INTERNATIONAL KIDNEY PAIRED DONATION (KPD) PROGRAM

between the National Transplant Center for Italy and the Alliance for Paired Kidney Donation for the United States of America

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The proposal for an international Kidney Paired Donation (KPD) Program is borne out of the need to increase the possibility of transplantation for recipients of immunologically incompatible pairs enrolled in existing national Programs. This possibility is so much more interesting if international collaboration involves countries with populations that are genetically different from those in the Mediterranean area.

For this reason, with reference to the Memorandum on health and medical sciences between Italy and the United States of America, signed in Rome on Sept 3rd 2021, the National Transplant Center (CNT) for Italy and the Alliance for Paired Kidney Donation (APKD) for the United States for America (USA) have agreed to investigate the feasibility of a KPD common project, that is the object of the present Program.

1. BACKGROUND

The progressive increase in the number of donor-recipient pairs studied for live donor kidney transplantation results in a growing number of transplants that cannot be performed due to immunological incompatibility between donor and recipient.

At present, the AB0 blood group incompatibility or a positive cross-match constitute about 30% of the reasons for rejecting a living donor for a specific recipient. Desensitization techniques and aggressive immunosuppressive therapies make these transplants possible, but with an increased risk of infectious complications and rejection. However, these procedures are still limited to certain specific cases.

Aiming to overcome these incompatibility barriers, KPD has been proposed as a feasible alternative and carried out in different countries with excellent results.

One of the main factors that positively influences the effectiveness of a KPD Program is the pool size of incompatible pairs. Pools sizes over 100 pairs have demonstrated significant improvements in the possibility for detecting good combinations compared with smaller pools. For this reason, different KPD Programs have evolved to include multiple transplant centers, both regionally and nationally. Furthermore, the implementation of more than two-way exchanges and the inclusion of altruistic donors to initiate transplant chains have delivered dramatic growth in the number of transplants achieved.

In the international arena, the Italian National Transplant Center (CNT) started in 2018 a KPD Program with Spain and Portugal in the context of the South Alliance for Transplants (SAT) and considers it important to activate a KPD Program also with the USA, in order to expand the therapeutic possibilities for patients awaiting transplantation.

The USA can offer greater possibilities of transplantation in that it has a large-size, with a geographically and genetically heterogeneous population; such features increase the chances of identifying compatible donors for difficult-to-match patients.

In the USA there are several organizations that have developed KPD Programs in accordance with the standards set by their National Competent Authority, United Network for Organ Sharing (UNOS). UNOS is a private, non-profit organization that manages the Organ Procurement and Transplant Network (OPTN) system in the USA under a contract with the Federal Government. One such organization is the Alliance for Paired Kidney Donation (APKD) that operates the only international paired kidney exchange Program in the USA, which includes thirty-nine hospital facilities (among which the University of Toledo Medical Center – UTMC - and Thomas Jefferson University Hospital -TJUH). All these hospitals are licensed and accredited acute care hospital with an accredited kidney transplant Program that is compliant with the OPTN standards.

The Agostino Gemelli University Hospital Foundation IRCCS / Catholic University of the Sacred Heart (Gemelli Hospital) is an Italy-based hospital authorized by the Italian Government to perform kidney transplants from living donors, that has shown interest for participating in international KPD Programs. However, it is desirable to involve all the Italian Kidney Transplant Centers interested in participating in the proposed International KPD Program.

2. OBJECTIVE

The main goal of this international KPD Program is to increase the possibilities of kidney transplantation for those patients with chronic renal failure and a willing incompatible living donor, due to AB0 incompatibility or positive cross-match donors.

The Program will be offered to difficult-to-match end-stage kidney disease patients, who have not found therapeutic possibilities under national kidney paired donation Programs.

The inclusion in the Program of pairs, who are enrolled on the basis of criteria that take into account economic factors, is excluded. The exchange of kidneys based on financial incompatibility is prohibited. Only pairs resident in USA or Italy can be enrolled in the Program.

The inclusion of compatible living donors may be considered, when a real benefit can be achieved with a paired exchange compared with the transplant with the original donor (differences in body surface area, significant age gap), according to national regulations.

3. ELEMENTS OF THE INTERNATIONAL KIDNEY PAIRED DONATION PROGRAM

This common international KPD Program will be settled on the basis of the following pillars:

- Participating hospital requirements
- Virtual cross-match algorithm
- Operating protocol that includes a pilot of the Program

- Governance of the Program

3.1. Participating Hospital Requirements

The requirements for transplant centers to participate in the international KPD Program include:

1. A minimum number of living transplants ≥10/year (averaged over the last three years prior to the inclusion).
2. Participation in the corresponding national KPD Program.
3. Well-documented experience in donor nephrectomy performed by minimally invasive techniques, according to the best practices (intra- or extra-peritoneal laparoscopic or robotic surgery). The technique should be based on clinical grounds and according to the donor surgeon preference in technique, based on the criteria of vascular anatomy, size of the abdominal cavity, previous surgery and technical implications for the recipient.
4. Acceptance of the rules that have been laid down in the Program.
5. Immunology laboratories that participate in the Program must be accredited by the European Federation for Immunogenetics (EFI) or the American Society for Histocompatibility and Immunogenetics (ASHI) in order to harmonize immunological criteria.
6. Designation of a key person responsible for the Program at each participating center (contact person).

3.2. Matching Algorithm

The matching between pairs will be performed based on the algorithm identified by APKD. APKD is required to provide the other parties to this protocol with appropriate documentation, detailing the algorithm functioning and the criteria on which it is based for the purpose of identifying compatible pairs.
The allocation software is managed by APKD in accordance with and in compliance with the regulations issued by the competent USA Authority.

3.3. Operating Protocol, Including a Pilot of the Program

3.3.1. The Matching Run

A match run will be carried out as often as whenever a new pair is enrolled in the Program, with the pool of remaining pairs active after each national match run is performed. The users of the international Program will be the people responsible for the national KPD Program at each country, who will also be the liaisons with the key person responsible for the Program

in the different participating transplant centers.

Before the inclusion of a pair in the Program, all the work up must be completed. It includes the clinical study, immunological characterization, angio-CT, to assess vascularization, specific informed consent, and authorisation or approval by an independent body (e.g. Ethics Committee, Third party committee as other legal requirements, according to national regulation).

3.3.2. Information on Results of Matching Runs

A secure platform will be available to share the information on the results of the matching runs as well as the clinical records of the donors or other necessary information, in accordance with Data Protection regulations. The procedure for the matching runs will be defined before running the pilot foreseen under art. 3.4 of this Program.

Moreover, an email will be sent to both the person(s) responsible for the Program at the national level and the key person from the hospitals to which the pairs belong.

The final combined pairs must be chosen on the basis of the assessment of virtual cross-match outcome.

3.3.3. Laboratory Cross-Match

Once the centers are informed and have accepted the proposed kidney exchange offer, the person(s) responsible at the centers will be in contact to coordinate the exchange of the complete clinical records of the donors and angio-CT images.

Once all transplant teams accept the offer identified through virtual crossmatching, the donors' blood samples will be sent to the HLA laboratories of the Transplant Hospital to perform a laboratory cross-match in order to evaluate the feasibility of the kidney transplant procedure.

The laboratory cross-match will be performed at each transplant hospital's immunology laboratory or at the Regional Transplant Coordination Center by using Flow Cytometry and/or complement-dependent cytotoxicity (CDC). The centers will agree on the type of samples that they need and the way of transport.

Responsibility for the final cross-match lies with the laboratory connected to the involved transplant center and must be completed in a timeframe consistent with the transplant centers' policies.

Cross-match results will be provided to the responsible person(s) for the corresponding national Program and to the key person of the transplant centers involved in the exchange. That information will be sent through the secure information platform. If a laboratory cross-match result is determined to be positive, the paired exchange offer will be cancelled or revised. In case any of the pairs has other possible combination, the process will start again.

If the laboratory cross-match is negative, the centers will inform their respective responsible person(s) at a national level and will arrange the date of the transplant procedure.

3.3.4. Transplant Procedure

Transplants should take place simultaneously if performed as cycles, but could be performed non-simultaneously if in chains at the discretion of the participating transplant centers. Ideally, the bridge donor in identified segments of a non-simultaneous chain should not wait longer than an interval of 30 days. If a donor becomes unavailable, or if any adverse event occurs (e.g., during donor nephrectomy,) that makes one of the kidneys not valid for transplantation, the remainder of the transplants of the kidney exchange offer will be carried out. In that case, the non-transplanted recipient will be given priority for a future non-directed donor or bridge donor or by the deceased donor waiting list as allowed by the National Competent authority.

3.3.5. Informed Consent and Data Protection

A specific informed consent concerning access to this specific Program and prospective exchange will be gathered from the couples enrolled on the respective waiting lists and before inclusion in the Program. The data of donors and recipients will be treated under a specific protocol for data protection, abiding by the rules of the country where data are handled. Consent to data treatment will be gathered as well from registered couples.

3.4. Pilot

3.4.1

The pilot phase includes the first three cases. CNT and APKD identify which kidney transplant centers are approved for carrying out transplantation in their respective countries. Only transplant centers approved by CNT and APKD can participate in the pilot phase of the present KPD Program, such as the Gemelli Hospital, UTMC and TJUH. These centers meet all the national regulatory requirements, as well as the requirements indicated in the common protocol, to participate in a kidney paired donation Program. At the end of the pilot phase, the parties provide for the re-evaluation of the agreement on the basis of the results achieved and of any critical issues that have emerged.

In the event of a positive outcome of the re-evaluation, the agreement can continue and be extended to other Italian or USA transplant centers that request it, through written approval of the CNT and APKD.

Each party can withdraw from this agreement at any time, subject to prior written communication to the other party with at least one month notice. The withdrawal must be exercised in order not to harm patients or the other party.

3.4.2

Each selected transplant center will designate a key person responsible for the Program who will interact with their corresponding colleagues at other participating transplant centers.

The responsible person(s) from the National Transplant Organizations will share the data correspondent to the incompatible pairs under terms compatible with privacy and legal provisions.

The transplant centers involved in the pilot study (including one nephrologist, one immunologist and one surgeon) will meet before the start of the Program, in order to share methodology, clarify doubts and clinical standards, as well as information concerning the logistics.
The APKD and transplant centers of all participating countries will guarantee the anonymity for all the pairs involved in this Program prior to transplantation/donation. If anonymity is not required by the Competent Authority for the transplant center where the transplant/donation is performed, then the recipient and donor information can be disclosed, but only if consented to by all involved patients and donors. The communication of the identity of donors and recipients to the Competent Authority should be necessary to ensure the traceability and security of the results of match runs under prior donor consent.

3.4.3. Including a pair in the Program:

i. Except as in Section 2 above, only immunological incompatible pairs resident in USA or Italy already included in the corresponding national KPD Program can be enrolled in this Program, once their clinical, psychological and immunological suitability assessment have been completed. Following the rules and regulations required by the Competent Authority of the pairs' country of origin, incompatible pairs will be authorized by national third-party.

ii. The pair will be included at the web platform only after all the immunological studies have been performed and the pair has been found suitable (see Annex 1).

iii. The evaluation for donor and the recipient of each pair must be completed (including angio-CT).

iv. A specific informed consent must be signed by donor and recipient from any incompatible pair, that includes authorization for cross-border personal data processing, before their identified data can be shared outside of their own country.

3.4.4. Web platform:

1. The pair's registry will be located in a platform available through secure login via the APKD clinical website.
2. The application assigns an ID code to every donor and recipient included in the data base in order to guarantee anonymity. Their personal details will be known exclusively by their own transplant center, and their National Competent Authority until such time as a match offer is identified.

3.4.5 Operating aspects:

1. Data from Italian pairs are sent from CNT to APKD, to be enrolled in the Program.
2. The matching runs will be performed by the APKD.
3. Before running the software, a validation of inserted pairs will be performed by the

Parties. After this phase, the Parties commits not to withdraw its pairs from the Program, unless exceptional situations, independent from the Parties.

4. Once a pair is selected through the matching algorithm, the pair must be temporarily excluded from the deceased donor waiting list until the real cross-match is performed.
5. Consent (free, specific and informed) should be given by the donor, according to National legislation and, for Italy, according also to European Union legislation. Authorisation or approval by an independent body (e.g. Court; Ethic Committee; third party committee) should be performed according to the legal rules established in the country where donation takes place.
6. APKD communicates to the CNT the results of the matching runs and to the involved transplant centers the data of the compatible donor-recipient pairs resulting from the identified cycles and chains.
7. During the pilot phase, the recipient of the Italian pair and that of the USA pair will be transplanted, respectively, at the Italian and USA transplant centers identified on the basis of this protocol. The involvement of any other transplant center will require the consent of both CNT and APKD. The donor of the Italian pair and that of the USA pair will undergo living donor nephrectomy procedures, respectively, at the USA and Italian facilities identified on the basis of this protocol. Once the pilot phase is completed, the organization design with respect to the location of transplant or retrieval hospital may be defined case by case.

3.5. Governance of the Program

The transplant Programs should be supervised by the Competent Authorities responsible for the national KPD Programs at each participating country.

APKD, as the organization in charge of the maintenance of the pairs' health information will inform properly about the possible combinations after each match run and develop an annual report on the results.

Policies on the publication of these results should be developed.

4. TASKS AND RESPONSIBILITIES OF INVOLVED PARTIES

4.1 Tasks and responsibilities of the Parties

The Parties are in charge of:

1. Ensuring the correct application of the corresponding national laws in force on the subject to protect the health of the donor and the recipient, as well as compliance with the provisions of this protocol by the health facilities of their country;
2. Monitoring the activities carried out in execution of this protocol, facilitating the connection between the structures involved;
3. Securing any other regulatory approvals that may be required for Recipients to undertake

treatment by Transplant Center.

4.2 Specific tasks and responsibilities of APKD

APKD is in charge of:

1. Identifying the algorithm based on which the pairs of donors - recipients will be combined.
2. Supplying appropriate documentation to the other parties of this protocol, about algorithm functioning and the selection criteria for identifying compatible pairs.
3. Guaranteeing that the allocation software complies with the regulations issued by the USA Competent Authority.
4. Facilitating pre-in-country consultation between Potential Recipients/Donors and Transplant Center while Potential Recipients/Donors are residing in Italy, through secure emails, teleconferences, and phone calls.
5. Scheduling all consultations and procedures for Recipients/Donors by Transplant Center.
6. Collecting clinical and immunological data of pairs enrolled in the Program, in a suitable database.
7. Executing the match run, with definition of the compatible cycles and chains, based on the criteria provided by the algorithm, and the results of the virtual cross-match
8. Periodic reporting to the CNT of transplants performed in the context of the implementation of this protocol.

4.3 Tasks and responsibilities of transplant centers

Transplant centers are in charge of:

1. Selecting the incompatible donor - recipient pairs to be enrolled in the present Program.
2. Evaluating the clinical, psychological and immunological suitability of donor-recipient pairs enrolled in the Program.
3. Acquiring the authorization documentation for donation and transplantation procedures, as per respective national legislation, for each single registered pair, and transmission of such documentation to the corresponding Competent Authority (CA).
4. Ensuring that each donor and recipient are physically present at Transplant Center for all Kidney Transplant Program activities.
5. Ensuring the execution of the nephrectomy and transplant procedures in compliance with local procedures, national regulations and international standards.
6. Being free to publish, present, or use any scientific data and results arising out of its performance of this Program (individually, a "Publication"). At least thirty (30) days prior to submission for Publication, Transplant Center shall submit to the Parties for review and comment any proposed oral or written Publication ("Review Period").
7. Ensuring clinical assistance after transplantation to transplanted patient, for an indefinite period of time.

8. Ensuring clinical assistance to the donor after retrieval in the foreign center, for an indefinite period of time.
9. Making follow-up data of recipients and donors available to the CA.

5. FINANCIAL ASPECTS FOR THE PILOT PHASE

5.1. Financial coverage of recipient transplant expenses

As far as the coverage of the expenses related to recipients, in the case of the USA recipients, they are covered according to the healthcare insurance of the recipients, and, for Italy, according also to National and European Union legislation.

5.2 . Financial coverage of donor kidney retrieval expenses

1. As regards the costs related to the clinical evaluation and the kidney retrieval procedure from the American donor, who donates for the Italian recipient, they are covered by the Italian National Healthcare Service.
2. As regards the financial coverage of the expenses related to the clinical evaluation and the kidney retrieval procedure from the Italian donor, who donates for the USA recipient, they are covered by an appropriate healthcare insurance of the recipient, according to current USA legislation.

5.3 . Financial coverage of real cross-match

As for the clinical responsibility and the costs related to sending the donor's biological material in order to carry out the actual cross-match, they are in charge of the hospital in charge of the recipient.

5.4. Financial coverage of travel and accommodation expenses of donor

As for the costs related to travel and accommodation expenses (for Italian and USA donor), they are borne out as follows:

1. For Italian donor, the costs will be covered by a specific funding of the project up to a maximum of 10.000 € for each donor.
2. For USA donor, the costs will be reimbursed by an appropriate healthcare insurance of the recipient, according to current USA legislation.

5.5. The provisions referred to in the previous paragraphs of this article are valid only for the pilot phase, at the end of which the financial aspects will be subject to reassessment as the entire Program pursuant to paragraph 3.4.1.

At present, for a similar Program in the European Union and the USA, it is acceptable to ship the kidney to the recipient hospital after the retrieval from the living donor. Suppose eventually the Governance of the Program (indicated in point 3.5) will consider safe such a procedure for the Program described herein. In that case, the costs related to the clinical evaluation and the kidney retrieval procedure, in the USA, from the American donor, who donates for the Italian recipient are covered by appropriate healthcare insurance, according to current USA legislation. Regarding the financial coverage of the expenses related to the clinical evaluation and the kidney retrieval procedure, in Italy, from the Italian donor, who donates for the USA recipient, they are covered by the Italian National Healthcare Service.

This Program is signed in Rome on September 8th 2022 in two originals, each in English and in Italian language, all texts being equally authentic.

For the National Transplant Center

The Director
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For the Alliance for Paired Kidney Donation

The Chief Executive Officer
Prof. Michael A. Rees

ANNEX I: Immunological Characterization of Donors and Recipients

Information on the immunological characterization of donors and recipients are detailed below:

HLA laboratories from hospitals participating in the KPD Program should perform HLA typing for the following HLA alleles in the recipient: HLA-**A**; HLA-**B**; HLA-**C**; HLA-**DRB1**; HLA-**DQB1**, HLA-**DRB3**, HLA-**DRB4**, HLA-**DRB5** and the following HLA alleles in his/her incompatible donor (or donors): HLA alleles HLA-**A**; HLA-**B**; HLA-**C**; HLA-**DRB1**; HLA-**DQA1**, HLA-**DQB1**, HLA-**DPB1**, HLA-**DRB3**, HLA-**DRB4**, HLA-**DRB5**. A DNA sample from any donor and recipient will be stored for further tests, if needed.

- The panel reactive antibodies (PRA) to determine the level of sensitization of each recipient should be calculated for HLA class I and class II antibodies.
- The presence of specific antibodies against HLA antigens in the recipients must be tested by Luminex technique and updated once a year (with additional updates if necessary, i.e. blood transfusion)
- Molecular nomenclature will be used to include the HLA typing on donors and recipient as well as the antibodies against HLA antigens.