The Canadian Council for Donation and Transplantation

Canadian Highly Sensitized Patient and Living Donor Paired Exchange Registries

October 28-30, 2005

Toronto, Ontario

Task Force Discussion Document

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Preface

It is my pleasure as Chair of the Transplant Committee for the Canadian Council for Donation and Transplantation (CCDT) to present the report of the Task Force for the Highly Sensitized Patient and Living Donor Paired Exchange Registries.

In Canada, we know that we have a growing problem of access for patients awaiting transplantation. There is an ever increasing gap between the number of patients awaiting transplants and the number of organs available for transplantation. This has resulted in premature death and an increasing financial burden on our health care system.

From 1998 to 2004, the wait-list for all organ transplants grew from 3,229 to 4,054 Canadians (Canadian Organ Replacement Register, 2005). Transplants done during the same period ranged from a low of 1,623 in 1998 to a high of 1,901 in 2000; overall, the transplant rate has not risen to match or meet wait-list numbers. In 2004, 234 Canadians died waiting for an organ transplant.

One growing segment of our wait-lists is the highly sensitized patients awaiting kidney transplants. Approximately 20-30% of the wait-list population in each province are sensitized with Panel Reactive Antibody (PRA) above 20% and yet these patients receive less than 5% of all deceased donor kidney transplants in Canada.

Sensitized individuals do not have fair access to deceased donor organs, as compared to non-sensitized patients. They wait much longer for transplantation than do their non-sensitized counterparts, often deteriorating medically or dying while waiting. Women are more affected by this issue in that 75-85% of sensitized patients waiting for their first kidney transplant are women. A second group are patients with willing live donors who, because of blood group or other immunologic incompatibilities, cannot receive an organ from their particular donor.

To address this issue, the CCDT hosted a Task Force meeting where Canadian and international experts gathered to consider successful programs in other jurisdictions and to propose a Canadian model. This report is the culmination of the Task Force discussions. The purpose of this report is to outline the components of Canadian model for highly sensitized patient and living donor paired exchange registries. Similar patient registries have been in operation for many years in the Netherlands with successful outcomes in reducing the numbers of sensitized patients awaiting transplantation.

On behalf of the CCDT, I extend our congratulations to the co-chairs, Dr. Peter Nickerson and Dr. Edward Cole, for driving the project from its inception to conclusion. You have produced an excellent report which will ultimately result in benefits to Canadian patients awaiting transplantation.

David J. Hollomby, MD, FRCP(C), FACP, FRCP(Glasg)

Foreword

The CCDT "Highly Sensitized Patient and Living Donor Paired Exchange Registries" Task Force examined current practices, literature and new technologies for the establishment of Canadian Registries for (a) the highly sensitized patient awaiting a kidney transplant on the deceased donor wait-list; and (b) those patients who, due to human leukocyte antigen (HLA) or ABO incompatibilities, are unable to accept a kidney from a living donor who is otherwise willing and able to donate. This is Phase I of a two phase process.

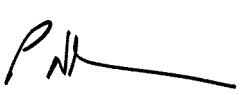
Underpinning the CCDT Task Force's work were the following key assumptions:

- Canadian Registries are required to provide the numbers needed to enhance the living and deceased donor pools for the highly sensitized patient, and for patients with ABO incompatible living donors.
- All provincial transplant programs have agreed to share organs between programs for the highly sensitized patient.
- The Council of Deputy Ministers (CDM) acknowledged the need for the provinces to upgrade all HLA labs to the same standard – a critical foundation required to build national registries.
- The CDM has approved the CCDT to develop a business case for Canadian Highly Sensitized Patient and Living Donor Exchange Registries to be presented to the CDM in June 2006.
- The model developed for a Canadian Highly Sensitized Kidney Patient Registry must be applicable for sensitized kidney, lung and heart patients on the wait-list.

Sponsored and supported by the CCDT, with support from the Canadian Society for Transplantation, the Task Force met in Toronto on October 28 to 30, 2005. There were 16 Canadian health care professionals on the Task Force representing programs from across Canada.

Supplemented with background research, the CCDT Task Force meeting featured presentations from leading experts from the United States and Europe, followed by facilitated group discussion aimed at exploring and achieving consensus, including recommendations around key issues related to the medical, scientific and administrative design of Canadian registries.

This report summarizes the proceedings and recommendations flowing from the CCDT Task Force. By forging consensus and reducing uncertainty, it is hoped that the report will serve as an instrument for change and improvement, laying a foundation for the establishment of Canadian Highly Sensitized Patient and Living Donor Paired Exchange Registries. The Task Force report will be used for broader consultation with the donation and transplant communities and as a foundation for Phase II, which will then involve a broader range of stakeholders to identify implementation considerations and recommendations for operation of these Canadian Registries.



Peter Nickerson
Co-Chair, CCDT Task Force

Ed Cole
Co-Chair, CCDT Task Force

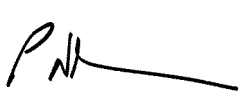
Acknowledgements

Any success and impact that the report from the CCDT Task Force will have is the result of a team effort. First of all, a special note of thanks goes to Beverley Curtis, Deborah Pankhurst, and Nancy Greene who worked tirelessly behind the scenes before, during and after the CCDT Task Force meeting to make it run smoothly and to ensure that we were able to produce the highest quality product. To the Task Force members, who captured the vision, pushed to find consensus, and worked enthusiastically over an intense few days to generate the best possible document – you have our deepest gratitude. To David Hollomby, thank you for your continued support for this project; it is a joy to work with you and your team.

To the larger Canadian transplant community and to those in health care administration who will pick up the torch that is this report, and make the vision of Canadian Registries become a reality, we want to thank you in advance. We believe that the fruits of this effort hold substantial potential to see unprecedented change in the delivery of transplant care in Canada and provide a new life for many of our patients who are at present otherwise condemned to wait.

The challenge now for all of us was eloquently stated by President John Fitzgerald Kennedy in his inaugural address:

> *All of this will not be finished in the first one hundred days. Nor will it be finished in the first one thousand days, nor in the life of this Administration, nor even perhaps in our lifetime on this planet. But let us begin.*



Peter Nickerson
Co-Chair, CCDT Task Force

Ed Cole
Co-Chair, CCDT Task Force

Executive Summary

The CCDT held a Task Force meeting on October 28 to 30, 2005 in Toronto, entitled "Highly Sensitized Patient and Living Donor Paired Exchange Registries." The initiative is being undertaken in two phases. The purpose of this first phase was to review existing international models and develop consensus medical/scientific/administrative guidelines for a Canadian model for these two patient registries. These guidelines will be reviewed by additional members of the donation and transplant communities for their feedback. Phase II will then involve a broader range of stakeholders to identify implementation considerations and recommendations for operations.

The specific objectives of the meeting were to:

1. Identify successful elements of highly sensitized patient and living donor paired exchange registries in other countries.
2. Recommend the required elements of the Canadian Highly Sensitized Patient and Living Donor Paired Exchange Registries.
3. Identify areas requiring further data gathering and analysis.

I. Canadian Highly Sensitized Patient Registry (CHSPR)

Learning from Other Countries

A number of speakers from the United States and Europe shared information about the success of their programs. Learning from international programs contributed significantly to the Task Force's understanding of the required elements and realistic potential for a highly sensitized patient registry.

Findings from international programs included:

- There is a level of patient sensitization at which immunomodulation is unlikely to work. The patient requires an "acceptable mismatched" organ to have a successful transplant.
- If an acceptable mismatched donor organ can be found, then the outcomes for broadly sensitized patients are about equal to non-sensitized patients.
- For these patients, defining antibody specificities and having access to a larger donor pool reduces waiting time and increases the probability of them receiving an acceptable organ.
- Since organs will travel between programs, it is critical to standardize techniques for measuring antibodies, conducting crossmatches, and undertaking proficiency testing to make this type of program work; a central reference laboratory is required for the program to function well.
- Assessing the HLA typing of the current deceased donor pool and the wait-listed highly sensitized pool of patients in Canada will be very helpful to predict the likelihood of the success of a CHSPR; computer analysis is needed.

CHSPR Performance Measures

Specific, measurable targets for the program were agreed upon. A management structure (details to be developed) would be responsible for assessing and reporting measures on an on-going basis.

Measure	Target
Percent reduction in sensitized patients waiting (achieved through transplants)	The registry will result in a 30% reduction over 5 years.
Outcomes (rejection rate, graft survival, patient survival, graft function)	The registry will achieve the same outcomes as the entire national cohort of all kidneys, for both the kidney allocated to the sensitized patient and any payback kidneys provided for rebalancing.
Safety	The registry will maintain current Canadian standards.
Transparency	Listing criteria, organ referral and allocation policies and registry results will be easily and broadly available, and comprehensible to the lay public.

CHSPR Critical Success Factors

It was noted by the group that the following contributing elements would be critical to achieving the success outlined above, namely:

- Having the registry accepted by the provincial Deputy Ministers of Health.
- Ensuring that key organizations [i.e., CCDT, organ procurement organizations (OPOs), Canadian Association of Transplantation (CAT), and Canadian Society of Transplantation (CST)] are recognized for their roles in this initiative, and that they and others in each transplant program have the opportunity to comment prior to the recommendations being finalized.
- Standardizing of HLA laboratories is necessary for the registry to work and will require significant resources. [CCDT (2005). Assessment and Management of Immunologic Risk in Transplantation, www.ccdt.ca]

CHSPR Listing Criteria

Listing criteria establish the requirements for a patient to be included on a CHSPR. The decision to list will be made at the local transplant centre, after medical/psychological assessment and immunologic work-up. A mechanism will be established (e.g., Canadian Steering Committee) to monitor adherence to listing criteria.

Listing criteria include:

- A virtual % PRA cut-off value that will result in 10% of Canadian deceased donor kidneys being transplanted into highly sensitized recipients through the Registry. The specific degree of sensitization for access will be determined following more detailed modeling of donor and recipient pools to determine what cut-off for the virtual % PRA would result in 10% of kidneys going to the pool per year.
- The patient is currently on dialysis.

Deceased Donor Organ Referral and Acceptance by the Registry

Once a deceased donor becomes available, then common practices for to how refer a donor organ to the CHSPR are required. Moreover, common operating principles governing whether an organ is accepted once referred to the registry are required to ensure transparency amongst participating centres.

Operating Principles

- Only one kidney per donor would be made available for allocation to the CHSPR.
- The local centre has first choice of which kidney they retain.
- Only kidneys that can be shipped and transplanted within 24 hours should ideally be made available; the hard cut-off is 30 hours. The receiving centre will have the option to decline based on cold ischemia time (CIT).
- An extended criteria donor (ECD) (sub-optimal) kidney may be offered, but the receiving centre has the option to decline.
- The donor centre will facilitate organ retrieval, with the receiving centre determining the transport route.
- If the final crossmatch at the receiving center is positive, the receiving centre will decide whether to proceed with the transplant, or transplant another patient, or return the organ to the pool; the latter is unlikely due to CIT. To be prepared, other recipients (including non-sensitized) at the receiving centre should be tested as potential back-ups to guard against the loss of a kidney.
  - There will be mandatory reporting of positive crossmatches to a Canadian Laboratory Steering Committee.
  - Positive crossmatches must be repeated retrospectively by a reference lab.
- The need to re-balance distribution of kidneys across regions to address net export deficits will be determined via quarterly audits; adjustments will be built into the algorithm to re-balance within the subsequent 6 months if needed.

CHSPR Organ Allocation Guidelines

Allocation guidelines determine the prioritization of how kidneys are allocated to individual recipients on the CHSPR.

Guidelines

Prioritization of Recipients (in descending order)

1. Blood group identical then compatible.
2. Pediatric patient (under age 18).
3. Length of waiting time as measured from the first day of dialysis.

II. Living Donor Paired Exchange (LDPE)

Learning from Other Countries

A number of speakers from the United States and the Netherlands shared information about the success of their programs. Learning from international programs contributed significantly to the understanding of the Canadian group about the required elements and the realistic potential of a living donor paired exchange registry.

Findings from international programs included:

- There are a minimum number of pairs that must be registered to make a LDPE registry work (minimum 100, but 150 much better); this number is feasible in a country with Canada's population size based on the Netherlands' experience.
- This type of registry will add new donors to the system, and will help to address the backlog of current patients.
- The matching process needs to optimize the number of pairs matched each time a computer run is done. Population homogeneity will affect the likelihood of success in matching.
- A recruitment effort is needed to get recipients, who have previously had an incompatible living donor declined as acceptable, to register for the program. Canada does not have records of specific cases where this has occurred.
- The registry cannot experience failures at the early stages as enrolment would be highly influenced by patient perceptions.
- There is a need for rigorous adherence to policies across programs. About 3 assessments are required for each acceptable living donor. This may create an additional resource burden that must be separately funded at a provincial level.
- The primary benefit is seen for ABO incompatible donor-recipient pairs and the number of highly sensitized patients transplanted through this program has been low based on experience in other programs; nonetheless, it offers a potential solution to this disadvantaged group.
- Canada can leverage the software programs that other countries have developed to predict the number of potential match-pairs that can be achieved in Canada.

LDPE Performance Measures

Specific, measurable targets for the registry were agreed upon. A central body (details to be developed) would be responsible for assessing and reporting measures on an on-going basis.

Measure	Target
The annual number of paired exchange transplants	The registry will complete 35 paired exchanges annually, without a reduction in the living donor rate, by the fifth year.
Outcomes of transplants, including donor outcomes	The registry will achieve the same outcomes as the entire national cohort of living donor kidney transplants.
Quality assurance	Common standard operating procedures (SOPs) will be in place at all participating programs, with a monitoring system to optimize quality.
Transparency	Listing criteria, matching guidelines and registry results will be easily and broadly available, and comprehensible to the lay public.
Pairs satisfaction	Satisfaction ratings will be equivalent to direct donor satisfaction levels.

LDPE Listing Criteria

Listing criteria establish the requirements for a recipient and their donor who are offered participation in the LDPE registry. The decision to list will made at the local transplant center, after medical/psychological assessment, immunologic work-up and completion of informed consent. Audits conducted by a Canadian Steering Committee will monitor adherence to listing criteria.

Listing Criteria
• ABO incompatible OR • Crossmatch positive with a donor-specific antibody present AND • Immunomodulation is not feasible or desired by the patient, due to the nature of sensitization. • If immunomodulation is feasible and the patient/donor wish to pursue this course but the local transplant centre does not offer it, then they should be referred to a transplant centre with a proven track record. • The donor is assessed as being “normal risk” as determined by the CCDT "Enhancing Living Donation Consensus Forum” (February 2006). • The recipient is assessed as being “acceptable risk” by the local program. • The recipient is assessed as being “acceptable risk” by the donor as determined by the CCDT "Enhancing Living Donation Consensus Forum” (February 2006).

LDPE Guidelines

LDPE guidelines address the common guidelines that programs would adopt when conducting paired exchange transplants. Common practices are vital to ensure that pairs are treated consistently by participating centres.

Guidelines
Mechanism of Matching Optimized computer algorithm will be used. The following elements will be taken into account: • Willingness to travel (yes/no type response). • Blood group identical, then compatible. Once a potential match pair is identified a screening crossmatch must be confirmed to be negative by the most sensitive current technique. All crossmatches must be confirmed by a second lab for the sensitized patients.
Procedures Pairs must agree to respect anonymity, and programs must take due diligence to attempt to ensure anonymity before an exchange proceeds. • Programs will obtain patient and donor input to their "right to know" via a common survey. • This policy will be evaluated later to determine suitability to patient and program needs. Transplants should occur simultaneously, based on incision time.
Donors will travel to recipient centres. • Rare exceptions could include both donor and recipient traveling to a third centre, or a kidney or recipient traveling if the donor is unable to travel (e.g., single parent without support).
If a problem arises during surgery: • If early enough, then both donor procedures and transplants should be aborted. This decision will be made by telephone by the surgeon performing the uncomplicated donor procedure. • If later, then proceed based on previously obtained donor consent to either auto-transplant or give the kidney to the top compatible patient on the local list and have the recipient receive the first nationally available compatible, normal risk deceased donor kidney. • If the recipient is temporarily unable to receive the kidney, it should go to the first patient on the local list of that donor's region. Then when the recipient is able to receive a kidney, they will be prioritized for a deceased donor kidney within the region that received the kidney for the top local deceased donor recipient. Consent should include the rare possibility that if one recipient becomes seriously ill during the procedure and does not recover he/she may never be able to be transplanted. • If the graft is lost within 48 hours of surgery, the recipient retains priority on the national list for the next suitable kidney.

III. Overarching Guidelines

LDPE Registry Structure and Processes

Input was obtained from the group as to appropriate organizational structures and processes for making Canadian registries work. There was a high level of consensus that:

- Various centralized initiatives would have to be in place for the registries to function effectively.
- To ensure trust, transparency and buy-in by all provincial programs, a provincially based organization would not be acceptable for providing the management function of the registries.

The structural, administrative and operational aspects of the registries will be developed in detail after broader input has been obtained.

IV. Summary

At the conclusion of the CCDT Registries Task Force Forum (Phase I), it was clear that significant progress had been made in establishing, through consensus, the performance goals and operational elements that will be required to be achieved to ensure the success of the Highly Sensitized Patient and Living Donor Paired Exchange Registries for Canadians.

The next steps for the Task Force will be the following:

- Distribute the report prior to a broad consultation with our partners and stakeholders that will take place at the CST/CAT Annual meeting in Mont Tremblant, Quebec (Task Force Phase II: March 2006).
- Seek input from the public and the "involved" public through surveys and consultation with non-government organizations (NGOs) (e.g., The Kidney Foundation of Canada)
- Model the feasibility of a highly sensitized patient registry given the current demographics of highly sensitized patients on wait-lists in Canada and the Canadian deceased donor pool.
- Model the number of donor-recipient pairs required on the living donor paired exchange registry to ensure its success.
- Work with the CCDT Information Management Project to develop the information technology support required for the registries.

At the end of this process, the CCDT Registries Task Force will produce a business case for the CCDT that will make recommendations for the implementation of these registries in Canada.

Recommendations to the CCDT

In addition to the aforementioned process, the CCDT Task Force recommends to the CCDT that the following enabling processes be prioritized:

- The CCDT follow-up with the provincial health ministries to determine what assistance can be provided to ensure that the HLA laboratory upgrade initiative is occurring in all Canadian transplant programs.
- The CCDT Living Donor Forum is made aware of the need to include living donor paired exchange donors in the scope of their mandate.
- The CCDT Information Management Project is made aware of the need for a living donor outcome database in support of the living donor paired exchange registry.

Part I:

Problem Definition

Problem Definition

One of the five pillars of the Canada Health Act is accessibility, defined by Health Canada as "reasonable access by insured persons to medically necessary hospital and physician services must be unimpeded by financial or other barriers." It can be reasonably argued that for the sensitized patient waiting for a kidney transplant, the Canadian health care system as it currently exists does not meet this standard. Indeed, in the CCDT publication, *Assessment and Management of Immunologic Risk in Transplantation* (2005), it was reported that **approximately 20-30% of the wait-list population in each province are sensitized with Panel Reactive Antibody above 20% and yet these patients receive less than 5% of all deceased donor kidney transplants in Canada.**

As sensitized individuals do not receive equal access to deceased donor organs, as compared to non-sensitized patients, they end up having a markedly prolonged wait-time even if they are eventually transplanted. Indeed, based on data reported in the above mentioned CCDT report, it is clear that the sensitized patient is more likely to have their medical condition deteriorate or even die while waiting as compared to the non-sensitized patient. Finally, as sensitization is a product of exposure to foreign HLA antigens, typically by pregnancy or blood transfusion, it is not surprising to learn that 75-85% of sensitized patients waiting for their first kidney transplant are women (CCDT, 2005). It can be concluded that sensitization poses a **considerable barrier limiting access** to kidney transplantation in Canada.

The reason sensitization creates this barrier is that for a given transplant center the diversity of the HLA antigens in the deceased donor pool of that center is insufficient to find a suitable "match" for the sensitized patient who has more restricted requirements in terms of matching as compared to the non-sensitized patient. A solution is required that will allow sensitized patients access to the larger pool of deceased donors that are available across Canada. Such is the context within which the Task Force is to determine the requirements of a **Canadian Highly Sensitized Patient Registry (CHSPR)** to address the issue of access for the sensitized patient.

While the aforementioned discusses the rationale behind a Canadian Registry as a strategy to address access for the sensitized patients to deceased donor organs, there is another strategy to consider – **Living Donor Paired Exchange (LDPE) Registry**. It is not infrequent that a number of individuals come forward to be evaluated as possible living donors for a given patient. However, due to either ABO blood group or HLA incompatibilities (i.e., the patient is sensitized to the potential donor) many living donors are excluded from further consideration and the patient has no option but to go on the deceased donor wait-list. In a recently reported Canadian study it was determined that of 180 living donors ruled out for kidney donation, 22% were ruled out on the basis of ABO incompatibility and 32% on the basis of HLA incompatibility (i.e., the recipient is sensitized and the crossmatch is positive) (Karpinski et al., in press, Am J Kid Disease).

If, however, these living donors were willing to donate their kidney to another patient with whom they are compatible in exchange for their loved one receiving a kidney from the other patient's potential but incompatible donor, this would add new donors to the pool of living donors, increase the total number of transplants performed in Canada and enable these two recipients to be transplanted more rapidly and with optimal organs, likely improving their long term survival. For this strategy to succeed, the number of recipient-donor pairs willing to participate in such a program must be sufficiently large (i.e., the local/provincial pool of pairs is too small). Such is the context within which the Task Force is to determine the requirements of a Living Donor Paired Exchange Registry.

Part II:

Canadian Highly Sensitized Patient Registry Guidelines

Canadian Highly Sensitized Patient Registry (CHSPR) Guidelines

The recommendations below were built upon learning from programs in place in the United States and Europe and the participants' own experiences and assessment of approaches that would work in a Canadian context. There was a high (typically unanimous) level of consensus around the recommended directions. The Task Force engaged in considerable discussion in developing these guidelines, and in each case assessed options from a number of angles. Participants recommended approaches that they supported or felt that their organizations could accept.

Speaker Highlights

The following points from the international speaker presentations were generally agreed upon:

- There is a level of sensitization at which immunomodulation is unlikely to work.
- For these patients, defining antigen specificities and having access to a larger donor pool increases the probability of sensitized recipients receiving an acceptable mismatched organ.
- It will be critical to standardize techniques for measuring antibodies, conducting crossmatches, and undertaking proficiency testing; having a central reference laboratory works well.
- If an acceptable mismatched donor organ can be found then the outcomes for broadly sensitized patients are about equal to non-sensitized patients.
- Assessing the HLA typing of the current deceased donor pool and the wait-listed highly sensitized pool of patients in Canada will be very helpful to predict the likelihood of the success of a highly sensitized patient registry; a computer algorithm is needed.

CHSPR Performance Measures

Specific, measurable targets for the registry were agreed upon. A management structure (details to be developed in Phase II) would be responsible for assessing and reporting measures on an on-going basis.

Measure	Target
Percent reduction in sensitized patients waiting (achieved through transplants)	The registry will result in a 30% reduction over 5 years.
Outcomes (rejection rate, graft survival, patient survival, graft function)	The registry will achieve the same outcomes as the entire national cohort of all kidneys, for both the kidney allocated to the sensitized patient and any payback kidneys provided.
Safety	The registry will maintain current Canadian standards.
Transparency	Listing criteria, organ referral and allocation policies and registry results will be easily and broadly available, and comprehensible to the lay public.

Rationale for Performance Measures

Percent Reduction in Sensitized Patients

Of the 3,000 patients currently wait-listed nationally (2005 numbers), about 25% or 750 are sensitized. At a PRA of 80% or higher, there are an estimated 400 to 500 patients. If 10% of these highly sensitized patients were transplanted per year, over 5 years this would represent 200 to 250 transplants or about 30% of wait-listed sensitized patients. This figure was viewed as both realistic and desirable to ensure that the registry has impact.

Outcomes

It was felt that this registry should achieve the same outcomes as are currently achieved for all kidney programs in Canada. This will drive a high standard for what constitutes an acceptable mismatch.

Safety

This dimension captures both local transplant program protocols (i.e., OPO, HLA Laboratory, and Transplant Centre SOPs), as well as those associated with sharing data and communicating with a central body and other transplant programs in Canada. Safety standards that are currently in place should be maintained.

Transparency

Since this registry will involve selecting recipients for participation and will cross provincial boundaries when allocating kidneys, scrutiny by the involved public could be high. Registry acceptance will be greatly enhanced by having listing criteria, organ referral and allocation guidelines and outcomes readily available to and easily understood by lay people.

Critical Success Factors

The following contributing elements would be critical to achieving the success outlined above, namely:

- Having the registry endorsed and funded by the provincial Deputy Ministers of Health.
- Ensuring that key organizations (i.e., CCDT, OPOs, CAT, and CST) are recognized for their roles in this initiative, and they and others in each transplant program have the opportunity to comment prior to the recommendations being finalized.
- Standardizing of HLA laboratories is necessary for the Registry to work and will require significant resources [CCDT (2005). *Assessment and Management of Immunologic Risk in Transplantation*, www.ccdt.ca].

CHSPR Listing Criteria

Listing criteria establish the requirements for a patient to be included on a CHSPR. The decision to list will be made at the local transplant center, after medical/psychological assessment and immunologic work-up. Audits conducted by a Canadian Steering Committee will monitor adherence to listing criteria.

In principle, it was agreed that listing criteria should be objectively based and kept to a minimum. Objective criteria would ensure fairness, while a minimum number of criteria would optimize access.

Criteria	Rationale
A virtual % PRA that will result in 10% of Canadian deceased donor kidneys being transplanted into highly sensitized recipients through the Registry. The specific degree of sensitization for access will be determined following more detailed modeling of donor and recipient pools to determine what cut-off for the virtual % PRA would result in 10% of kidneys going to the pool per year.	This cut-off does not unduly disadvantage the rest of the waiting patients, while at the same time constituting affirmative action to facilitate equitable access for all waiting patients.
The patient is currently on dialysis.	This ensures fairness for all wait-list patients and provides a measurable end-point for determining wait-time.

Deceased Donor Organ Referral and Acceptance by the Registry

Once a deceased donor becomes available, then common practices for how to refer a donor organ to the CHSPR are required. Moreover, common operating principles governing whether an organ is accepted once referred to the Registry are required to ensure transparency amongst participating centres.

Operating Principles	Rationale
Only one kidney per donor would be made available for allocation to the Highly Sensitized Patient Registry.	This will encourage local donor activity, and ensure support from transplant programs.
The local centre has first choice of which kidney they retain.	This will ensure support from transplant programs (i.e., they will not be disadvantaging their own patients to support the registry).
Only kidneys that can be shipped and transplanted within 24 hours should ideally be made available; the hard cut-off is 30 hours. The receiving centre will have the option to decline based on CIT.	There is an increasing risk of poor outcomes beyond a CIT of 24 hours.
An ECD kidney may be offered, but the receiving centre has the option to decline.	Each centre has different guidelines for ECD kidneys and will need to operate within these.
The donor centre will facilitate organ retrieval, with the receiving centre determining the transport route.	This is consistent with current practice.

Operating Principles (cont'd)	Rationale
If the final crossmatch at the receiving centre is positive, the receiving centre will decide whether to proceed with the transplant, or transplant another patient, or return the organ to the pool; the latter is unlikely due to CIT. To be prepared, other recipients (including non-sensitized) at the receiving centre should be tested as potential back-ups to guard against the loss of a kidney.	This approach allows the local centre to follow their existing guidelines for transplanting or re-directing kidneys.
• There will be mandatory reporting of positive crossmatches to a Canadian Laboratory Steering Committee. • Positive crossmatches must be repeated retrospectively by a reference lab.	It will be critical to assess lab proficiency via audits/review whenever a final positive crossmatch happens in order to minimize recurrence and ensure trust amongst participating programs.
The need to re-balance distribution of kidneys across regions to address net export deficits will be determined via quarterly audits; at the 6 month mark, adjustments will be built into the algorithm to re-balance within the subsequent 6 months if needed.	Re-balancing will ensure support from OPOs and transplant centres and will not create an imbalance in provincial dialysis costs. The approach to rebalancing must be transparent, equitable and ethical to the public.

CHSPR Organ Allocation Guidelines

Allocation guidelines determine the prioritization of how kidneys are allocated to individual recipients on the CHSPR.

Allocation Guidelines	Rationale
Prioritization of Recipients (in descending order)	
Blood group identical then compatible.	This will prevent the "O" blood group wait-listed patients being disadvantaged on the registry.
Pediatric patient (under age 18).	Pediatric patients are currently given priority in all programs.
Length of waiting time as measured from the first day of dialysis.	The longer the waiting time, the greater the risk of post-transplant mortality. "First day of dialysis" measure ensures objectivity and standardization.

Part III:

Living Donor Paired Exchange Guidelines

Living Donor Paired Exchange (LDPE) Guidelines

The recommendations below were built upon learning from programs in place in the United States and the Netherlands and the participants' own assessment of approaches that would work in a Canadian context. There was a high (typically unanimous) level of consensus around the recommended direction. The Task Force engaged in considerable discussion in developing these guidelines, and in each case assessed options from a number of angles. Participants recommended approaches that they supported or felt were consistent with the current philosophy of their programs.

Speaker Highlights

The following points from the international speaker presentations were generally agreed upon:

- There are a minimum number of pairs that must be registered to make a LDPE registry work (minimum 100, but 150 much better); this number is feasible in a country with Canada's population size based on the Netherlands' experience.
- This type of registry will add new donors to the system, and will help to address the backlog of current patients.
- The matching process needs to optimize the number of pairs matched each time a run is done. Population homogeneity will affect the likelihood of success in matching.
- A recruitment effort is needed to get recipients, who have previously had an incompatible living donor declined as an acceptable, to register for the program. Canada does not have records of specific cases where this has occurred.
- The registry cannot experience failures at the early stages, as enrolment would be highly influenced by patient perceptions.
- There is a need for rigorous adherence to policies across programs. For each acceptable living donor, about 3 assessments are required. This may create an additional resource burden that must be separately funded at a provincial level.
- The primary benefit is seen for ABO incompatible donor-recipient pairs and the number of highly sensitized patients transplanted through this program has been low based on experience in other programs; nonetheless, it offers a potential solution to this disadvantaged group.
- Canada can leverage the software programs that other countries have developed to predict the number of potential match-pairs that can be achieved in Canada.

LDPE Performance Measures

Specific, measurable targets for the registry were agreed upon. A central body (details to be developed) would be responsible for assessing and reporting measures on an on-going basis.

Measure	Target
Annual number of paired exchange transplants	The registry will complete 35 paired exchanges annually, without a reduction in the living donor rate, by the fifth year.
Outcomes of transplants, including donor outcomes	The registry will achieve the same outcomes as the entire national cohort of living donor kidney transplants.
Quality Assurance	Common SOPs will be in place at all participating programs, with a monitoring system to optimize quality.
Transparency	Listing criteria, matching guidelines and registry results will be easily and broadly available, and comprehensible to the lay public.
Participants/Pairs satisfaction	Satisfaction ratings will be equivalent to direct donor satisfaction levels.

Rationale for Performance Measures

Annual Number of Paired Exchange Transplants

Learning from other country programs showed that Canada could expect about 35% of pairs in the registry to be matched, if enough pairs were listed. If an assumption that a minimum of 100 pairs for a Canadian program is made, this would yield an average of 35 paired exchanges per year. This figure represents a reasonable proportion (about 10%) of the current direct living donor transplants performed in Canada. It was noted that this registry would likely be influenced by the annual living donor rate; at a minimum, it was agreed that LDPE should not negatively impact the overall living donor rate.

Outcomes of Transplants, Including Donor Outcomes

It was felt that this registry should achieve the same outcomes as are currently achieved for direct living donor transplants in Canada. This will maintain the standard of what constitutes an acceptable match. It is also important to track donor outcomes to ensure that the registry is meeting the needs of all participants.

Quality Assurance

This dimension of success will be critical to on-going support for the registry as it addresses the need to avoid errors at all cost. This measure will ensure that only programs that are both willing and able to provide the level of quality assurance needed will participate. Some of the components discussed included lab support, database tracking, administrative and Ministry

support, communication across programs, uniform informed consent, and the ability to provide laparoscopic nephrectomy to donors who prefer it.

Transparency

Scrutiny by the public and, in particular, potential participants will be high for the registry as it involves providing a donor kidney to a non-related recipient. Program acceptance will be greatly enhanced by having listing criteria, matching guidelines and outcomes readily available to and easily understood by lay people.

Participants/Pairs Satisfaction

The experience of participants during and after exchanges has the ability to significantly influence the reputation of the registry over time. Mirroring the current experience for direct living donor transplants will ensure that LDPE will help to attract new donors to the system on-going.

LDPE Listing Criteria

Listing criteria establish the requirements for a recipient and their donor to be offered participation in the LDPE registry. The decision to list will be made at the local transplant centre, after medical/psychological assessment, immunologic work-up and completion of informed consent. Audits conducted by a Canadian Steering Committee will monitor adherence to listing criteria.

In principle, it was agreed that listing criteria should be objectively based and kept to a minimum. Objective criteria would ensure fairness, while a minimum number of criteria would optimize pairings.

Criteria	Rationale
ABO incompatible OR Crossmatch positive with a donor-specific antibody present AND Immunomodulation is not feasible or desired by the patient, due to the nature of sensitization.	Either of these conditions creates an unacceptable match between the recipient and the living donor.
If immunomodulation is feasible and the patient/donor wish to pursue this course but the local transplant center does not offer it, then they should be referred to a transplant centre with a proven track record.	Immunomodulation should be eliminated as an optimal alternative for the recipient based on centre-specific risk assessment.
The donor is assessed as being “normal risk” as determined by the CCDT "Enhancing Living Donation Consensus Forum” (February 2006).	Maintains consistency with Canadian guidelines.

Criteria (cont'd)	Rationale
The recipient is assessed as being "acceptable risk" by the local program.	Ensures support of the local transplant program and maintains consistency with their practice guidelines.
The recipient is assessed as being "acceptable risk" by the donor as determined by the CCDT "Enhancing Living Donation Consensus Forum" (February 2006).	Maintains consistency with Canadian guidelines and ensures donor support.

LDPE Guidelines

Paired exchange guidelines address the common guidelines that programs would adopt when conducting paired exchange transplants. Common practices are vital to ensure that pairs are treated consistently by participating centres.

Guidelines	Rationale
Mechanism of Matching Optimized computer algorithm will be used. The following elements will be taken into account:	
• Willingness to travel (yes/no type response).	This will significantly impact match probability.
• Blood group identical, then compatible.	This approach will not disadvantage the "O" blood type recipient.
Once a potential match pair is identified a screening crossmatch must be confirmed to be negative by the most sensitive current technique. All crossmatches must be confirmed by a second lab for the sensitized patients.	Confirms that all unacceptable HLA antigens were listed for sensitized patients.
Procedures Pairs must agree to respect anonymity and programs must take due diligence to attempt to ensure anonymity before an exchange proceeds.	In the absence of having patient/donor input on this issue, the group determined that a long-term guideline could not be recommended. International experience showed a range of preferences by pairs. In the near term, it was agreed that the LDPE registry should be prepared to do its best to provide anonymity for participants. To avoid unwanted breaches of privacy and possible coercion, participants should be asked to respect anonymity as a condition of both listing and of a specific exchange. Patient/donor survey input will be critical to a re-evaluation of this approach.
• Programs will obtain patient and donor input to their "right to know" via a common survey. • This policy will be evaluated later to determine suitability to patient and program needs.	

Guidelines (cont'd)	Rationale
Transplants should occur simultaneously, based on incision time.	Simultaneous transplants will minimize drop-outs. Scheduling must factor in differences in time zones. The key element is communication between the operating rooms after the patients are anaesthetized.
Donors will travel to recipient centres. • Rare exceptions could include both donor and recipient traveling to a third center, or a kidney or recipient traveling if the donor is unable to travel (e.g., single parent without support).	Potential complications for the recipient are greater than for the donor. It is best for recipient care that the follow-up center is the implantation centre. It is better for donors to travel than kidneys to avoid complications related to CIT. It is assumed that donor travel costs are fairly addressed.
Consider Donor 1 giving to Recipient 2 and Donor 2 to Recipient 1. If a problem arises during surgery with Donor 1: • If early enough, then both donor procedures and transplants should be aborted. This decision will be made by telephone by the surgeon performing the uncomplicated donor procedure. • If later, then proceed based on previously obtained Donor 2 consent to either auto-transplant the kidney back to Donor 2 (cancelling both transplants), or proceed with giving Donor 2 kidney to the top compatible patient on the Recipient 1 local list and have Recipient 2 receive the first available compatible normal risk deceased donor kidney from region of Recipient 1. • If Recipient 1 is temporarily unable to receive the kidney after donor operations have occurred, Donor 1 gives to Recipient 2 as planned. Donor 2 kidney is given to top compatible patient on local list (of Recipient 1). If and when Recipient 1 is subsequently able to receive a kidney, they will be prioritized for a deceased donor kidney within Region 1. Consent should include the rare possibility that if one recipient becomes seriously ill during the procedure and does not recover he/she may never be able to be transplanted. • If the graft is lost within 48 hours of surgery, the recipient retains priority for the next suitable kidney as above.	The overall principle is to maintain fairness for the pairs, in the event that one exchange cannot be completed after surgery starts. Recipients who are not successfully transplanted will receive priority to achieve the shortest possible wait time for them as they will have already donated a living donor kidney to the pool. While donors will retain control over the final destination of their kidney, for practical purposes they must consent in advance to their preferred option. The region donating the deceased donor kidney to the outstanding recipient is appropriately the one that gained the living donor kidney.

Part IV:

Overarching Guidelines

Overarching Guidelines

Registry Structure and Processes

Input was obtained from the group as to appropriate organizational structures and processes for making Canadian registries work. There was a high level of consensus that various centralized initiatives would have to be in place for the registries to function effectively. Below are the suggestions for how key elements should be addressed. These elements would be developed in greater detail in the preparation of a business case. There was general consensus that to ensure trust, transparency and buy-in by all provincial programs, a provincially based organization would not be acceptable for providing the management function of the registries.

Activity	Approach
Integrity of laboratory data	A Canadian Lab Steering Committee would conduct proficiency testing and audits. At least one reference laboratory should be identified to provide back-up as needed to the HLA labs. Local centers would also require rigorous testing procedures (as described in *Assessment and Management of Immunologic Risk in Transplantation*, www.ccdt.ca).
Accuracy of data analysis and data entry	Standardized SOPs must be developed with both a central and local audit.
Adherence to listing/allocation protocols	A central body would conduct regular audits.
Conducting matches	A central body would conduct computer-based matches.
Tracking outcomes	A central body would track and report outcomes. A proper database will need to be developed and ideally should be part of an expanded database to monitor transplant outcomes for all recipients and donors
Trouble-shooting	A Canadian Steering Committee and call-centre should be available in real-time to assist local centres.

Other Related Issues

Throughout the course of the meeting, a number of ideas were generated by the group that were related to the agenda items, but were not specific topics for discussion. These are noted below for consideration by the Task Force as it moves ahead:

- It is critical that a central database be set up to allow us to measure transplant outcomes in the degree of detail needed for proper quality improvement, reporting and research.
- Canada should not hold up the Canadian Registries while upgrading local laboratories.
- This process should help CSA address standards gaps.
- It will be important to put the registries into the context of long-term plans for Canadian approaches; for example, what other patient groups should be addressed over time?
- It will be important to access a public advisory group for input from the public and the "involved" public. The Task Force should assess the opportunity to set up a donor outcome registry.
- The issue of re-setting the wait-list date in the event of organ failure should be referred to the CCDT Kidney Allocation Consensus Forum.

Part V:

Summary and Recommendations

Summary

At the conclusion of the CCDT Registries Task Force Forum (Phase I), it was clear that significant progress had been made in establishing, through consensus, the performance goals and operational elements that will be required to be achieved to ensure the success of the Highly Sensitized Patient and Living Donor Paired Exchange Registries for Canadians.

The next steps for the Task Force will be the following:

- Distribute the report prior to a broad consultation with our partners and stakeholders that will take place at the CST/CAT Annual meeting in Mont Tremblant, Quebec (Task Force Phase II: March 2006).
- Seek input from the public and the "involved" public through surveys and consultation with non-government organizations (NGOs) (e.g., The Kidney Foundation of Canada).
- Model the feasibility of a highly sensitized patient registry given the current demographics of highly sensitized patients on wait-lists in Canada and the Canadian deceased donor pool.
- Model the number of donor-recipient pairs required on the living donor paired exchange registry to ensure its success.
- Work with the CCDT Information Management Project to develop the information technology support required for the registries.

At the end of this process, the CCDT Registries Task Force will produce a business case for the CCDT that will make recommendations for the implementation of these registries in Canada.

Recommendations to the CCDT

In addition to the aforementioned process, the CCDT Task Force recommends to the CCDT that the following enabling processes be prioritized:

- The CCDT follow-up with the provincial health ministries to determine what assistance can be provided to ensure that the HLA laboratory upgrade initiative is occurring in all Canadian transplant programs.
- The CCDT Living Donor Forum is made aware of the need to include living donor paired exchange donors in the scope of their mandate.
- The CCDT Information Management Project is made aware of the need for a living donor outcome database in support of the living donor paired exchange registry.

Appendices

Appendix A: Glossary

ABO Incompatible Donor	An individual who cannot donate an organ to a recipient due to the presence of antibodies in the recipient's serum that would attack the donor's blood group antigens located on the donated organ.
Acceptable Mismatch	While not identical to the HLA antigens of the recipient, the donor organ contains HLA antigens that the recipient has not formed an HLA antibody against.
AHG-CDC Crossmatch	An HLA crossmatch (see below) performed using cell death as the readout to indicate a positive test result. It is considered less sensitive than a Flow crossmatch.
AHG PRA	A PRA assessment (see below) using cell death as the readout to indicate a positive test result. It is considered less sensitive than an ELISA or Flow PRA assessment.
ASHI	American Society of Histocompatibility and Immunogenetics: this organization has developed standards in the U.S. for HLA tissue typing, crossmatching and HLA Ab specificity analysis. In addition, it is recognized in the U.S. as an accrediting body for histocompatibility laboratories.
CAT	An association of health care professionals committed to facilitating and enhancing organ and tissue donation and the transplant process.
CCDT	Canadian Council for Donation and Transplantation.
CDC crossmatch	(or NIH CDC crossmatch): an HLA crossmatch (see below) performed using cell death as the readout to indicate a positive test result. It is considered the least sensitive crossmatch method.
CDC PRA	A PRA assessment (see below) using cell death as the readout to indicate a positive test result. It is considered the least sensitive PRA method.
CIT	Cold ischemia time.
CSA	Canadian Standards Association: an organization which provides standards to the Standards Council of Canada for consideration as a National Standard of Canada.
CST	Canadian Society of Transplantation: a scientific organization of health care professionals associated with solid organ transplantation in Canada.

CORR	Canadian Organ Replacement Registry: a national information system that records, analyzes and reports the level of activity and outcomes of vital organ transplantation and renal dialysis activities. CORR is funded through the federal and provincial ministries of health through the Canadian Institute for Health Information (CIHI), which manages CORR.
Donor Center	A health care facility that procures a deceased donor organ.
ECD Kidneys	Extended criteria donor kidneys are kidneys that are beyond the normal criteria used for predicting which deceased donor kidneys will function normally post-transplant but which have been shown in studies to still provide a clear benefit to those patients who receive such a kidney.
ELISA PRA	A PRA assessment (see below) using colour change as the readout to indicate a positive test result. It is considered less sensitive than a Flow PRA assessment but more sensitive than an AHG PRA assessment.
ESRD	End stage renal disease: a state requiring dialysis or kidney transplantation for survival.
Flow crossmatch	An HLA crossmatch performed using cell surface fluorescence as the readout to indicate a positive test result. It is considered the most sensitive crossmatch test.
Flow PRA	A PRA assessment (see below) using surface fluorescence on microparticle beads coated with HLA molecules as the readout to indicate a positive test result. It is considered the most sensitive PRA assessment available at present.
Histocompatibility laboratory (or HLA laboratory or tissue typing laboratory)	A laboratory affiliated with one or more ODOs, and one or more transplant centres, that has the responsibility for the HLA tissue typing of donors and recipients and for performing crossmatch (i.e., histo-compatibility) testing to determine if the organ recipient has preformed antibodies directed at the donor HLA molecules. The presence of such preformed HLA antibodies directed at the donor represents an immune risk to the recipient for early rejection or graft loss.
HLA	Human leukocyte antigen: differences between donor and recipient HLA molecules stimulate the recipient immune system to reject the graft. This can be overcome with immunosuppressive medications (i.e., anti-rejection drugs).
HLA Ab	Human leukocyte antigen directed antibody: an antibody which is capable of causing early rejection or graft loss if directed at the donor HLA molecules.

HLA crossmatch (or T-cell crossmatch or B-cell crossmatch)	An evaluation for the presence of HLA Ab in the recipient's serum that is directed against the HLA molecules of the donor. The presence of donor specific HLA Ab is an immunologic risk factor for early rejection or graft loss. T-cells are generally used as targets for Class I IgG donor specific antibodies, while B-cells can be used to detect both Class I and Class II IgG donor specific antibodies.
Immunologic Risk	This refers to a patient who has laboratory or clinical evidence of prior exposure to the organ donor HLA antigens (e.g., via blood transfusion, pregnancy or prior transplant). This risk is at present determined in the lab via PRA and HLA crossmatch assessment.
Immunomodulation	The concept is that while the patient may be sensitized to a given donor, this barrier could be overcome by inhibiting the immune system of the patient. This requires therapeutic measures that are more extensive, expensive, and expose the patient to greater risk of infection than normal levels of immunosuppression normally do.
Living Donor Paired Exchange (LDPE)	The concept is that while patient X may be sensitized or ABO incompatible to their specific living donor, they would not be to another living donor for patient Y. Likewise, patient Y who has a positive crossmatch or ABO incompatible to their own living donor would not react to the donor for patient X. By exchanging donors, both patients (X and Y) are able to be transplanted now with a negative crossmatch or with ABO compatibility (i.e., low risk).
NGO	Non-government organization.
ODO or OPO	Organ donation organization or organ procurement organization: group responsible for procuring donor organs for the purpose of transplantation.
PRA	Panel reactive antibody: a measure of the degree to which a person has been sensitized (i.e., exposed and developed antibodies to foreign HLA molecules usually via blood transfusion, pregnancy or prior organ transplant) to the different HLA molecules that exist in the general population. The higher the % PRA the greater the degree of sensitization which is associated with a decreased likelihood that a deceased donor organ will be acceptable (i.e., a negative HLA crossmatch).
Recipient Center	A health care facility that transplants an organ into a patient.
Sensitized Patient	A patient who has been exposed to foreign tissue antigens (HLA) and developed an immune response (i.e. HLA Ab) against the foreign HLA molecules.

Serologic Crossmatch	A CDC or an AHG-CDC crossmatch.
Solid Phase Assays	These are tests using purified HLA molecules as targets (ELISA, Flow based).
SOP	Standard operating procedure.
UNOS	United Network for Organ Sharing: the US based organization that is charged in the United States with deceased donor organ allocation on a national level.

Appendix B: Task Force Committee

Dr. David J. Hollomby
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Health Sciences Centre
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Dr. Edward Cole
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Canadian Council for Donation and Transplantation

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Appendix C: Canadian Participants

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Dr. John Dosseter (Ethicist-Council Member)

Ms. Kimberly Young (Chief Executive Officer)

Canadian Association of Transplantation
Ms. Maureen Connelly

Facilitator: Ms. Deborah Pankhurst
Symmetrics International

Logistics: Ms. Nancy Greene
GCSI-Natsource

Regrets

While invited and desiring to attend, the following individuals/programs were unable to participate due to other commitments: Dr. Ken West (President, Canadian Society of Transplantation); Calgary; Saskatoon; Hamilton; Ottawa.

* Nova Scotia represented Atlantic Canada.

Appendix D: Speakers

Dr. Howard Gebel
Emory University Hospital

Dr. James Gloor
Mayo Clinic

Dr. Dorry Segev
Johns Hopkins Hospital

Prof. Dr. Ilias Doxiadis
Leiden University Medical Center

Dr. Marry de Klerk
Erasmus MC, University Medical Center Rotterdam

Dr. Mary S. Leffell
Johns Hopkins Hospital

Dr. E. Steve Woodle
University of Cincinnati College of Medicine

Appendix E: Task Force Meeting Agenda

October 28: Highly Sensitized Patient Registry

Day 1 Agenda

Time	Activity	Responsibility
09:00	Welcome / Meeting Purpose / Introductions (Kingsway Room)	P. Nickerson
09:15	Agenda, Workshop Process & Key Assumptions	D. Pankhurst
09:40	Presentation: New Drug Therapies to Overcome Sensitization	James Gloor
10:10	Questions & Answers	
10:25	Workshop: What points should we highlight?	D. Pankhurst/Group
10:55	Presentation: Acceptable Mismatches	H. Gebel
11:25	Questions & Answers	D. Pankhurst/ Group
11:40	Workshop: What points should we highlight?	
13:00	Presentation: European Acceptable Mismatch Program – Overall Concept and Design	I. Doxiadis
13:20	Questions & Answers	
13:30	Presentation: European Acceptable Mismatch Program – Logistics and Regional Distribution	I. Doxiadis
13:50	Questions & Answers	
14:00	Workshop: What points should we highlight?	D. Pankhurst/Group
14:30	Canadian Workshop: What information should we focus on to design a Canadian system?	D. Pankhurst/ Canadian Group
	How should we define success for a highly sensitized patient registry?	
17:00	Close	

October 29: Highly Sensitized Patient Registry – Canadian Only Workshop (con't.)

Day 2 Agenda

Time	Activity	Responsibility
08:00	Welcome / Day 2 Purpose *(Kingsway Room)*	E. Cole
	Review Agenda, Workshop Process & Ground Rules	D. Pankhurst
08:15	Workshop:	
	Review decision algorithm for renal transplants	D. Pankhurst/ Canadian Group
	What criteria should be used for referral to a national Highly Sensitized Patient Registry?	
09:30	What guidelines should be used for allocating organs to the national Highly Sensitized Patient Registry?	Teams
	Living Donor Paired Exchange Registry	
11:10	*Presentation*: Mathematical Modeling of Living Donor Paired Exchange	D. Segev
11:30	Questions & Answers	
11:40	*Presentation*: Ohio Living Donor Paired Exchange Program and National Implications	S. Woodle
12:10	Questions & Answers	
12:25	Workshop: What points should we highlight?	D. Pankhurst/Group
13:30	*Presentation*: Netherlands Living Donor Paired Exchange Registry: Program Approach	M. de Klerk
14:00	Questions & Answers	
14:15	*Presentation*: Netherlands Living Donor Paired Exchange Registry: Laboratory Methods	I. Doxiadis
14:35	Questions & Answers	
14:55	Workshop: What points should we highlight?	D.Pankhurst/Group
15:10	*Presentation*: HLA Testing for Living Donor Paired Exchange Programs	M. Leffell
15:30	Questions & Answers	
15:40	Workshop: What points should we highlight?	D. Pankhurst/Group
16:10	Canadian Workshop: What information should we focus on to design a Canadian system?	D. Pankhurst/ Canadian Group
17:15	Close	

October 30: Living Donor Paired Exchange Registry – Canadian Only Workshop

Day 3 Agenda

Time	Activity	Responsibility
09:00	Welcome / Day 3 Purpose *(Kingsway Room)*	P. Nickerson
09:10	Review Agenda, Workshop Process & Ground Rules	D. Pankhurst
09:20	Workshop: How should we define success for a living donor paired exchange registry?	D. Pankhurst/ Canadian Group
10:45	Workshop: Review the decision algorithm for renal transplants What should the criteria be for listing?	
13:00	Workshop: What approach should we take to implementing exchanges?	Teams
14:45	Workshop: What approach should we take to managing and monitoring the Highly Sensitized and Living Donor Paired Exchange Registries?	Teams
16:15	Next Steps	P. Nickerson
16:30	Closing Remarks	Chairs
	Evaluations	Group

Appendix F: Speaker Summaries

Immunomodulation Strategy

Dr. Jim Gloor – Highlights

Dr. Gloor is a Transplant Nephrologist from the Mayo Clinic (Rochester, Minnesota) where the transplant group has been pioneer in conducting clinical studies to determine how to optimize immunomodulation as an approach to successfully transplant a kidney into highly sensitized patients. After the presentation and Q&A session the following points were identified by the Task Force as key to note for the subsequent Canadian Registries discussion:

- There is an AHG-T-cell crossmatch titre above which one will not attempt immunomodulation:
  - 1:32 is convincing
  - 1:16 is questionable.
- A lot of unknowns:
  - it is still experimental; concerning re: setting registry rules.
  - may need to restrict to centers that can manage new lab technologies to support such a program.
- Immunomodulation should be local; not a dimension of national registry:
  - centres should share learning (e.g., a Canadian wide database for such patients).
- Canadian outcome database could be based on results of patients receiving IVIG
  - retrospective analysis will be critical.
- Focused on living donors:
  - provides greater opportunity for control
  - could consider moving pairs to centers that can handle protocols
  - need access to technology and expertise – may not be applicable to all centers.
- Centers should be across the country to manage follow-up and minimize travel.
- Canadian-based central lab will be needed (or workshop grouping of labs).
- Frequency of protocol biopsies – important for following increased risk patients.
- Post-transplant management (e.g., splenectomy)? Measuring flow cytometry after transplant?
- All elements of treatment seem to work to some degree:
  - what is the best approach for each type of patient?
  - must treat T-cell memory
  - what about Class-II antibodies?
  - what's the cut-off point?

References

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Doxiadis IIN, Duquesnoy RJ, Claas FHJ. Extending options for highly sensitized patients to receive a suitable kidney graft. *Current Opinion in Immunology* (2005) 17: 536-540.

Acceptable Mismatch Strategy

Dr. Howard Gebel – Highlights

Dr. Howard Gebel is a Transplant Immunologist and Co-Director of the HLA laboratory at Emory University (Atlanta, Georgia) whose group has been using high resolution HLA antibody specificity analysis as a key to identifying acceptable mismatches for highly sensitized patients. This information is then used to identify acceptable kidney donors from UNOS for highly sensitized patients on the Emory waitlist. After the presentation and Q&A session the following points were identified by the Task Force as key to note for the subsequent Canadian Registries discussion:

- Defining HLA antibody specificities and having access to a donor pool works:
  - increasing probability of recipient receiving an organ
  - doubled number of sensitized recipients transplanted.
- The group that benefits are broadly sensitized, and outcomes are about equal to un-sensitized:
  - achieved without extra immunomodulation.
- Need to standardize technology for measuring antibodies and proficiency testing (local and central).
- Standardize crossmatch.
- Must analyze donor population regionally and nationally.
- Computer-based algorithm will be useful for predicting likelihood of success.
- Need to decide the number and type of antibodies to test.
- Need to establish the thresholds that you can cross:
  - definite unacceptable vs. acceptables
  - what level of positive crossmatch should be accepted on a national list?

Dr. Ilias Doxiadis – Highlights

Dr. Doxiadis is a Transplant Immunologist at Leiden University (Netherlands) and runs the Eurotransplant Acceptable Mismatch Program for highly sensitized patients on the renal transplant wait-list. This group has had >20 years of experience with an acceptable mismatch approach and has recently reported both short and long-term outcomes. After the presentation and Q&A session the following points were identified by the Task Force as key to note for the subsequent Canadian Registries discussion:

- Very important to know what frequency of HLA antigens and blood group in your donor population.
- Reasonable approach to increase rate of transplants, but will take a number of years to reduce the highly sensitized patients on the renal transplant wait-list.
- Risk that we could consume all of the organs into this program over the first few years if the entry criteria is not stringent enough.
- Payback is part of the overall scheme – re-balancing is the criterion if 2 or more patients suitable for an organ.
- Reason that the program works is that the number of transplants done are small.
- Ethical issue: must not force "sensitization" to get on the list.
- Six countries were able to do it.
- Can we do a national list for all patients?
- Can we model the 400 deceased donors that are available in Canada in a given year to achieve the level of success we are trying to generate?

References

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Living Donor Paired Exchange Registry Strategy

Dr. Dorry Segev / Dr. Steve Woodle – Highlights

Dr. Dorry Segev is a Transplant Surgeon at John Hopkins University (Baltimore, Maryland) and has been a leader in developing computer based modeling for Living Donor Paired Exchange Registries to determine the optimal strategy for maximizing the number of transplants.
Dr. Steven Woodle is a Transplant Surgeon at the University of Cincinnati (Cincinnati, Ohio) and has been a leader in setting up the Ohio Living Paired Exchange Registry as well as expanding this concept to a National level in the USA. After the presentations and Q&A sessions the following points were identified by the Task Force as key to note for the subsequent Canadian Registries discussion:

- There has to be a critical mass to make this work:
  - Between 100-250 pairs are the minimum.

- Highly sensitized even more challenging than ABO incompatible.
- Can do historical assessment of current wait-list, or do a mailing.
- Increased coordinator time to run programs.
- Willing to travel is important:
  - cost implications.
- Can simulate iterations of match runs to determine probability of success.
- Core nucleus of highly sensitized patients will persist on the list.
- Could immunomodulate mildly positive match – have tended to keep off LDPE in Ohio.
- Patient-driven rather than Transplant Program driven.
- Optimize paired donations before list exchange.
- If both pairs want to travel, should be allowed to.
- Accessing the transplant wait-list is a good approach:
  - does not put onus on recipient to find donor.
- Need to have an "out" for the proposed donor so you can turn down exchange if there are issues.

Dr. Marry de Klerk/ Dr. Ilias Doxiadis – Highlights

Dr. Marry de Klerk (Rotterdam) and Dr. Ilias Doxiadis (Leiden) have been key drivers of a Living Donor Paired Exchange Program in the Netherlands. Recently the success of this program has been reported in the literature. After the presentations and Q&A sessions the following points were identified by the Task Force as key to note for the subsequent Canadian Registries discussion:

- Cooperation needed:
  - Transplant Centres
  - HLA Labs
  - OPOs.
- Good feasibility:
  - 16 million population - 100 pairs => 48% transplanted
  - needed to Advertise and Market to patients.
- What's acceptable to a society re: anonymity.
- No concern about age matching in Netherlands.
- Double-checking of data and of crossmatches.
- Do careful assessment of recipient; then look only for "mis-fit" of donor; does not require as high level of blood analysis.
- Homogeneity of population a factor.
- Better patient medical records re: transfusions, previous organ donors, etc.
- Crossmatches should be based on entry criteria.
- In early stages, cannot have transplant failures.

- Need to market program:
  - doctors and Kidney Foundation.
- Need broad commitment nationally.
- Well-defined protocols are needed.
- Logistics for families must be considered.

Dr. Mary S. Leffell – Highlights

Dr. Mary Leffell is the Medical Director of the HLA lab at John Hopkins University (Baltimore, Maryland) and is a key driver of the Living Donor Exchange Program at John Hopkins. In addition, Dr. Leffell has been involved with UNOS in developing lab practice guidelines for living donor exchange. After the presentation and Q&A session the following points were identified by the Task Force as key to note for the subsequent Canadian Registries discussion:

- Should err on the side of being conservative up-front:
  - don't do the very highly sensitized.
- Strong set of guidelines required for participating centres:
  - inviolate
  - enforcement (e.g., oversight committee).
- Quality Assurance:
  - high level needed.
- Doing the work up-front in terms of specificity analysis to save time and money afterwards.
- Extra work and cost therefore funding for HLA Labs is key.
- Repeating test for mismatches every 3 months:
  - most up-to-date assessment.
- Minimizes unexpected crossmatches:
  - minimize rejection due to antibodies.

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Appendix G: Pre-Meeting Reading

Highly Sensitized Patient and Living Donor Paired Exchange Registries Task Force

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Appendix H: CCDT Fora and Reports

The following reports from CCDT fora are posted on the CCDT website (www.ccdt.ca):

Severe Brain Injury to Neurological Determination of Death (April 2003)

The report is endorsed by the CCDT, CCCS, Conference of Chief Coroners and Medical Examiners of Canada Canadian Association of Emergency Physicians, Canadian Neurological Society, Canadian Neurosurgical Society, Canadian Neurocritical Care Group, Canadian Association for Transplantation, Canadian Society for Transplantation, Quebec Transplant, Trillium Gift of Life Network and its ICU Advisory Group, Alberta Hope and Wellness, BC Transplant Society.

Medical Management to Optimize Donor Organ Potential (February 2004)

The report is endorsed by the CCDT, CCCS, Canadian Association for Transplantation, and Canadian Society for Transplantation. Publication of recommendations and proceedings is in process (CMAJ, CJA).

Assessment and Management of Immunologic Risk in Transplantation (January 2005)

Clinical and laboratory specialists from transplant programs across Canada convened to examine current practices, literature and new technologies for the assessment of human leukocyte antibodies (HLA) pre-transplant with the goal of being able to develop recommendations on best practices. Consensus recommendations will be used to improve immunologic risk assessment and management in transplantation with the goals to improve solid organ transplant outcomes; improve equity of access to organ transplants for highly sensitized patients; reduce the wait-list time for highly sensitized patients; and increase the number of organ donors.

Donation after Cardiocirculatory Death (February 2005)

Post-forum public survey shows substantial support for proceeding with this type of donation in Canada.