum data set, which corresponds to the 65% of the total.

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Coordination of evaluation of methodologies of transplantation performance (WP5)

I. Introduction

A distinguishing feature of organ transplantation is that large amounts of data are obtained on characteristics of patients on the waiting list, donors and recipients, and on transplant outcomes. These data are used to inform transplant practice, to monitor the outcomes in particular transplant units, to facilitate organ allocation and to inform patients about likely outcomes. **The aim of this work package is to review current arrangements for data collection, analysis and dissemination across Europe**, and to propose methods that are useful in the analysis of transplant data

The work began with a comprehensive state of the art review of transplant methodologies, which forms Deliverable 5.1. The aim of this review is to summarise the techniques that are currently being used by the partner organisations in the analysis of outcomes following transplantation and in the comparison and monitoring of centre performance. The review includes details on all factors that are taken account of in these analyses. The opportunity was also taken to outline the data collection process in each country, the funding arrangements for data collection, statistical analysis and audit, the computer software used in data analysis, and how statistical results are made available to the public.

This state of the art review was followed by a study of statistical methods that are particularly valuable in summarising, analysing and monitoring data on transplant outcomes. In addition, further consideration is given to the risk factors that are currently being used in modelling transplant outcomes, which will in turn lead to recommendations that will influence subsequent data collection and statistical practice. **The results of this form Deliverable 5.2.**

Organ allocation schemes are designed to ensure that organs are allocated to potential recipients in ways that are fair, transparent and consistent across all transplant centres in a country. However a scheme operates, its design must ensure that organs are allocated efficiently, both to obtain maximum benefit from a donated organ. Another key consideration of any allocation scheme is that of ensuring equity of access for patients both to the transplant list and then to any appropriate donated organs. Any organ allocation scheme is ultimately a compromise between the requirements for efficiency and equity, and simulation methods are commonly used in the development and modification of organ allocation schemes. This is examined in detail in Work package 3 on organ allocation schemes, but in Deliverable 5.3, there is particular emphasis on their role in evaluating the impact of changes in allocation schemes on patient or graft survival.

The methodological work in this work package has opened up the way for future collaborative work with European Transplant organisations in a number of interesting and challenging areas. These have been set out in Deliverable 5.4.

II. Summary of results

II.1. State of the art of evaluation methodologies (Deliverable 5.1)

The review of current practice in the analysis of transplant data indicated that there were large differences in the extent of transplant activity across European transplant organisations. These differences stem from variation between the ALLIANCE-O partners in terms of the numbers and types of organs that are routinely transplanted and the numbers of individual transplant centres.

Methods used in France, Italy and the UK to analyse transplant outcomes are very similar. Each of these countries routinely uses statistical models to explore how the outcome following solid organ transplant is influenced by various factors, through analyses of survival rates and survival times following kidney, liver and cardiothoracic transplantation. Other countries use mainly descriptive methods. In allowing for differences between individual patients, that is case-mix, the models used by France, Italy, Spain and the UK include similar risk factors. Centre performance monitoring procedures have been implemented in the UK and are being developed in France. In both cases, risk-adjustment has been applied.

This review has shown that while some countries are using very sophisticated statistical methods on a routine basis, others are in the process of introducing methods that meet the needs of their own transplant communities and governments. It has also become clear that the participating countries have very different levels of resource devoted to the quantitative analysis of transplant outcomes, with very few statisticians in all countries except the UK.

II.2. Proposal for standardised methods to monitor the performance of different transplantation teams and standardised risk factors (Deliverable 5.2)

The deliverable describes some of the aims of analysing transplant data, which include investigations into how graft and patient survival depend on factors associated with the donor, the recipient and the transplant procedure, methods for identifying if there has been an underlying change in graft or patient survival at a centre, and methods that ensure that organ allocation procedures are operating in the desired manner.

These analyses serve many different purposes, but in particular they allow national organisations responsible for the conduct of organ transplantation to ensure that organ allocation is equitable, and that optimal use is made of organs that become available. The results of analyses such as these also lead directly to the development of clinical practice for the greater benefit of patients. Proper provision of a statistical analysis and audit service in a national transplant organisation is therefore essential for the development of organ transplantation.

Recognising this, Deliverable 5.2 provides a summary of methods that have proved to be helpful in the analysis of transplant data. Of necessity, the review of methodological practice is highly selective, but it does concentrate on the most commonly encountered techniques in the analysis of transplant data. Moreover, most of the methods can be implemented using software that is readily available. It is therefore hoped that this review will serve as a guide to transplant units who are introducing methods for monitoring and analysis.

The material on monitoring centre performance is of particular importance. Indeed, the methods based on CUSUM charts described in Section 4 of the deliverable, are now well established in certain areas of medicine. However, these techniques are not widely used in transplantation at present, and yet they are fundamental to determining whether organs allocated to particular centres are being transplanted safely. This is of course an area that is particularly sensitive. Centres may be concerned at the very idea of a monitoring process being in place. However, as long as the introduction of such schemes is handled delicately, and clinicians are involved at all stages of the process, it comes to be viewed as non-threatening. In order to alleviate the concerns of centres who undertake more difficult cases, and who therefore expect inferior results, risk adjustment for case-mix is essential.

II.3. Review of simulation tools for exploring the merits of different allocation schemes (Deliverable 5.3)

Simulation tools for studying organ allocation procedures have been developed in Work package 3 of this project. A particularly valuable use of simulation methodology is to study the impact of organ allocation schemes on the survival of patients or grafts. There are two main approaches to the actual simulation technique that can be used; these are described and their merits discussed. Regardless of the actual simulation technique used, a key element of any survival study is the specification of a model for the survival times of patients or grafts appropriate to the population under consideration. The use of such a model is also discussed in detail. Implementing the methods that are described in this deliverable will enable transplant organisations to determine the impact of new or modified allocation schemes on survival following transplantation.

II.4. Development of further collaborative work (Deliverable 5.4)

Following discussions with ALLIANCE-O partners, a number of areas for future collaborative work in the analysis of transplant data have been identified. The principle opportunities are concerned with centre monitoring, that is organovigilance, the development of allocation rules to optimise benefit following transplantation, and further development of comprehensive simulation models. Moreover the partners agree that there would be great value in the exchange of data to allow analyses of factors affecting the occurrence of rare events, to compare outcomes across countries and to facilitate a meta-analysis of outcome data across Europe. There also appears to be a role in the development and dissemination of statistical methods in transplantation.

There has already been collaborative work out with ALLIANCE-O that has led to the introduction of centre monitoring procedures in France. It is anticipated that in the months following the completion of the ALLIANCE-O project, contacts will be maintained between a numbers of organisations, with work continuing in some of these areas.

III. Recommendations for evaluation

- 1. Methods need to be in place for data collection and analysis** to ascertain factors impacting on graft and patient outcome. This in turn will inform allocation procedures and clinical practice.
- 2. In order to ensure appropriate data collection, validation and storage**, as well as statistical analysis, national transplant organisations need a fully resourced statistics and audit service.
- 3. Monitoring procedures**, such as methods described in Deliverable 5.2, are needed to ensure that the outcomes from transplant centres are in line with expectation. Such procedures should be developed collaboratively with the centres to be monitored. This enables early action to be taken if a centre is seen to have experienced deterioration in performance.
- 4. Simulation methods** should be routinely used in the development and modification of organ allocation schemes.
- 5. Further collaboration** on the collection and analysis of transplant data across Europe should be facilitated.

Fundamental research linked to organ donation (WP6)

I. State of the art of existing programmes

This analysis of existing research programmes and activities on a national level should allow **identification of main focuses and needs** in basic research and **possible strategies to enhance the performance of research and avoid duplication**.

The Deliverable 6.1 introduction reveals the difficulties and obstacles encountered while inventorying the projects. An entire section is dedicated to a brief overview of the research landscape in each country with particular reference to organ transplantation and donation. Even though the national research systems vary according to the participating countries, there are a lot of common characteristics. In each country two basic approaches are known as the bottom up and top down approaches are used to funding of research and exist in all kinds of variations.

Research in the domain of organ transplantation is mainly conducted in transplant units, universities, university hospitals and medical research institutes. As far as the funding is concerned public, private and a combination of both are common in all countries, with a decreasing tendency of public funding.

A large number of private institutions such as non-profit organisations/foundations and also the pharmaceutical industry (e.g. Novartis, Fujisawa, Wyeth, Roche etc.) contribute to research linked to organ transplantation. All participants encountered extreme difficulties in order to obtain valid information on the privately funded sector. Hence projects that are solely funded out of private source have been neglected in the inventory.

The state of the art report thus aims at giving an overview of existing projects/programs that have been detected. We also discovered that there are few national or international strategies designed to enhance or coordinate research in this domain. Of the ALLIANCE-O member-states only Spain has a platform designated for research in organ transplantation that allows for national collaboration and cooperation amongst the individual projects and which enhances strategic research. The Agence de la biomédecine has since 1995 a research calls for projects directly linked to organ transplantation, as well as tissue and cell transplantation. This allows the Agence to have an overview on what kind of research trends are pursued in France, with funding contribution from other sources.

The inventory of the research programmes contains more than 500 (semi) publicly funded projects. The participants to the project tried to collect the following information on research projects that were started or terminated between 2000 and 2005:

- Contact data
- Project title
- Abstract
- Level and source of funding

During the search for research projects the significance of an inventory of the existing programmes became evident. We discovered that a very large number of individual and collaborative research projects exist in this field. An increasing number of databases provided information on a wide variety of current and completed research projects. However, they only cover a part of the existing project and neglect privately funded projects as already stated above.

For analytical purposes and in order to make general conclusions possible we chose the following categories which, to our belief, all together define fundamental research better than any singular definition. Basically we resorted to the experience of the Spanish research network and have adopted the categories chosen within that network.

To make sure economic, social, legal, psychological, ethical aspects of organ transplantation and donation are included as well and to allow for all important/interesting programs to be listed we added the three highlighted categories.

The chosen categories according to which we categorized more than 500 projects are the following ones:

A1	Epidemiologic Studies
B2	Alloreactivity and Tolerance
C3	Preservation, Ischemia
D4	Alternative Therapies/Treatments
E5	Complications & Co morbidity
F6	Acute and chronic failure of the graft
G7	Immunosuppression/Immunology
H8	Quality and Safety of organ transplantation
I9	Quality of life and socio – economic impact
J10	Socio-cultural-legal – economic-ethical-religious etc. aspects of organ donation/transplantation
K11	Transplantation potpourri (for everything that does not fall within any category but still is of interest and importance)

The results of the Deliverables 6.1 and 6.2 have been shared with the Project TRIE.

II. Position paper

- The aim of Deliverable 6.2 was **to identify the main focuses and needs in basic** research and to present possible **strategies to enhance the performance of research** and to **avoid duplication**.
- We had to acknowledge that the projects we collected are probably only the tip of the iceberg and that the number of existing projects can not even be estimated and that an analysis of the projects we collected as far as the contents and topics of the research projects are concerned would not be target oriented.
- Hence it became apparent that a different approach would be needed in order to meet the requirements of this deliverable. Since apart from Spain and France there is no national body in the participating countries that would be dedicated at least partly to the organisation and coordination of research in the field of organ donation, procurement and transplantation.

The group reached a general consensus on what should be the key tasks, functions and responsibilities of a national body dedicated to research in the field of donation, procurement and transplantation. They are stated below. Ideally this national body would evolve to become the first address where research program makers and sponsors as well as scientist and research institutions would turn to with any question related to research in the field of organ donation, procurement and transplantation. It goes without saying that the establishment of the national body would have to be in accordance with national and European legislation:

- ☉ **Take into consideration national peculiarities and legislation.**
- ☉ **Allow for a multidisciplinary approach.**
- ☉ **Be an independent body.**
- ☉ **Be a source of information (open to everybody).**
- ☉ **Coordinate research and offer services that facilitate cooperation and communication (classic and innovative communication and information tools: e.g. links, data base; newsletter; congresses; workshops, platform; forum).**
- ☉ **Take care of public relations and dissemination.**
- ☉ **Where possible, provide funding of research activity**
- ☉ **Enhance transparency and trust in research.**

Taking into consideration that nowadays research is not limited to national boundaries and a Europe-wide network of the national organisations was proposed for discussion during the second half of the workshop. Again responses were unanimously positive. All the qualities required for the national body most certainly are also relevant when taking it a step further and lifting it to a European level.

However we can not call for a European network without pointing out the additional benefit of such a network. The benefits become apparent when we look at the results of our discussion and the consensus finding of the participants as far as the additional purposes of the European Network should ideally be:

- Define goals and benchmarks in order to oblige national authorities to take actions and measures in the following areas:
 - ⊕ Improve organ donation and transplantation
 - ⊕ Transplant outcomes (define levels of excellence)
 - ⊕ Living donation
 - ⊕ NHBD
 - ⊕ Conversion rate
 - ⊕ Islet transplantation (cells)
 - ⊕ Xenotransplantation
 - ⊕ Others
- Focus on fields where it is indispensable to cooperate (e.g. small number of cases)/coordinate the use of infrastructure.
- Enhance European competitiveness.

Ethical and legal aspects (WP7)

Legal and ethical difficulties in the field of organ donation and transplantation were identified and analysed. Based on the findings the working group elaborated the following conclusions and positions in deliverable 7.2:

I. Upcoming EU legislation

In the light of the planned establishment of a basic quality and safety framework within the European Union the ALLIANCE-O Group suggests a focus on the following aspects:

- ⊕ Ensure traceability and reporting of serious adverse events and reactions.
- ⊕ Installation of registries that collect donor and recipient data.
- ⊕ Special attention is needed for Non-Heart Beating Donation or Donation after Cardiac Death (NHBD or DCD), extended criteria donor (ECD) and Living donors.
- ⊕ The Registries should be designed to allow for correlations between donor and recipient data (Donor risk index/recipient risk-levels) and ensure standardized post-transplant care for all recipients and their follow up.

Confidentiality should be maintained in all cases.

II. Post-mortem organ donation

1. There are two major prerequisites for post-mortem organ donation:

- ⊕ **No retrieval prior to certification of death.**
- ⊕ **No retrieval without consent of the donor or his next of kin.**

The choice between the legal concept of presumed consent and informed consent is amongst others based on historical, social and cultural reasons. The detailed analysis revealed within the ALLIANCE-O working group that the two concepts do not differ in day to day practice and that the family or next of kin must be in favour of donation in order to proceed with the donation process. A change of the legal framework therefore would not be a guarantee for an increase in donation rates.

2. Referral of the potential donor and refusal rate

The main task of all persons and institutions involved in organ donation is thus to increase consent rates within the legal framework. This can only be achieved by raising public awareness of the necessity and advantages of organ donation and transplantation. The major focus must nevertheless be on the training of the personnel in charge of the family approach. When considering how to increase the organ donation rate a close look at the number of personnel and the procedures in place to ensure the referral of all potential donors is required. It is undisputed that together with the consent rate the rate of referral of potential donors is one of the main factors influencing the donation rate in each country.

Appropriate policies need to be agreed and implemented to ensure that all potential donors are referred to the organ procurement organisation(s) (OPO) responsible for organ donation and procurement. This requires the following tools:

- ⊖ **Tool to evaluate the true donor potential.**
- ⊖ **Tool to monitor the referral and the performance of the hospital.**
- ⊖ **Tool to allow for referral of immanent death as soon as possible.**

Only when policies are in place that ensures that all potential organ donors are referred to the OPO and consent rates maximised will a considerable increase in donation rates across the Europe be achieved. The efficiency of the OPOs can be best expressed by the so called conversion rate. The conversion rate indicates how many potential donors³ eventually become effective donors⁴.

The goal therefore should be:

- ⊖ **100 % Referral.**
- ⊖ **85 % Conversion rate.**

3. Reimbursement of donor hospitals

The participation of hospitals in organ donation must not be a disincentive activity. Reimbursement of all activities facilitating the organ donation process irrespective of whether it results in the retrieval of transplantable organs (futile donation) must be ensured.

4. Incentives for *post-mortem* organ donation

So far in none of the participating countries incentives to the donor during their lifetime or to the family or next of kin are foreseen. Often quoted examples for such incentives are a reduction of taxes or health insurance in order to motivate individuals to express their consent to *post-mortem* organ donation during their life time or to offer the family support towards funeral costs. Allowing for such incentives is a 'slippery slope' towards remuneration of *post-mortem* donation. Therefore:

The ALLIANCE-0 group opposes to incentives to the donor or his next of kin for *post-mortem* organ donation.

5. Non-resident-donors

Organ donation from non-resident donors should be facilitated in each country according to national provisions. It needs to be ensured that if the deceased consented to donate, organs can be retrieved and transplanted in the country he died. To facilitate the recognition of consent to *post-mortem* donation the diffusion of donor cards is recommended.

³ A potential donor is a deceased person without absolute medical contraindications with brain death diagnosis initiated and completed.

⁴ Deceased person, from which at least one solid organ was retrieved for transplantation purposes (Definition from DOPKI-Project).

6. Minorities and Organ donation

Specific initiatives to increase organ donation in specific ethnic minorities should be developed.

7. Unconditional consent

In practice the wishes of the donor are respected as far as is reasonable and possible unless adherence of these wishes would result in a violation of law (e.g. organ trafficking).

According to the legal provisions of the participating countries directed *post-mortem* donation is prohibited. Neither the donor nor the relatives can choose the potential recipient of the donated organs. However practice shows that exceptions are required for exceptional cases.

- ⊙ **Allocation must follow national principles.**
- ⊙ **Discrimination of possible recipients must be prohibited.**
- ⊙ **Member states should define procedures on how to handle exceptional cases.**

8. Non-Heart Beating Donation

When enabling NHBD it is important to: introduce an appropriate (legal) framework for NHBD and to insure that this donor type is an addition and does not replace Heart Beating Donation.

9. Quality and Safety

It is very difficult to determine the most appropriate time for tests and examinations evaluating donor suitability. Tests are mandatory in order to ensure the quality and safety of the organs transplanted. The right balance needs to be established through an adequate framework in order to:

Minimize the risks of transplantation for the recipient as far as possible without violating the donor rights at stake.

10. Extended Criteria Donor (ECD)

Install a registry that collects donor and recipient data following transplantation of organs from ECDs and allows for correlation of this data is necessary. Such a registry must be based on a donor risk index and recipient risk levels.

Elaborate a common definition of ECD based on the data from the registry.

Transplant surgeons and physicians in charge of the recipient and follow up in this field need to be educated adequately in order to ensure that all centres are capable to use ECD. Centre profiles should be publicly available and patients should be adequately informed about the possibilities of ECD. Informed consent of patients registering for transplantation should include information about allocation rules and possibilities to receive ECD organs.

11. Access of “Non-residents” to transplantation

Access of non-residents to transplantation medicine should be given due consideration in a European perspective, in order to be solved on a national level from a legal point of view. Any regulation should however be in accordance with national constitutions as well as European law (e.g. Art. 12, 18, 39, 43, 49 TEC and Council Regulation (EC) no 1408/71).

The best solution is prevention and to ensure the development of transplantation systems in all EU-member states and harmonise the donor rates by raising them to the highest possible level.

12. International organ exchange

Cooperation should be facilitated for specific patient groups (children, high urgency patients, immunologically sensitive patients).

For this purpose the establishment of minimum quality and safety standards for international organ exchange is required.

13. “Double listing” and accounting for waiting time abroad

Double listing in more than one national transplant system is avoided. In addition patients who relocate from one European country to another should be able to maintain their accrued waiting time.

III. Living donation

- **There is a consensus** that living donation must be on a non monetary and voluntary basis. Legal prerequisites **need to be taken to ensure this as far as possible.**
- It should be ensured that *post-mortem* donation is not neglected over living donation. Living donation must be an add-on. The recipient should be offered the possibility of transplantation from a deceased donor when suitable organs are available.
- **Informed consent of the living donor must include the following aspects:**
 - ⊕ Possible medical risks
 - ⊕ Side effects
 - ⊕ Necessary care afterwards
 - ⊕ Social, psychological and financial risks
 - ⊕ Alternative treatments for the recipient and success rate (individual recipient risk)
- **Living donor registries should be installed** that collect information on medical, social, psychological and financial effects and is part of the standardized follow up care for the living donor.

III. CONCLUSION AND FUTURE DIRECTIONS OF ALLIANCE-O

1. From a very intense and productive effort to proposals

The organisations involved in organ transplantation in the seven countries worked intensively for three years to make the ALLIANCE-O project successful.

The six technical work packages (WP) allowed us to go into details on each step of the organ transplantation process, from donation, allocation, safety and quality to methods for the evaluation of results, fundamental research programmes and ethical concerns. Each partner country participated in each WP. The analysis and the proposals represent a consensus of all of them.

The “State of the Art” analysis generally reveals big differences and discrepancies among partner countries. Some are due to the size of the country or the number of transplantation teams, but many of the differences cannot easily be explained.

Each work package allowed us to make proposals or recommendations to strengthen the activity. Some proposals involve the national or regional funding (obviously a very important factor) required to optimise the organisation of organ transplantation and organ retrieval activities, including training, quality and safety management, information systems, evaluation of results and organ allocation procedures.

The huge amount of money spent to provide dialysis for patients with end stage renal disease in all of our countries, must be considered *per se* as the strongest incentive to organise organ retrieval with the most relevant efficacy, kidney transplantation being the most cost-effectiveness treatment.

Many of the proposals imply collaboration between member states. The goal is to establish more powerful strategies, but not to reach a unique uniform system:

- common definition of terms is mandatory to share experience and results
- common approach in tools used for organisation, training, education, allocation, safety, quality and evaluation, could avoid duplication of work and save time.

Many of these tools already exist and have been developed by one or the other countries, and they must be better translated and disseminated. The improvement of the existing tools could also be shared to increase their pertinence and decrease the need for investments in each country.

These proposals concern all steps of activity for heart beating and non-heart beating, living donors. Some of them are immediately applicable; some others require additional implementation work.

2. The conclusions of ALLIANCE-O are very strong

Organ transplantation is a success story but organ shortage leaves people dying in all countries, with an important discrepancy between national rates.

The different state of the art studies carried out allowed us to define what direction we had to follow and make practical recommendations. It is also clear we already have tools to improve the activity, the results and monitoring. However, the first step in any country is the sufficient funding of hospitals and a dedicated organisation for creating or reinforcing the human and technical resources.

3. Future perspectives for ALLIANCE-O efforts

a) The results of the coordination action:

These 3 years of common work have considerably strengthened the links-between the ALLIANCE-O group members and have clarified our common interests. All of us are convinced of the added value of European coordination on specific subjects. The question is how and for what.

The consortium is now eager to implement the actions after this first step of coordination, analysis and proposals. A possible direction for the future of the ALLIANCE-O group could be to apply a new ERANET coordination action. Many countries are willing to cooperate with the current group and it would be easy to enlarge it. However our consortium is not really interested in resuming work on the benchmarking analysis. New examples would probably not change our conclusions and the proposed actions.

Planning an ERANET (+) project is a very ambitious choice for which ALLIANCE-O participants thought they would probably not have proper resources.

Finally, the consortium examined the proposed actions for each WP in order to define what kind of actions should be pursued at the ALLIANCE-O group level, avoiding actions already taken in charge by other organisations. The main goal is still to avoid the duplication of work. In this purpose we will exclude actions already undertaken by organisations such as the Council of Europe: (*Ethics, Guide on safety and Quality*), the European Union (*Proposal on cooperation and safety directive, cooperation with new or future member states*), or EOEO (*logistic cooperation*).

b) Future directions:

Our proposal is to pursue the work initiated by most of our workpackages. Each organisation member would participate in one of the working groups, to make proposals and recommendations of the ALLIANCE-O project on a voluntary basis. The overall objective is to share expertise and capitalize knowledge about Organ Transplantation by setting up technical groups for relevant topics.

List of proposed actions:

It was proposed to list, for each WP, which actions the members would be interested in working on in priority:

- For Expanding Donor Pool (WP2), most of the proposals are already covered by DOPKI or ETPOD projects. All ALLIANCE-O participants being also part of these projects, we will not duplicate this work.
- For Allocation (WP 3), it was decided to gather proposals emerging from the WP 3 and 5 in a single place. Two actions were validated:
 - common simulation tool for allocation rules appliance
 - development of allocation rules based on transplantation results
- For Safety, Quality (WP 4):
 - ⊕ Concerning safety, many proposals (rare diseases, knowledge database and patients database, expanded criteria donor database) are already covered in DOPKI and do not need additional work from our group. With regard to recommendations, all ALLIANCE-O participants are also members of the Council of Europe “Group on Transplantation” and involved in the preparation of the guide on safety and quality. Furthermore, the European Union intends to initiate a brainstorming on this topic.
 - ⊕ Concerning quality, all the members are interested in pursuing the work towards common indicators and methodology for hospital coordination certification and for transplantation teams auditing. Brainstorming about the use of a European donor form is also planned.
- For Evaluation methods and tools (WP 5) the fruitful collaboration leading to shared methodologies between France, Italy and UK must continue and focus on:
 - ⊕ Common definition of terms and dataset
 - ⊕ Development, dissemination of statistics models
 - ⊕ Data Base Quality standards
 - ⊕ Centre Monitoring: Common methodology for transplant result analysis (including Cusum)
 - ⊕ Methodology of data exchange for specific evaluation

- For Fundamental Research (WP6), the group decided not to pursue in this direction beyond the work already done. Some of us are already involved in a project called TRIE which focuses on these research aspects.
- For Ethical and legal issues (WP 7), the subjects should not overlap with the Council of Europe or WHO work, but databases or tools should be developed to take into account specific questions in this field:
 - ⊕ Children common data base
 - ⊕ Non-residents
 - ⊕ Minorities data
 - ⊕ Tourism, trafficking survey
 - ⊕ Double listing of patients

Concerning these various issues, the standardisation of the definitions of terms and of methods and the interoperability of information systems could become a transversal topic for the traceability, the evaluation of results, the allocation of organs and the simulation of new allocation schemes. Information technologies can also be used to support expertise and knowledge management.

c) Organisation and enlargement of the future ALLIANCE-O:

Each group of action will be coordinated for the time being by the present WP leader (Euro-Transplant proposes to coordinate the Allocation group). Each group will work on voluntary bases, reporting to a common annual meeting. France will continue the coordination secretariat work for one year to ensure continuity; it will then rotate every 2 years.

The technical groups will be opened to any European national or transnational organisation officially involved in procurement, allocation or transplantation.

As many EOEO members have expressed their interest in joining our project, we will organise the next ALLIANCE-O meeting at the same time that the 2008 EOEO meeting.

This new organisation will start without specific funding, but this will be welcome in order to allow travels for countries having no dedicated resources and to set up or strengthen specific actions (computer simulation tools for instance)

d) New developments at the European Commission level concerning their proposal for coordinated actions in the field of organ transplantation could change these plans.

ANNEXES

ANNEX 1: The Article 152

European Community. Treaty of Amsterdam amending the Treaty on European Union, the Treaties establishing the European Communities and certain related acts, signed at Amsterdam, 2 October 1997.

(Official journal of the European Communities, No. C 340, 10 November 1997, pp. 1-308)
EC.98.018 The former Article 129 of Title X (Public health) of the Treaty establishing the European Community (see IDHL, 1992, 43, 257, EEC 92.31), henceforth Article 152 of Title XIII (Public Health), reads as follows: <http://europa.eu/scadplus/leg/en/lvb/a16000.htm#a16003>

ANNEX 2: List of main actions and recommendations from working groups:

• **Council of Europe**

List of recommendations and publications in the organ transplantation field

- ⊕ [Recommendation \(2006\)16](#) of the Committee of Ministers to member states on quality improvement programmes for organ donation
- ⊕ [Recommendation \(2006\)15](#) of the Committee of Ministers to member states on the background, functions and responsibilities of a National Transplant Organization (NTO)
- ⊕ [Recommendation \(2005\)11](#) of the Committee of Ministers to member states on the role and training of professionals responsible for organ donation (transplant "donor co-ordinators")
- ⊕ [Recommendation Rec \(2004\)19](#) of the Committee of Ministers to member states on criteria for the authorisation of organ transplantation facilities
- ⊕ [Recommendation \(2004\)7](#) of the Committee of Ministers to member states on organ trafficking
- ⊕ [Recommendation \(2003\)12](#) of the Committee of Ministers to member states on organ donor registers
- ⊕ [Recommendation 2001\)5](#) of the Committee of Ministers to member states on the management of organ transplant waiting lists and waiting times
- ⊕ [Recommendation No R\(97\)16](#) of the Committee of Ministers to member states on liver transplantation from living related donors
- ⊕ [Resolution \(78\) 29](#) - Harmonisation of legislations of member States relating to removal, grafting, 1978
- ⊕ Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine: [Convention on Human rights and Biomedecine, 1997](#)

- ⊕ Additional Protocol to the Convention on Human Rights and Biomedicine, concerning transplantation of organs and tissues of human origin, 2002
- ⊕ Recommendation 1611 (2003), of the Parliamentary Assembly, on Trafficking in organs in Europe
- ⊕ “Guide to safety and quality Assurance for Organs, Tissues and Cells” in February 2002. Council of the European Union
- **Commission of the European Communities**
 - ⊕ **Directive 2004/23/CE** of the European Parliament and Council, relating to the set up of quality and safety standards for donation, procurement, control, transformation, storage and distribution of human cells and tissues, 2004.
 - ⊕ Communication from the Commission to the European parliament and the Council, organ donation and transplantation: policy actions at EU level, 2007
 - ⊕ Impact assessment, 2007
 - ⊕ Report Europeans and organ donation, Publication May 2007, Special Eurobarometer
- **World Health Organization**
 - ⊕ WHA57.18. (2004) on organ procurement and transplantation
Other resolution: WHA40.13 (1987), WHA42.5 and WHA44.25 on organ procurement and transplantation;
 - ⊕ Draft guiding principles on human organ transplantation 1991 that emphasize voluntary donation and non-commercialization of human organs
 - ⊕ Ethics, access and safety in tissue and organ transplantation: Issues of global concern. Madrid, Spain, 6-9 October 2003.
- **World Medical Association**
 - ⊕ World Medical Association Statement on Human Organ Donation and Transplantation, adopted by the 52nd WMA General Assembly in Edinburgh, Scotland during October 2000 and revised by the WMA General Assembly, Pilanesberg, South Africa, October 2006.

ANNEX 3: Description of the ongoing European funded projects in the field of transplantation

Project Name	Aims	Field	DG Programme	Coordinator	Status (end date)	Duration	Total Budget
ALLIANCE-O	Coordination of National Research Programmes regarding Organ Donation and Transplantation	Organs	ERANET FP6 DG RTD	Agence de la biomédecine	Ongoing (Oct 2007)	3 years	2 M€
DOPKI	Improving the Knowledge and Practices in Organ Donation	Organs	Coordination Action FP6 DG RTD	Organización Nacional of Trasplantes (Spain)	Ongoing (Dec 2008)	3 years	1,6 M€
EQSTB	Analysis of the factors influencing the final tissue quality and security for their transplantation	Tissues/ Cells	DG SANCO	Hospital Clinic of Barcelona	End May 2007	3 years	750 K€
EUSTITE	Harmonisation of tissue establishment inspection and accreditation systems	Tissues/ Cells	DG SANCO	Istituto Superiore di Sanita (Italy)	Kick-off Dec 2006	3 years	2,5 M€
EUROCET	Database and Internet Portal covering aspects of organs, tissues and cells donation in Europe	Organs/ Tissues/ Cells	DG INFSO	Istituto Superiore di Sanita (Italy)	End Feb 2007	18 months	3 M€
ETPOD	Adaptation/improvement for training programs on organ donation (TPM)	Organs	DG SANCO	Hospital Clinic of Barcelona	Signed Dec 2006	3 years	1,3 M€
TRIE	Transplantation Research integration a cross Europe	Organs/ Tissues/ Cells	DG RTD FP6	Université Libre Bruxelles	2007	18 months	450 K€

Annexes to WP4

Annex 1 “Common best practices for quality systems”

DONATION Sub-Process

- **Education and Training**

Education and Training Programme on the donation phases:

- ⊕ Identification of the Potential Donor.
- ⊕ Diagnosis of cerebral death.
- ⊕ Consent/Authorisation or objection to donation.
- ⊕ Legal consent/authorization.
- ⊕ Maintenance of the donor.
- ⊕ Donor suitability.
- ⊕ Notification of allocation agency (ET).
- ⊕ Feed-back and support to families.
- ⊕ Organ suitability.
- ⊕ Co-ordination of safety.
- ⊕ Co-ordination of transport.
- ⊕ Retrieval and preservation of the graft.

Characteristics of the programme:

- ⊕ Theoretical and practical.
- ⊕ Certificated.
- ⊕ Accredited by the national transplantation authority.
- ⊕ Customized to different categories of professionals (workers of ICU, coordination, etc) and to competencies.
- ⊕ Final assessment of competence.
- ⊕ Initial programme plus continuous education.
- ⊕ Mutual recognition of the programme in the different EU countries.
- ⊕ Specific courses on the single phases of the donation process.

- **Data collection and validation**

Existence of:

- ⊖ National donation form containing all data related to the donation process.
- ⊖ Data validation procedure compliant with the organizational structure (H, regional, national levels); the procedure shall be based on recommended/standard/operative procedures.
- ⊖ Data should be comparable in the different countries allowing collaborative studies; minimum set of data shall be defined.

- **QMS and auditing**

QMS should be implemented in all organizations involved in donation activities Internal and external auditing:

- ⊖ Of all units involved in the process: local, regional and national coordination.
- ⊖ All phases of the process shall be audited.
- ⊖ Periodical scheduling of audits.
- ⊖ Auditing and follow-up procedures shall be validated at the national level and shared at the EU level.
- ⊖ The existence of a document that shall contain all audit procedures according to national and European standards.
- ⊖ Every audit has to define the geographical level of the action, the author of the results and the objective of the actions. Results of the audit should be analysed at a regional and national level.

- **Accountability for performance**

- ⊖ Quality programme with a monitoring system of the phases (quality indicators).
- ⊖ A minimum indicator set shall be defined at a national level; this should be shared and comparable at the European level (see DOPKI).

- **Stakeholders Surveys to test the perception of the service**

- ⊖ Identification of the stakeholders, health care professionals, donor families, patient associations, Institutions, etc.
- ⊖ Identification of the tools to measure the perception of the service for example: questionnaires sent to health care professionals involved in the process, donor action survey, etc.
- ⊖ Internal/external communication of data and indicators of donation activity.
- ⊖ Regular reports.

- **Information and public communication**

Continuous information based on a strategic national information programme that defines:

- ⊕ Target (general public, opinion leaders, minorities, religious leaders, professionals).
- ⊕ Tools (National campaign, information day, website, free toll number, press communication etc.).
- ⊕ Monitoring tools (press release analysis, donor card, opinion polls).

See WP7 (ethical aspects) for a further analysis.

ALLOCATION Sub-Process

- **Registration of all potential recipients on the Waiting List(s)**

Existence of a public document reporting the procedures and criteria of registration on a national waiting list according to the health status of the potential recipient.

All patients awaiting a transplant shall be registered on waiting list, patients awaiting a living donation included.

- **Allocation rules:**

Existence of a policy for the definition of allocation rules.

Rules covering all organ allocation should include and define:

- ⊕ Methods to define, verify and revise the allocation criteria.
- ⊕ Methods of communication and dissemination of the rules to all structures involved in the donation to transplantation process and to the public (transparency).
- ⊕ Methods to apply the allocation algorithms (ex. priority of assignment for urgencies, paediatrics, etc; methods of geographical assignments).

- **Registration of proposals, refusals and final acceptance**

Procedures for the registration of all offers for each type of organ that could show the results of the offer (accepted, refused, allocated, retrieved, transplanted) in order to ensure the traceability and transparency of the allocation process.

- **Organ Allocation Quality Management System**

Quality Management System (QMS) should be implemented in all organizations involved in allocation activities and auditing shall be developed including the application of rules.

TRANSPLANTATION Sub-Process

- **Standard criteria for registration and removal from waiting list**

Transparent procedures for registration, maintenance and removal from waiting list, including appropriate medical criteria of the recipient on the waiting list.

- **Policy to ensure cold ischemic time is minimized**

Procedures and surveys to ensure an efficient organ distribution and allocation to allow optimal ischemic time.

- **QMS and auditing**

QMS should be implemented in all organizations involved in transplant activities.

Transplant centres auditing on:

- ⊕ All phases of the process shall be audited (including acceptance, declination of organs).
- ⊕ Every audit *a priori* has to define the geographical level of the action, the author of the results and the objective of the actions; results of the audit should be analysed at a regional and national level.

- **Continuous provision of information to patients**

Information shall be given to patients on the waiting list, this information should include:

- ⊕ The registration on waiting list.
- ⊕ Status on waiting list plus any change or removal.
- ⊕ Mean time on waiting list (including regional waiting list for some countries).
- ⊕ Mean waiting time of transplanted patients.

- **Education and training**

Ensure professionalism and competency of all health care professionals who work with recipients:

- ⊖ Identification of the education program.
- ⊖ Definition of the competency levels.
- ⊖ Hospital, team or individual certification/authorization of competencies.
- ⊖ Mutual recognition between EU Countries should be developed.

FOLLOW-UP and QUALITY of LIFE Sub-Process

- **Data collection standardization**

Data collection shall be carried out in the framework of a national standardization program with the aim of assessing at least the following outcomes.

- ⊖ Patients survival.
- ⊖ Organs survival.
- ⊖ Quality of life.

Data collection shall be performed all through the lifetime of every transplant.

- **Minimum data set and common methodologies**

The national program shall include:

- ⊖ Definition of the objectives of the analysis.
- ⊖ Minimum data set agreed with clinicians.
- ⊖ A methodology for the calculation of the patient and graft survival that could ensure the results comparison.
- ⊖ Regular reviews.
- ⊖ The participation to the programme shall be mandatory.
- ⊖ Methods for the use and the publication of the results.

Data should be comparable in the different countries allowing collaborative studies; standardized data set and a shared methodology should be defined.

- **Definition and identification of post-transplant adverse events and reactions**

Presence of a “vigilant monitoring system” including:

- ⊖ Identification of the competent authority.
- ⊖ Policy and protocols for the reporting of adverse reaction/events.
- ⊖ Appropriate advisory group for discussion and decision.
- ⊖ Policy and protocols for the actions.

- **Provide relevant information to society and all stakeholders**

There should be tools for the provision of information to the general public and all stakeholders available at the national level and managed by professionals of the field. Some communication tools include:

- ⊖ Report (at least on an annual basis).
- ⊖ Website.
- ⊖ Information material.
- ⊖ Free toll number.
- ⊖ Scientific publications.
- ⊖ National Meetings.

Information should be customized for each category of user. Specific attention should be given to the mass-media with regard to communication by appropriately trained personnel.

Requisites for the whole Process (all sub-processes included)

- **Information System**

There is a need for the existence of an information system for data collection, management and processing. This should include donation, allocation, transplantation and follow-up process namely:

- ⊖ National transplantation form containing all data related to the donation and to transplantation.
- ⊖ Data collection and management on organ allocation to support the organ allocation system in compliance with the allocation guidelines.

The information system should be shared by all stakeholders involved in the processes, and it should be adapted to the organizational model of the Country (local, regional, national organization). Moreover it should be compliant with the rules, guidelines and procedures that regulate the single sub-process.

The information system should allow the traceability of the whole process, together with the management of the severe adverse events and reactions.

The information system should ensure the data quality in terms of completeness and coherence through dedicated validation procedures and auditing. Moreover, it should ensure the capability to create activity indicators regarding each sub-process.

- **Standards of safety criteria**

Safety standards including:

- ⊕ risk / benefit evaluation for recipient / graft and extended donor criteria guidelines.
- ⊕ traceability rules.
- ⊕ safeguards concerning the procedures (i.e. recipient consent, etc).
- ⊕ definition of specific risk follow-up.
- ⊕ management of adverse events.

Annex 2: First outline of the European Donation form

CATEGORY	SUB-CATEGORY	ID	ITEM	ACRONYM
GENERAL DATA		01	Donor_code	
		02	Date_time_notification	
		03	Hospital	
		04	Local coordinator	
		05	Contact person	
ICU ADMISSION		01	Date_time_icu	
		02	Date_time_intubation	
DONOR DATA		01	Donor type	
		02	Date_birth	
		03	Age	
		04	Gender	
		05	Weight	
		06	Height	
		07	Chest perimeter	
		08	Abdomen perimeter	
		09	Ab0	
		10	Cause_death	
		11	Date of death	
OBSERVATION CEREBRAL DEATH		01	Date_time start	
		02	Date_time end	
CONSENT		03	Opposition	
		04	Type opposition	
		05	Legal authorization	

CATEGORY	SUB-CATEGORY	ID	ITEM	ACRONYM
DONOR MEDICAL HISTORY		01	Neoplasia	
		02	Nephropathology	
		03	Epathopathology	
		04	Cardiopathology	
		05	Pneumapathology	
		06	Pancreaspathology	
		07	Parasitaire	
		08	Diabete	
		09	Hypertension	
		10	Neuropathology	
		11	Other pathologies	
		12	Previous_oper	
		13	Trauma	
		14	Alcohol	
		15	Smoking	
		16	Drugs	
PHYSICAL/CLINICAL DATA		01	Blood pressure	
		02	Hypotension (duration)	
		03	Temperature	
		04	Diuresis	
		05	Diuresis last h	
		06	Cardiac arrest (time - duration - irreversible)	
		07	Cardiorespiratory reanimation (duration)	
		08	CVP	
		09	Heart rate	

CATEGORY	SUB-CATEGORY	ID	ITEM	ACRONYM
LABORATORY		01	Date_time values	
	HEMATOLOGY	15	Prothrombine	PT
		18	White blood cell count	WBC
		19	Platelettes	
		20	Haemoglobin	Hb
		24	Haematocrit	PCV
	BIOCHEMISTRY	02	Na+	
		03	K+	
		04	Ca2+	
		05	Cl-	
		06	Alk. Phos.	AP
		07	Glucose	
		08	Bilirubine Tot_Dir	
		09	Amylase	
		10	Lipase	
		11	Glut oxalacetic trans (GOT)	AST
		12	Glut pyruvic trans (GPT)	ALT
		13	Gamma glutamil trans (GGT)	GGT
		14	Creatinine	
		16	Troponine	
		17	Urea	BUN
		21	LDH	
22	TOTAL Protein			
23	Albumin			

CATEGORY	SUB-CATEGORY	ID	ITEM	ACRONYM
LABORATORY (suite)	MICROBIOLOGY	34	Blood colture	
		35	Urine culture	
		36	Trach_sec	
	SEROLOGY	25	HIV 1-2	
		26	HBsAg	
		27	AntiHbs	
		28	AntiHbc	
		29	HCV	
		30	Anti CMV IgG	
		31	Anti CMV IgM	
		32	Syphilis	
		33	HTLV I II	
		URINE	37	Glucosio
	38		Protein	
	39		Sediment - RBC	
40	Sediment - WBC			
41	Sediment - Casts			
DIAGNOSTICS		01	Abdominal echography	
		02	Chest X Ray	
		03	ECG	
		04	Cardiac ECHO	
BLOOD GAS AND VENTILATION		01	FiO2%	
		02	PEEP	
		03	PaO2	
		04	PaCO2	
		05	PH	

CATEGORY	SUB-CATEGORY	ID	ITEM	ACRONYM
BLOOD GAS AND VENTILATION (suite)		06	HCO3	
		07	Sat O2	
		08	FiO2 1,0 / PEEP 5	
		09	PaO2	
		10	PaCO2	
		11	PH	
		12	HCO3-	
		13	Sat O2	
THERAPY		01	Antibiotics	
		02	Diuretics	
		03	Adrenaline	
		04	Dobutamine.	
		05	Noradrenaline.	
		06	Blood transfusion	
		07	Dopamine	
		08	Plasma expander	
		09	Other medication	