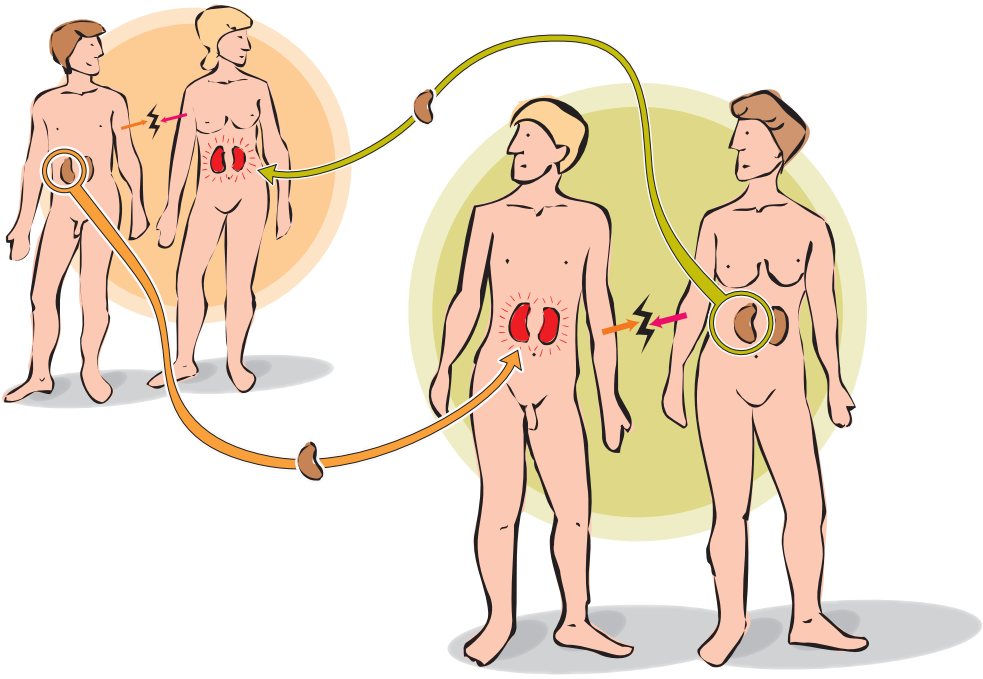
The Dutch Living Donor Kidney Exchange Program



Marry de Klerk

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The studies described in this thesis were performed at the Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands.

The publication of this thesis was financially supported by:
Dutch Transplant Foundation (Nederlandse Transplantatie Stichting)
Dutch Transplant Society (Nederlandse Transplantatie Vereniging)
Astellas Pharma B.V.
Novartis Pharma B.V.
Roche Nederland B.V.
Genzyme B.V.

Cover and chapter 10 design by Erik d'Ailly. This illustration was made for the article 'Geven om te nemen', Volkskrant May 24, 2003 following the first living donor kidney exchange procedure in The Netherlands.

Printed by Ridderprint offsetdrukkerij b.v., Ridderkerk

ISBN: 978-90-5335-270-0

The Dutch Living Donor Kidney Exchange Program

Het Nederlandse donorruil programma voor niertransplantatie

Proefschrift
ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College van promoties

De openbare verdediging zal plaatsvinden op
donderdag 22 april 2010 om 13.30 uur

door

Marry de Klerk

geboren te Ridderkerk

PROMOTIECOMMISSIE

Promotor:	Prof.dr. W. Weimar
Overige leden:	Prof.dr. F.H.J. Claas
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CONTENTS

Chapter 1

General Introduction

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Quoted from Strategies to expand the living donor pool for kidney transplantation

Frontiers in Bioscience, 2008, 13: 3373-80

INTRODUCTION

Kidney transplantation is the optimal option for patients with an end-stage renal disease. The first successful transplantation with a living genetically related donor has been performed since 26 October 1954, when an identical twin transplant was performed in Boston. In the years that followed, efforts to enable non-twin transplants unfortunately failed because effective immunosuppression was not yet available. It took until the early sixties after the discovery of azathiopirine that also deceased donor kidney transplantations became possible. In the eighties of the last century the wait time for a kidney transplant was approximately one year. Since that time the success rate of organ transplantation has significantly improved which attracted large numbers of transplant candidates. As the number of deceased organ donors did not increase, the wait time on the list steadily grew and at the moment patients in most Western countries face wait times up to 5 years before a deceased donor kidney is offered. Unfortunately an increasing proportion of them will never be transplanted because their clinical situation deteriorates to such an extent that they are delisted or die on the wait list. For the Netherlands we estimate that this proportion is approximately 30%. A strategy to expand the kidney donor pool includes the use of non-heart beating (NHB) donors. Educational programs in the Netherlands have resulted in an increase in the number of kidney transplants derived from NHB donors from almost 20% in the year 2000 to 43% in 2004, while in the years that followed the numbers of NHB donors stabilized. So the NHB donors have not led to expansion of the deceased kidney donor pool. Possibly substitution from heart beating to non heart beating donation procedures took place, resulting from pressure on the facilities of intensive care units. In the Netherlands, it has been suggested that the main reason for our failure to increase the number of deceased organ donors is the lack of donor detection. This is certainly not the case; both in 2005 and in 2006 almost all potential donors in the Netherlands (96%) were recognized as such and for the vast majority (86%) our national donor registry was consulted. The problem is not donor detection but the high refusal rate by the next of kin, which is inherent to our legal system. Our organ donation act dictates an opt-in system, and therefore all adult citizens are asked to register their consent for the use of their organ for transplantation purpose after death. In the Netherlands approximately 25% of the adults are now registered as potential donors, 15% have explicitly refused and thus for 60% it remains unknown. Especially in case of potential donors of the latter category high refusal rates up to 70% haven been found. Apparently next of kin argue that while the possibility was given to everybody to register as donor, their relative did not do so, therefore they are unaware of consent and thus reluctant to give permission for donation. We feel that an opt-out organ donation system would be very much helpful to expand the deceased kidney donor pool. However, we are aware that even if all potential

deceased donors became actual donors, there still would be a shortage of donor kidneys. Therefore the use of kidneys from living donors is an obvious way to go. These transplants result in a superior unadjusted graft survival compared to deceased donor kidneys. It has been calculated that the difference in 10 years survival between living and deceased donor kidney transplantation is 34 % (Figure 1).

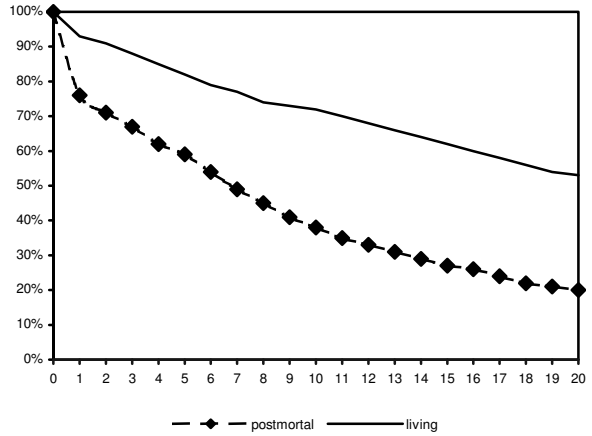

Figure 1. Unadjusted graft survival of 13.000 deceased donors and 2500 living donor kidney transplants performed in the Netherlands between 1966 - 2006

Thus not only in terms of quantity, but also because of quality, living kidney donation is a good option. Moreover, due to the use of minimally invasive surgical techniques the morbidity for the living donor is acceptable, the mortality risk of donor nefrectomy is low, and long-term survival of kidney donors is unaffected. With the introduction of more effective immunosuppressive regimens based on calcinurin inhibitors, it appeared that HLA matching became less important and good results could also be obtained in poorly matched donor-recipient combinations. Thus gradually the pre-requisite for living kidney donors to be genetically related disappeared. Subsequently it became clear that the graft survival of these poorly-matched transplants from living genetically unrelated donors was excellent (1). As a result, increasing numbers of these transplantations were performed with kidneys derived from genetically unrelated, but emotionally related donors. Especially spouses gained a lot by donating: by helping their life-companions they could consequently lead a healthier life together. Therefore it is not surprising that spouses and partners for a large part have been responsible for the significant increase in living donation numbers over the last decade. Living genetically unrelated donors accounted in 2008 for 2472/5967 (41%) of living donation in the U.S.A., 479/1088 (44%) in the Eurotransplant area, 210/411 (51%)

in The Netherlands and 53/107 (50%) in Rotterdam. In the USA 29% (725/2472) of the living unrelated donors were spouses, 70% (333/479) in the Eurotransplant area, 45% (95/210) in the Netherlands and 58% (31/53) in Rotterdam (Figure 2).

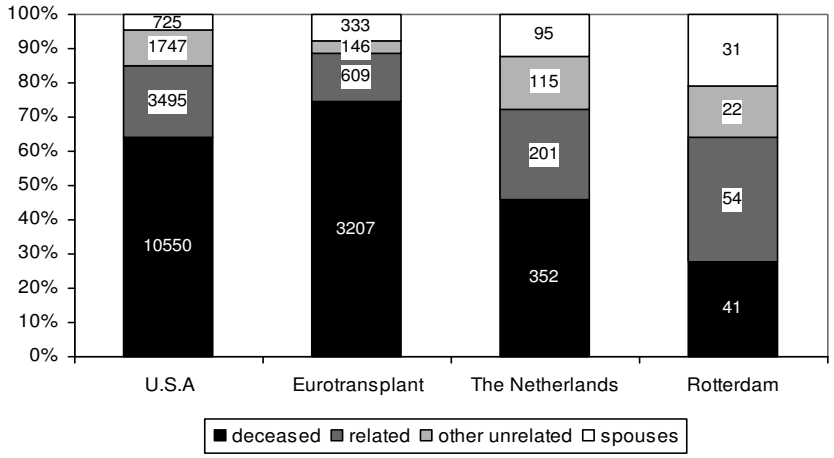

Figure 2. Donor source for kidney transplantations in 2008

The figure also shows the proportional contribution of living donation for the total kidney transplant programs. Unfortunately not all willing donors can donate directly, due to a positive cross match or an ABO blood type incompatibility. In these cases, exchanging donors could be a solution. A living donor kidney exchange program was originally described by Felix Rapaport in 1986 (2). He proposed anonymity between donor-recipient pairs and that the operation had to be carried out in two different centers at the same time. After the donation-procedures the kidneys were supposed to be transported to the acceptor center. Five years later in 1991 the first real living donor kidney exchange procedure between two families was performed in South-Korea (3). Because of cultural and religious reasons the organ exchange between living donors is easier to accept than the concept of brain death and cadaveric donation. Therefore the majority of kidney transplants are dependent on living related or unrelated donors. In 1995 Park introduced a living donor kidney exchange program with no limit in combinations (up to six pairs). His team performed 101 living donor kidney exchange procedures from 1995 to 2003 (11 per year). Several centers in the USA started in 2000 and 2001 living donor kidney exchange programs. Living donor exchanges is legal in the USA because there are no valuable considerations under the National Organ Transplant Act of 1984. There

is no strict anonymity between the donor-recipient pairs. It is possible to meet or contact the other couple some days after the transplantation but all couples must agree on this. Most of these procedures took place within the same center. To increase their kidney exchange program regional or national collaboration is a necessity. One of the greatest obstacles to the implementation of such a program is the need for the donor to travel to the recipient center which might be a logistic problem for a vast country. Therefore recently the old proposal of Rapaport to ship the donor kidneys has been revitalized (4). Other initiations to implement living donor kidney exchange programs took place in Canada and United Kingdom. In Canada they performed the first living donor kidney exchange procedure in November 2005. There is a great deal of support and excitement for a national exchange program across the various transplant programs in Canada, but a lot of logistic barriers are still to overcome. The United Kingdom changed their law in September 2006. The new Human Tissue Act and the Human Tissue Act (Scotland) will allow non-directed donations. UK Transplant is exploring how best to facilitate these new exchange program.

AIM OF THIS THESIS

The aim of this thesis was to set up a living donor kidney exchange program in The Netherlands in collaboration with the seven transplant centers. We explored under which conditions such a program could be realized and discussed the various ethical issues adherent to such a program. To address logistic, a protocol was written that included rules for registration, allocation and immunological, surgical and follow-up procedures. The process of the program was evaluated several times after it starts in January 2004.

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Chapter 2

Cross-over transplantation: a new national programme for living kidney donation

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Ned Tijdschr Geneeskd 2004, 148(9): 420-3

ABSTRACT
In The Netherlands, cross-over kidney transplantation has been introduced as an extra option in the living kidney donation programme. In cross-over transplantation, patients who cannot be given their own partner's kidney for immunological reasons are given a kidney from the partner of another patient in exchange for a kidney from their own partner. There is no difference in the medical indications and contra-indications between direct and indirect living donation. There are no ethical obstacles since the net gain for the two couples is not different from that of direct living kidney donation and because the exchange takes place on the basis of equality. One should be aware that the extra possibilities may result in more psychological pressure on potential donors. It is important that the donation procedures start at the same moment and that the wishes of patients and donors for anonymity be preserved. A successful living donor kidney exchange program requires a large pool of donors and patients. Therefore, this has been organised in a national programme. The Dutch Transplantation Foundation is responsible for the allocation of cross-over kidneys. Organ trade will thus be impossible. The seven Dutch centres for kidney transplantation have developed a protocol.

INTRODUCTION
On 15th April 2003, the first so-called 'cross-over transplantation' in the Netherlands took place in the Erasmus Medical Center in Rotterdam. In this exchange the partner of dialysis patient A donated a kidney to patient B, while the partner of patient B simultaneously donated a kidney to patient A. Donation from donor A to recipient A and from donor B to recipient B was impossible in both cases for immunological reasons. This impossibility was converted into a possibility due to donor exchange and resulted in two successful kidney transplantations. In this article we describe the medical and logistical considerations for this type of transplantation; we also consider the psychological and ethical aspects that played a role in the preparation and implementation of this cross-over transplantation. We also refer to the national living donor kidney exchange program that commenced on 1st January 2004 in which all 7 Dutch kidney transplant centers are participating.

BACKGROUND
In the past 35 years, kidney transplantation has developed from a medical experiment amongst a select group of patients into the treatment of choice for many. Currently more patients in the Netherlands are treated with a functioning graft than with haemodialysis or peritoneal dialysis. This success, however, has a downside. Since more and more patients are in need of transplantation while the number of cadaver kidney donations has remained stable over the previous few decades, the number of patients on the waiting list has grown. The median waiting

time calculated from the first day of dialysis is currently 1470 days, which is a little longer than 4 years. Various attempts to increase the number of post-mortal donations, such as non-heart beating donors and the Donor Register, have not resulted in a reduction in the wait time. The number of kidney transplantations can, however, be expanded via living donation. The advantages are evident. Not only is the wait time shorter, both the short and long term results are significantly better than for post-mortal kidney transplantation. Furthermore, living kidney donation offers the possibility avoiding dialysis altogether: transplantation can be carried out before there is a definite need for dialysis. Initially only direct relations were accepted for kidney donation, since then however it has been demonstrated that transplantation with a kidney from a genetically unrelated donor leads to similarly good results. Genetically unrelated donors are usually partners of the patient, but other 'emotionally related' donors are also possible. Of the 199 living kidney donations that took place in 2002 in the Netherlands, in 69 of cases a genetically unrelated donor donated their kidney.

It is, however, not always possible to carry out a living kidney transplantation with the intended donor-recipient pair. Both blood group incompatibility and the presence of antibodies against the donor in the recipient can make this procedure impossible on immunological grounds. Cross-over transplantation can offer a solution.

HISTORY

In 1986 Rapaport was the first to describe the possibility for cross-over transplantation[1]. One of the conditions that he suggested for carrying out such a procedure was that the two donor-recipient pairs should remain anonymous. In order to achieve these donations should take place simultaneously in two different hospitals, after which the kidneys should be transported to the recipient's center. This description of cross-over transplantation written by Rapaport was merely a suggestion: he never carried the procedure out in practice.

The first cross-over transplantations were carried out 5 years later in 1991 by Park et al. in South Korea[2]. It should be noted that in South Korea post-mortal kidney transplantation is seldom, if ever, carried out due to cultural and religious reasons: therefore the possibilities for alternative forms of living donation are greater. Currently in South Korea cross-over transplantation is carried out many times per year. In this program is it common for pairs to meet prior to transplantation. Contrary to the suggestion of Rapaport there is therefore no anonymity. The first and until recently the only cross-over transplantation in Western Europe was carried out in 1999 in Switzerland by Thiel and Kirste[3]. The procedure was carried out with a donor-recipient pair from Germany and a donor-recipient pair from Switzerland. For both pairs the donor was unable to donate to the patient directly

due to blood group incompatibility. As the German law requires that only genetically unrelated donors who have a long and close relationship with the recipient can donate, it was necessary for these pairs to meet. Even prior to the publication of this Swiss cross-over transplantation, there was much discussion about the possibilities for this and other alternative forms of living kidney donation[4,5]. Many symposia and journals have extensively explored the possibilities for expansion of the conventional donor pool. Although it became clear that cross-over transplantation could depend on a broad input from the medical world, this did not, however, lead to the development of a standardized program. In the Netherlands, it was largely individual patients who insisted on cross-over transplantation. The Health Commission has considered this form of kidney transplantation and took a positive view of it in a recently published report “News roads to organ donation” (Nieuwe wegen naar orgaandonatie)[6]. An exploratory inventarisation was conducted in Rotterdam as part of a pilot study to investigate the acceptability and practical feasibility of a living donor kidney exchange program[7]. Results from this study suggest when a direct transplantation could be carried out with a donor-recipient pair due to medical reasons all involved were very motivated to carry out across-over transplantation. It also became clear that all respondents had a preference for strict anonymity. With the use of a computer program in which blood type, HLA and unacceptable HLA antibodies could be inputted, it was determined which donor-recipient pairs could be matched together. In collaboration with the department of immunohematology and blood transfusion at the Leiden University Medical Center (Professor doctor F.H.J. Claas), an investigation was conducted to assess whether the new combinations generated by the computer program could be paired based on the cross-matches. This appeared to be the case. It was even possible to match pairs in a small group of 14 donor-recipient pairs who were strongly immunized and thus had a lengthy wait time. Living donor kidney exchange was increasingly becoming a real possibility.

SPECIAL CONSIDERATIONS

In addition to the aforementioned research into feasibility, a multidisciplinary consultation between various departments of the Erasmus Medical Center took place with the aim of investigating which topics needed further deliberation. The topics discussed were of a medical, logistical, psychosocial and ethical nature. The departments of Internal Medicine, General Surgery, Medical Psychology and Psychotherapy, and Medical Ethics of the Erasmus Medical Center participated in this consultation. In the following section we report on the various conclusions of this consultation.

Medical indications. We suppose that there should be no difference between direct and indirect living kidney donation with regard to medical indications and contra-indications for donors and recipients. Strongly immunized recipients can also participate in the living donor kidney exchange program. Strongly immunized patients are those with antibodies against a wide range of donors due to prior transplantations or regular blood transfusions, as well as women who are immunized against their partners as a consequence of pregnancy, which makes direct donation impossible. The surgical treatment to be followed for living donor kidney exchange is no different from the current practices use for direct kidney donation with a living donor.

Participation. A successful living donor kidney exchange program requires a large pool of donors and recipients. Donor-recipient pairs with both blood type incompatibility and immunization problems should participate. This is particularly important as the most common blood type incompatibility in the Netherlands occurs between a recipient with blood type O and a donor with blood type A. According to the principles of living donor kidney exchange it should be possible to find a suitable reverse blood type combination for these pairs. This is not always easy, however, since such reverse combinations are rare: individuals with blood type O can donate directly to patients with blood type A, unless there are immunization problems. Therefore, candidates for living donor kidney exchange should be recruited from both the blood type incompatible and positive cross match pools. The success of the outlined living donor kidney exchange program depends on the participation of a large number of donor-recipient pairs. Satisfactory participation is only possible when the program is organized on a national scale and is not limited to individual transplant centers. The allocation of kidneys to be donated indirectly should also only be conducted by a national organization: the Dutch Transplant Foundation. All 7 Dutch kidney transplantation center have agreed upon the allocation criteria.

Implementation. One logistical issue is conducting both donation procedures simultaneously. Conducting these procedures simultaneously can minimize the chance that one of the two donors has second thoughts and withdraws from the procedure at the last minute. It is also essential that the commencement of the procedure is guaranteed and will not be cancelled due to interfering emergency procedures. The chance that the procedure will indeed take place in two different hospitals is large seeing as the registration and allocation of the donor kidneys is carried out independently by the Dutch Transplant Foundation for donor-recipient pairs from the whole of the Netherlands. We have chosen to refer the healthy donor to the transplant centre of the intended recipient. The recipient undergoes

transplantation in his or her own center where the medical history of the patient is well known. Consequently, it is likely that the recipient and his or her original donor are admitted to two separate centers, which requires extra supervision and coordination.

Coercion. The presence of a patient with end stage renal failure in your immediate environment can cause psychological pressure to consider living donation among potential donors. Articles in newspapers and patient magazines are full of information about the lengthy wait time for post-mortal kidney transplantation and the success rate of living kidney donation. An example of this is the new report of the Health Counsel 'News roads to organ donation'. Responsibility for this decision is taken out of potential donor's hands when there is blood type incompatibility or a positive cross-match, providing them with a means of escaping this psychological pressure and the donation itself. By the introduction of the living donor kidney exchange program, these medical reasons not to donate are removed which leads to increased risk of pressure on the potential donor to donate. Care should therefore be taken that the possibility of living donor kidney exchange does not lead to living donation becoming an unavoidable civil duty. The danger of putting too much pressure on potential donors – which is certainly a reason for reservations – needs to be weighed against the chance that the program offers to motivated donors to help their family member or friend by donating indirectly rather than having to endure the wait for a post-mortal kidney. From the viewpoint of the recipient the program also has advantages. It is now possible that the most motivated and emotionally involved person who offers their kidney can now actually become a donor, albeit indirectly.

Anonymity. There is no consensus in the literature about the desirability of anonymity. Rapaport[1] advises anonymity, Park et al. and Thiel[2, 3] et al. however indicate a preference that the donor-recipient pairs become acquainted with one another. There are pros and cons of both points of view. The practical advantage of anonymity is that it is not necessary to arrange meetings prior to transplantation. The risk of such meetings is that they can cause extra stress, generating such negative emotions that one of the parties decides against participating in the procedure. This would be very disappointing for the other donor-recipient pair. Extra tension can also be caused between the pairs when the results of the transplantation are not the same. Another argument for anonymity is that the recipient can be liberated from the feeling of eternal gratefulness to their (original) donor. One can also imagine, however, that donating an organ to a stranger as well as receiving an organ from an unknown donor can cause feelings of unease, which could be alleviated or avoided by such a meeting. It is noteworthy that of the

14 donor-recipient pairs in our pilot study, there was unanimous agreement that the procedure should remain anonymous. This consensus was for us the decisive factor in choosing anonymity.

Organ trade. Trading organs is illegal. Living donor kidney exchange does however inherently involve a transaction, exchange or trade. The donor kidney is given to a stranger and a kidney for a friend or family member is expected in return. One can wonder whether this is the first step on the road towards organ trade. In our opinion this is not the case. Participation in the living donor kidney exchange program implies similar motivation to those who donate directly. The main goal is helping a family member or friend, only the method differs. When compared to direct donation the net gain is the same: the donor receives nothing and the patient does not receive anything more than if the donation had been a direct one. The way in which the living donor kidney exchange takes place is suggested to be acceptable as within the Dutch program the exchange is based on fairness. In other words, the net gain for both participating pairs should be comparable. It is therefore important that donor-recipient pairs do not seek other pairs suitable for an exchange. The Dutch Transplant Foundation is an organisation able to carry out this task responsibly according to the allocation criteria agreed upon by all transplant centers. In this way organ trade is out of the question.

THE FUTURE

The 7 kidney transplant centers in the Netherlands have discussed the above considerations. They came to the conclusion that national collaboration is of great importance. A national protocol has been established based on medical and logical aspects of the living donor kidney exchange program and also on the psychological and medical ethical considerations. The protocol describes which criteria that the participating patients and donors must fulfil, how they should be worked-up for transplantation, how the donor-recipient pairs can be registered with the program, how the matching and allocation of the kidneys will take place and how the surgical treatment will be planned. The matching will be carried out by the Dutch Transplant Foundation. It is among other things the responsibility of the Dutch Transplant Foundation to assure equality among the matched donor-recipient pairs. The National HLA Reference Laboratory at the Leiden University Medical Center will offer support in the area of immunological feasibility. In addition to the aforementioned protocol a patient leaflet will also be developed. The living donor kidney exchange program was launched on the 1st January 2004.

Willij Zuidema and Annemarie Luchtenburg, transplant coordinators, dept. Internal Medicine, Transplant Unit, collected data for the inventarisation study and

supervised the first paired exchange; Professor J. Passchier, psychologist, dept. Medical Psychology and Psychotherapy, and Ms. T. Visak, medical ethicist, dept. Medical Ethics (all: Erasmus Medical Center, Rotterdam) reviewed the first version of this article.

Conflict of interests: none. Financial support: none reported.

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Chapter 3

Acceptability and feasibility of cross-over kidney transplantation

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In: Gutmann T, Daar AS, Sells RA, Land W (Eds). Ethical, Legal, and Social Issues in Organ Transplantation. D-49525 Lengerich: PABST science publishers, 2004, 255-262

INTRODUCTION

The waiting time for a post-mortal kidney transplantation steadily increases in the Netherlands, in spite of the new law on organ donation, the donor register and all the extra media attention. In the year 2002 the waiting list of Eurotransplant counted 1,350 patients waiting for a post-mortal kidney transplantation. Living kidney donation is a good alternative. At the Erasmus Medical Center in Rotterdam the first living related kidney transplantation has been carried out in 1983. First, only living-related persons could opt for donation. Later, also genetical unrelated individuals, as spouses, partners or good friends were accepted as donor. It has been shown that there is no difference between the graft survival of donated kidneys of living related vs. living unrelated donors (1). Living kidney donation is not always feasible due to blood group incompatibility or a positive cross-match between potential donor and the recipient. Cross-over kidney transplantation could be the solution for these unlucky donor-recipient pairs. An apparent double impossibility to donate could, in this way, be turned around into two successful donations.

The present article describes history, feasibility and acceptability of this mode of transplantation. The feasibility has been analyzed on the basis of blood group and negative cross-matches, both with recent and historical sera. The willingness of donors and recipients to participate in this form of transplantation has been examined using a questionnaire. If donor-recipient pairs were interested in cross-over kidney transplantation, they were asked under what conditions they would participate.

In the present article the history of cross-over kidney transplantation will be shortly described. Also some of the experiences of this form of transplantation, carried out in countries outside the Netherlands, will pass in review. Afterwards the immunological and ethical results of this study will be described.

History and experiences outside the Netherlands

In 1986 it was Rapaport who suggested cross-over kidney transplantation (2). A strict form of anonymity between the two donor-recipient pairs, was one of his conditions to carry out this form of transplantation. To realise real anonymity, he suggested operating both donor-recipients pairs in two different transplantation centres. In both centres transplantation should be carried out at the same time. As soon as both donation-procedures had been carried out, the kidneys had to be transported to the recipients at the other transplantation-centre.

The first cross-over kidney transplantation has been done in 1991 by Park in South-Korea (3). For South-Korea cross-over kidney transplantation was a good supplement to the “donated kidney market”, because in South-Korea post mortem kidney transplantation is nor socially nor legally accepted. In 1997 already 38

cross-over kidney transplantations were carried out in South-Korea. One of Park's preconditions was a thorough exploratory meeting with the two donor-recipient pairs to inform them about the procedure and the expected results. During this meeting the two donor-recipient pairs get acquainted. The two transplantations take place at the same time. In this way it will be impossible for one of the two pairs to retract from the procedure as soon as "their" recipient has been operated. One of the disadvantages, according to Park, was the high psycho-sociological pressure for donors and recipients and possible conflicts between the two pairs when the results of both transplantations would not be the same. Another problem that could arise was a longer waiting time for recipients with blood group O.
In 1999 Thiel carried out a cross-over kidney transplantation between a couple from Germany and a couple from Switzerland (4). Both kidney transplantations were carried out in Basel (Switzerland). In both cases a blood group incompatibility was the reason that donation within the couple was not possible. Thiel choose for the solution that the two donor-recipient pairs had to get acquainted with each other. For this, he gave two reasons. The first was that both transplantations would be carried out in the same transplantation centre and at the same unit. So it would be impossible to maintain anonymity. The second reason was the German law. According to the German law it is only allowed for living unrelated persons to donate a kidney when there is a very close friendship. The last reason totally excludes anonymity, so getting acquainted was necessary. Another condition for Thiel was that both kidneys had to be of the same quality. All four persons involved (two donors and two recipients) signed an agreement for the procedure (informed consent). A clear disadvantage of cross-over kidney transplantation is that there is no way back for potential donors. This gives a heavy burden on the shoulders of potential donors. Another potential psychological problem for the donor is the possibility that his donated kidney will function well, while the kidney donated to his partner is not functioning.

MATERIAL AND METHODS

To trace all donor-recipient pairs for this study, it was necessary to make an inventory of all potential recipients, who had visited our transplantation centre with a potential donor and where the transplantation procedure could not be performed due to blood group incompatibility or a positive cross-match. From all recipients we checked whether they were still in good condition on the waiting list. All potential candidates received information in writing about cross-over kidney transplantation and were asked to co-operate in a study in our transplantation centre. Donor-recipient pairs that reacted positively to our letter were invited to visit the transplantation centre for cross matching and to fill in the questionnaire.

Study group

Ultimately, our study group consisted of fourteen donor-recipient pairs. Ten donors could not donate a kidney directly to their recipients due to a positive cross-match. A donor specific transfusion (DST) procedure was five times the cause of this positive cross-match. Four recipients were sensitized as a result of previous kidney transplants. One recipient had a positive cross-match due to random blood transfusion. This recipient also had a kidney transplantation in the past. Four donor-recipient combinations were not possible due to a blood group incompatibility. The relation between recipient and donor was in ten instances spouses, there were three parent-child combinations and one time donor and recipient were good friends.

The group donors consisted of nine males and five females. The group recipients consisted of seven males and seven females. The median age of the donors was 52 years (28 – 64 year) and the recipients were 44 years (20 – 66 year). The median waiting time of the recipients on the Eurotransplant waiting list was 896 days (0 – 1874 days). The blood group of the recipients were six times blood group A and eight times blood group O. The median recent PRA was 23 % (0 – 79%) and historic 35 % (0 – 96%). All ten recipients with a positive cross matches had detectable unacceptable HLA antigens. The number of unacceptable HLA antigens varied from 1 to 19, with a median of 7. Specific details of the recipients can be found in table 1.

Computer match program

Blood group, A-, B-, en DR-acceptable and unacceptable HLA antigens of all fourteen donor-recipients pairs were entered into a computer program. This computer program is a mathematical algorithm compiled in visual-basic. The computer program produced for each donor a list of all recipients to whom they could donate a kidney. The same was done the other way around, the program produced for each recipient a list of all donors from whom they could receive a kidney. In the end the computer program generated a list with the maximum number of donor-recipient pairs that could be matched together in our study population.

Cross-matches

The immunohematology laboratory of the University Medical Centre of Leiden (Reference laboratory of Eurotransplant) carried out cross-matches of all new donor-recipients pairs, generated by the computer on the basis of acceptable and unacceptable mismatches. Both the CDC and the FACS-test were used.

	RECIPIENTS									
	M/F	**Age**	**Bl.gr**	**w.time**	**H%**	**R%**	**Unacc HLA**	**Relation to donor**	**Reason cross-over**	**Reason positive Cross-match**
1	F	44	O+	875	60	42	11	Spouse	Pos. Cross-match	DST
2	F	44	O+	1267	11	8	7	Spouse	Pos. Cross-match	DST
3	F	57	A+	711	13	0	1	Spouse	Pos. Cross-match	DST
4	F	53	A+	951	62	38	11	Spouse	Pos. Cross-match	1 kidney transpl. in the past
5	M	24	A+	804	96	79	19	Child	Pos. Cross-match	3 kidney transpl. in the past
6	F	48	A+	1874	51	33	15	Spouse	Pos. Cross-match	DST
7	M	38	O+	916	88	63	7	Spouse	Pos. Cross-match	2 kidney transpl. in the past
8	F	57	O+	274	66	63	19	Spouse	Pos. Cross-match	DST
9	M	34	A+	1085	19	4	3	Spouse	Pos. Cross-match	Random blood-transfusion / 1 kidney transpl. in the past
10	M	38	A+	1107	79	29	12	Friend	Pos. Cross-match	2 kidney transpl. in the past
11	M	43	O+	1783	5	0	0	Spouse	Blood group incompatibility	-
12	M	29	O-	139	17	17	0	Child	Blood group incompatibility	-
13	M	20	O+	81	0	0	0	Child	Blood group incompatibility	-
14	F	66	O-	0	0	0	0	Spouse	Blood group incompatibility	-

Tab 1. Specific details of all recipients of the study group

Questionnaire

All donor-recipient pairs visited the kidney transplantation coordinator of the transplantation centre. The coordinator informed recipient and potential donor about purpose of the study and basic details of a kidney cross-over transplantation. There were separate questionnaires for recipient and donor. All questions were multiple-choice questions. One of the subjects of this questionnaire was the willingness of the donors and recipients to participate in a cross-over kidney

transplantation. If they were interested in this program, they were asked under what conditions they would participate (for example under strict anonymity or after getting acquainted). Another question was whether the recipients felt their illness as a severe daily problem. The donors were asked if they would be interested in the functioning of their donated kidney. Afterwards some pairs gave more verbal explanation about their point of view. In table 2 the questions and answers to these questions are shown.

RECIPIENT	
Current perception of illness:	62 % daily problem 38 % no problem
Willingness to participate in the cross-over program:	86 % good solution 14 % doubts
Preference for anonymity or getting acquainted:	100 % anonymity
When compelled to receive information about the donor, do they want to know age and gender:	31 % yes
Did they speak with their relatives about the cross-over program:	43 % yes
DONOR	
Willingness to participate in the cross-over program:	86 % good solution 14 % doubts
Preference for anonymity or getting acquainted:	100 % anonymity
Do they want to know the function of the donated kidney:	69 % yes
Did they speak with their relatives about the cross-over program:	57 % yes

Table 2. Questionnaire recipient and donor

RESULTS

Feasibility – computer program

On the basis of blood group and A-, B-, and DR-acceptable and unacceptable HLA antigens, we were able to create five new cross-over combinations. These cross-over combinations were realised with eight donor-recipient pairs from the group with a positive cross-match and with two donor-recipient pairs from the group with a blood group incompatibility. For ten recipients it was possible to create a new donor-recipient pair. Five times this was a recipient with blood group A and five times this was a recipient with blood group O. So for five of the six recipients with

blood group A it was possible to create a new donor-recipient pair (83 %). For five of the eight recipients with blood group O it was possible to create a new donor-recipient pair (63 %).

Feasibility – cross-matches
Cross-matches have been performed of all these ten new donor-recipient pairs. The cross-matches have been performed with recent and historic sera. Two of ten cross-matches proved to be positive.
The first positive cross-match proved to be due to a DQ-unacceptable HLA antigen. The DQ-acceptable and unacceptable HLA antigens were not routinely entered into the computer program. The other positive cross-match has been found with historic serum of a recipient who has had already two kidney transplantations before. We were not able to detect the specificity. Due to these two positive cross-matches, two cross-overs were not possible. The other three cross-overs were possible, so six of the fourteen donor-recipient pairs could participate in the cross-over kidney transplantation program.

Acceptability
The results of the questionnaire show that 62 % of the recipients consider their illness as a severe daily problem. Cross-over kidney transplantation would be an option for 86 % of the donors and recipients. All donors and recipients prefer anonymity. If the donors and recipients were forced to receive information of the other donor-recipient pair, only 31 % wanted to know age and gender of the donor. 69 % of the donors stated that they would be interested in the functioning of their donated kidney.

DISCUSSION
Cross-over kidney transplantation is an indirect way of a living kidney donation. There are similarities but also differences between cross-over kidney transplantation and direct living related kidney donation. The similarities are motive and motivation of the donor. In both cases, the donor donates a kidney and the recipient receives a kidney. In both cases the donor himself decides if he wants to donate or not. For both forms of kidney transplantation it will be necessary to inform the donors about all potential risks and health damage. Different from routine living donation the donor might not know who will receive his kidney nor will he necessarily be informed about the function of his donated kidney. Furthermore, coercion to the donor will be very high. As soon as a person opts to be a potential donor there are only a few possibilities to withdraw from the procedure. For sure, a positive cross-match or a blood group incompatibility with his primary recipient is no longer a reason not to donate.

An important difference for the recipient between indirect and direct living kidney transplantation is that he might not know who the donor of the donated kidney is. One of the possible conditions for a cross-over kidney transplantation is anonymity between the two donor-recipient pairs. This anonymity has advantages but also disadvantages.

Anonymity

The first advantage of anonymity is that the transplantation centre will not be burdened with the organisation of acquaintance-meetings between the two donor-recipient pairs. Another advantage of anonymity is that there will be no extra psychological pressure or conflicts between the two pairs when the results of the two transplantations are not equal. With anonymity there is no chance that donor-recipient pairs will withdraw from the procedure due to negative feelings after a get together-meeting. A disadvantage of anonymity is that the donor will not be informed about the functioning of his donated kidney. So the donor will not know if his donation has been of any use to his actual recipient. Anonymity will be very difficult to realise if both transplantations will be carried out in the same transplantation centre. Moreover, when donors and recipients are forced to undergo the procedure under circumstances of anonymity, donors and recipients might appreciate this as an insult to their autonomy. However, from our questionnaire we can conclude that this is only a theoretical problem because all potential donors and recipients preferred anonymity.

CONCLUSIONS

Even within a relatively small group of fourteen donor-recipient pairs there are possibilities to match pairs, even for highly sensitized long waiting recipients. Cross-over kidney transplantation is a viable option.

With respect to cross-over kidney transplantation many advantages and disadvantages can be pointed out. In our opinion it is the opinion of the potential donor and recipient must prevail. And, according to the questionnaire, they seem to be very enthusiastic about cross-over kidney transplantation. The questionnaire shows that all donors and recipients prefer anonymity. The donors may be curious about the functioning of the donated kidney later on. However, this information should not be provided without precautions, as there remains an inherent possibility that they will become disappointed. Therefore, an informed consent for all participants in a cross-over procedure is needed before any information is to be unveiled.

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Chapter 4

Methodology of the Dutch living donor kidney exchange program

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Organs, Tissues and Cells, 2008, 2: 83-6

SUMMARY
Over the last decade, strategies to expand the living kidney donor pool have become increasingly diversified. A number of desensitization protocols were developed to make transplantations possible in patients with incompatible donors due to a positive cross-match or blood type incompatibility. In our opinion logistic solutions should be given preference over these more medical demanding programs. In the Netherlands we embarked on a living donor kidney exchange program in January 2004. It proved to be rather successful as for 55% (132/242) of the patients a solution could be found. The purpose of this article is to describe the methodology of this program. We claim that the success of a living donor kidney exchange program depends on trust between the transplant centers, strict adherence to the protocol, supervision by an independent allocation organization and a central laboratory responsible for the cross-matches.

INTRODUCTION
Living donor kidney transplantation is an attractive option for patients with an end-stage renal disease. It results in superior patient and graft survival while risks for the donor are minimal. For transplant candidates with willing, but not compatible donors due to the presence of circulating ABO isoagglutinins or anti-HLA antibodies, thus with a positive 'red' or 'white' cross match, living donor kidney exchange could be a solution. The benefit of such an approach is two-fold. First, recipients do not need to be desensitized and therefore will not be subjected to the morbidity inherent to desensitization protocols with their increased immunosuppressive load, clotting disturbances due to plasmapheresis procedures, and the unpredictable rejection episodes. Second, it is not expensive: only logistic hurdles have to be taken while the donation and transplantation procedures can be performed on a routine basis. However, first a number of preconditions should be fulfilled. The national law should permit living kidney donation to a specific person in the absence of a genetically relationship or of a long lasting social commitment with the recipient. If this is not the case e.g. in Germany, or in France, and in the United Kingdom before 2007, the transplant community of that particular country should take the necessary attempts to change the law in order to make non-directed donation permitted. Then we should pay attention to ethical and psychological aspects e.g. loss of medical excuses for donors, the potential slippery slope to organ trade, the issue of anonymity between donor-recipient pairs, and especially the acceptability of donor kidney exchange by patients and donors (1). A pilot study could be performed which will inform you about the willingness of your recipients and their donors to participate and to learn about their preference for anonymity or acquaintance with the other couple. In the Netherlands we have performed such a pilot before we embarked on our program (2). As we found that

all potential cross-over pairs interviewed preferred anonymity, we decided as a rule to exchange donor kidneys on an anonymous basis. After legal and ethical topics, logistics issues should be discussed during consensus meetings with all participating nephrologists, surgeons, HLA immunologists and transplant co-ordinators. In the present article we describe how we in the Netherlands organized our program that proved to be very successful during the last four years (3).

LOGISTICS

When several transplant centers collaborate within one exchange program, trust in each other is of utmost importance. We decided that the donors should travel to the recipient center in order to keep the ischemia time as low as possible and to completely avoid the potential problems resulting from shipping the kidneys. Therefore you should almost blindly believe that your colleagues have kept themselves strictly to the medical criteria for the donors as well as they should blindly believe your adherence to the protocol. Furthermore it is important to have one independent organization to supervise the exchange procedures. The key role of such an organization should be to ensure that allocating and matching will take place in a fair and unbiased way. This organization should not have a direct relationship with patients. In The Netherlands we established in 1997 the Dutch Transplant Foundation, in order to realize the aims of the Dutch law on organ donation. The main objectives of our law are to guarantee a fair system of allocation of organs and tissues purely on medical criteria, to increase the availability of organs and tissues for transplantation purposes and to prevent any commercial use of donor organs. The Dutch Transplant Foundation is the official body responsible for the execution of the transplant law which mainly concerns deceased donor organs and tissues. In our living donor kidney exchange program independent allocation is crucial too, and thus we decided that the Dutch Transplant Foundation should be responsible for the supervision, allocation and coordination of these living donor kidneys. In this respect a national co-ordinator plays an important role. His/her specific responsibilities include informing the centers about the date of the match procedure, registration of the participants, matching of the exchange pairs by our computer match program, informing the centers about the match possibilities and the results of the cross matches. Other responsibilities are managing a database with detailed information of all donors-recipient pairs, contributing to the development of protocols and patient information brochures, acting as a central point for information, analysing the results of the match procedures and organizing twice a year a national meeting with nephrologists, surgeons, HLA laboratory workers and transplant co-ordinators of all the seven centers to evaluate the program. Another part of our program is the laboratory responsible for the cross matches between newly coupled donors and

recipients. Blood samples don't have to be send to all participating centers and it ensures that all cross-matches will be performed with the same tests and techniques. Obviously, in the Netherlands we decided for our national Reference laboratory for Histocompatibility in Leiden, which also happens to be the Eurotransplant Reference Laboratory. This laboratory was founded in 1967 in Leiden in order to increase the reliability of transplantation-related histocompatibility testing, including HLA typing, crossmatching, and screening for HLA specific antibodies.

PROTOCOL

Medical criteria for donor and recipient

The pre-operative screening of potential transplant recipients follows the guidelines developed during an International Conference on the Care of the Kidney Transplant Recipient in Lisbon in 2006 (4). These are recommendations keeping in mind that the work-up of each patient should always be individualized. Guidelines for the evaluation of living donors are described by kidney transplant physicians and surgeons on an International Forum held in Amsterdam, The Netherlands, from April 1 to 4 in 2004 (5). Especially, the work-up of donor and acceptor are the same for both direct and indirect (cross-over) donation. If the BMI is higher than 35 kg/m2 the surgeon will encourage the donor to lose weight before kidney donation. After the medical work-up the living donor will meet the social worker for a psychosocial evaluation. They discuss the feelings and expectations of the donor about upcoming surgery and confirm aftercare plans. In this interview the social worker will check the motives for donation, the relationship to the recipient and if there is any pressure. The social worker will also inform the donor about the financial costs. Medical expenses are covered by the medical insurance of the recipient. On indication a psychologist may be consulted. In a study of Kranenburg et al we concluded that there is no need for routine additional emotional or psychosocial support by a psychologist for donors and recipients in an exchange program (6). The donor-recipient couples just need some more practical support when they were to be admitted to different hospitals. The local transplant co-ordinator can easily provide this support. The nephrologists, surgeons and anaesthesiologists should accept the cross-over donor and acceptor as suitable candidates, just as is the case in a routine direct donation. Only thereafter donor-recipient couple can be registered for the exchange program.

Registration procedure of participants

Four times a year a match procedure will take place, in January, April, July and October. The exact date of the match procedure is notified to the transplant centers six weeks in advance by the national co-ordinator. Transplant centers have to

register both new candidates who enter the exchange program for the first time and register candidates who unsuccessfully participated in a previous match procedure. For all candidates, accurate tissue typing results from both donor and acceptor must be available. For the acceptor an up to date screening for HLA specific antibodies is necessary. Sera and lymphocytes from newly registered donors and recipients must be on hand in our National Reference Laboratory for Histocompatibility in Leiden to speed up the procedure. Two days before the intended match procedure the national co-ordinator will send a list with all the registered pairs to each transplant center to check the information. The day before the match procedure all recipients who are on the waitlist for a deceased kidney will be registered for one day on a Not-Transplantable (NT) code.

Allocation – and matching criteria

On the day of the match procedure the computer match program identifies suitable donor-recipient combinations for an exchange. If one donor-recipient pair can be matched to several pairs further selection is needed provided the maximum number of new combinations is met. The next allocation criterion is blood type, first identical than compatible. For example, first blood type O donors will be matched with blood type O recipients. Thereafter selection takes place according to match probability (MP) (7). The MP takes into account the prevalence of acceptable HLA antigens for the recipient within the actual crossover donor population. This criterion is to ensure that the recipient with the smallest chance of finding a compatible donor in the pool will be ranked first. Further selection includes wait time counting from the first day of dialysis. Criteria like CMV serology, donor or acceptor age, gender, pre-emptive transplant possibility or PRA are not included in our match program. In the first year 2004 the computer program made exchanges with two pairs; from 2005 it was possible to match combinations of three donor-recipient pairs and from October 2007 the computer program is able to make exchanges between any numbers of pairs but for practical reasons we decided for the moment not to go beyond a four way exchange. After the computer has generated a report with the potential match possibilities, the national co-ordinator informs each transplant center about the match results of their registered candidates. Patients for whom no solution is found are put back on a transplantable code. The centers receive a report about the overall outcome of the match run, the matched pairs and the numbers of two, three of four ways exchanges. The report of the match run is sent to our National Reference Laboratory for Histocompatibility in Leiden. The matched recipients who are on the waitlist for a deceased kidney will remain temporarily removed, until the final result of the cross-matches become definitive.

Cross matches

The National Reference Laboratory verifies whether the potential combination between donor and recipient is compatible before starting the actual cross match procedure. The techniques we use for the cross matches are standard CDC complement dependent lymphocytotoxicity in combination with an ELISA screening. In case of a positive cross match the computer program will select the next feasible combination. The procedure stops when no new couples can be created from the remaining candidates. The final results of all negative donor-recipient combinations are sent to the national co-ordinator who informs each center about the outcome of the cross matches. Recipients that dropped out because of a positive cross match return to the waitlist for a deceased kidney and can be registered for the next cross-over match run. Recipients with negative cross matches with their new donors are removed from the waitlist for a deceased donor kidney. The centers receive information about the number of pairs in the exchange combination and about the transplant centers that are involved in the new combinations. The transplant centers inform their patient and donor about the further procedure.

Surgical and follow-up procedures

The local transplant co-ordinator or transplant nurse arranges the exchange procedure. The protocol prescribes that the donor travels to the recipient center. A report of medical evaluation of the donor is sent to the recipient center. In the next month the recipient center invites the new donor for a meeting with nephrologist, surgeon, anaesthetist, social worker and transplant co-ordinator. They will explain the local procedure, and if necessary additional diagnostic or therapeutic interventions will take place. Some centers want to repeat the cross-match with their own techniques. The surgeon gives details about the nephrectomy because each transplant center has his own technique. If donors are accepted as suitable candidates in all centers the surgical procedures must be scheduled within two months. During this time lapse donor-recipients complications might occur. The transplant center will immediately inform the national co-ordinator about this including the reason for it. If there is a definitive problem, the donor-recipient pair will leave the program. Depending on the severity of a temporary problem the exchange procedure may be postponed or the newly formed couples independent of each other are registered for a new match run. Surgical procedures take place simultaneously. The day before the operation transplant centers inform each other on the condition of patient and donor. On the morning of donation and transplantation surgeons contact each other by phone before they start the operation. If during the donation procedure the donor kidney proves to be unsuitable for implantation the intended recipient will receive priority listing on the

Eurotransplant waitlist for a deceased kidney. If during the transplantation procedure the recipient appears to be unsuitable to receive, the donated kidney will be offered to the first recipient on the waitlist of Eurotransplant. If the problem of the recipient is temporarily and the patient is recovered, the recipient will also receive priority on the waitlist for a deceased kidney. During in hospital stay, health care workers will maintain strict anonymity between donor and recipient. As usual the follow-up of the recipient is done by his own nephrologists. The follow-up visit for the donor with his operating surgeon will be arranged two or four weeks after the procedure. Thereafter, a lifetime annual review is done by the nephrologists of the center where he originally came from. Figure 1 shows a time schedule of the exchange procedure.

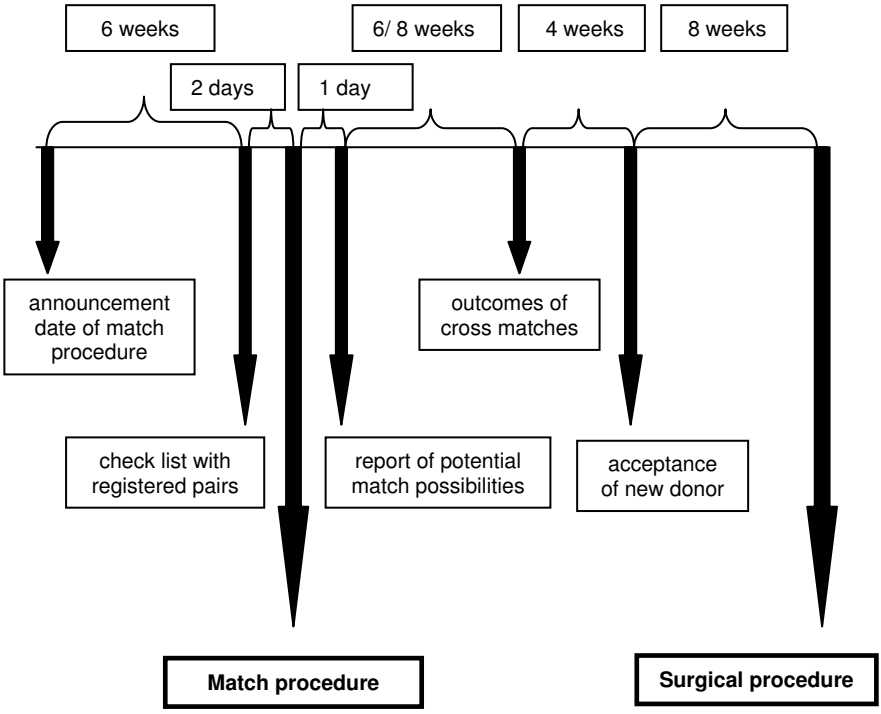

Figure 1. Time schedule of the exchange procedure

SUMMARY
While preparing for a living kidney exchange program attention has to paid to the following: The national law should allow the procedure. Donors and recipients should be thoroughly informed about the program. In a pilot study one can analyze under which conditions they will be proposed to participate in an exchange program. Anonymity could be one of the conditions. Traveling of the donor to another center, dependent on the distance, could be another. The statement of a donor can be: “one week in another hospital in exchange for a better life is an excellent option”. Moreover, it is especially the recipient who benefits from his/her donor’s travel. Ischemia times remain as short as possible and shipment of kidneys is avoided (8). However, a good relationship and trust between surgeons of the various transplant centers is necessary as they are operating on ‘each other’ donors. Other important factors are the independent organization that is responsible for the allocation, the independent laboratory responsible for the cross matches and the appointment of a national cross-over transplant co-ordinator.

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Chapter 5

The Dutch national living donor kidney exchange program

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Am J Transplant., 2005, 5: 2302-5

ABSTRACT
The wait time for deceased donor kidney transplantation has increased to 4-5 years in the Netherlands. Strategies to expand the donor pool include a living donor kidney exchange program. This makes it possible that patients who can not directly receive a kidney from their intended living donor, due to ABO blood type incompatibility or a positive cross match, exchange donors in order to receive a compatible kidney. All Dutch kidney transplantation centres agreed on a common protocol. An independent organization is responsible for the allocation, cross matches are centrally performed and exchange takes place on an anonymous basis. Donors travel to the recipient centres. Surgical procedures are scheduled simultaneously. 60 pairs participated within one year. For 9/29 ABO blood type incompatible and 17/31 cross match positive combinations, a compatible pair was found. Five times a cross match positive couple was matched to a blood type incompatible one, where the recipients were blood type O. The living donor kidney exchange program is a successful approach that does not harm any of the candidates on the deceased donor kidney wait list. For optimal results both ABO blood type incompatible and cross match positive pairs should participate.

INTRODUCTION
In the Netherlands approximately 400 (24/million inhabitants) deceased donor kidney transplants are performed on an annual basis. This number has remained constant over the last 20 years, while an increasing influx of new patients on the wait list resulted in wait times of 4-5 years. Strategies to expand the kidney donor pool in our country have included programs both for non-heartbeating donors and for living (non) related donors. In 2004 the proportion of deceased donor kidney transplants derived from non-heartbeating donors already exceeded 42% (171/402) and the number of living kidney donations increased to 250 providing 38% of the total number of transplanted kidneys in the Netherlands. These efforts, however, have as yet not resulted in a shorter national wait list. Therefore other options were explored, e.g. a program for living donor kidney exchange or cross-over kidney transplantation. Such a program makes it possible for patients that cannot receive a kidney from their intended donor, due to ABO blood type incompatibility or to a positive serological cross match, to exchange donors in order to receive a kidney. The concept was described by Rapaport in 1986 (1), but despite several proposals (2,3), did not find it's way into clinical practice in Europe or in the USA until recently. In South Korea, where brain death is socially nor legally accepted, and donor exchange is the only alternative for living kidney donation in case of incompatibility, a cross-over program is already operating for more than 10 years (4). At the moment the attitude towards living donor exchange is rapidly changing in the western world and a number of initiatives have been

undertaken on a local or regional scale (5,6). We here report our one year experience with a national living donor kidney exchange program in which all kidney transplant centres in the Netherlands participated.

LOGISTICS AND PATIENTS

Before embarking on a clinical program we explored in a pilot study the acceptability of donor kidney exchange for our patients and the feasibility of a computer based allocation program (7). It became clear that both potential donors and recipients were eager to participate, but strongly preferred anonymity. The allocation program is based on ABO blood type compatibility, while predefinition of unacceptable HLA antigens by extensive antibody screening is used to predict negative cross matches. We also undertook a study on the ethical and psychological aspects, in which we considered a number of topics: the influence of 'donation by strangers' on the motivation and willingness of donor-patient couples; the issue of anonymity; the loss of the possibility of 'medical excuses' for unwilling donors and the view that cross-over is a first step to commercial organ donation. We concluded that none of these issues seems to propose a disorderly or unethical situation (8). However in our opinion donor kidney exchange is barter and thus vulnerable to economic forces. Therefore, we strongly advocated the allocation of kidneys to be the responsibility of an independent organization i.e. the Dutch Transplantation Foundation. In the mean time a national committee was formed consisting of representatives of the kidney transplant centres in the Netherlands, the National Reference Laboratory for Histocompatibility and the Dutch Transplantation Foundation. Participants agreed on a protocol in which medical criteria for donor and recipient, the registration of candidates, matching-, allocation-, surgical- and follow-up procedures were described. All patients and donors were molecularly typed for HLA-A,-B,-C, -DR and DQ on a medium resolution level. Sera of the patients were screened for HLA alloantibodies using standard complement dependent lymphocytotoxicity and ELISA. HLA antigens toward which the patients had formed specific alloantibodies were considered not acceptable mismatches, which means that donors with these antigens were not selected for these patients. Consensus was achieved on a computerized allocation algorithm based on blood type, first identical than compatible, and match probability. The match probability is a value build up by the frequencies of the for a recipient compatible blood types and unacceptable HLA antigens within the actual donor pool. Other criteria are wait time counting from the first day of dialysis and donor age. Allocation procedures to match compatible combinations were scheduled every 3 months. Cross matches between the new donors and recipients were to be centrally performed in the National Reference Laboratory for Histocompatibility. Thereafter the donors of the newly formed pairs would travel to the recipient's transplant centre, where the final

decision for surgery is made. A final decisive cross match was performed in the tissue typing laboratory affiliated to the transplant centre of the recipient. Donation procedures in the 2 centres are planned within 3 month's of allocation and are simultaneously performed.

Four match procedures, in which a total of 60 donor-recipient combinations were enrolled, have been performed in the year 2004. There were 31 couples that participated once, 17 twice, 11 three times and 1 even in all 4 rounds. We enlisted 29 ABO blood type incompatible and 31 pairs with positive lymphocyte cross matches. Tables 1 show the demographic data of the donors and their recipients, stratified for ABO blood type incompatibility and cross match positivity. In the latter group long waiting sensitized female recipients with partners as intended donors predominated. In table 2 the blood type distribution of the 29 ABO blood type incompatible couples is given. The A to 0 combination was most frequently seen (16 pairs), followed by 6 A-B or B-A combinations.

	ABO blood type incompatible n = 29	cross-match positive n = 31
Gender recipients (male/female)	17 / 12	8 / 23
Gender donors (male/female)	12 / 17	18 / 13
Age recipients (median, range)	51 (22-72)	50 (16-69)
Age donors (median, range)	53 (38-74)	53 (29-71)
PRA % historic (median, range)	2 (0-100)	28 (5-100)
Wait time months (median, range)	19 (0-84)	26 (0-69)
Donor type:		
Partner (male/female)	8 / 11	15 / 5
Child / parent	1 / 4	1 / 3
Sibling / other relative	2 / 1	2 / 2
Nonrelative	2	3

Table 1. Donor and recipients characteristics

	Recipient			
Donor	A	B	O	Total
A	-	4	16	20
B	2	-	3	5
AB	2	-	2	4
Total	4	4	21	29

Table 2. Blood type distribution of the 29 ABO blood type incompatible pairs

RESULTS

For 40 couples, 14/29 ABO blood type incompatible and 26/ 31 cross match positive (p=0.008, X^2-test), the computer program predicted on the basis of blood type and unacceptable HLA antigens 47 exchange possibilities resulting in 94 new combinations. Because 21 of these 40 potentially exchangeable pairs could be matched with more than one (median 3, range 2-12) other pair, a further selection was made on the basis of match probability. This resulted in 26 combinations that proved to have negative cross matches thereby demonstrating the accuracy of the antibody determination in the HLA laboratories and the allocation algorithm. The drop out rate during this last procedure was comparable for both groups: 36% for the ABO blood type incompatible group and 35 % for the cross match positive group, suggesting the fairness of the selection by match probability. There was no necessity for further selection on the basis of wait time or donor age. In 19 cases a new combination was already found in a first computer search, while for 5 patients a second and for 2 a third procedure was needed. The chance for a donor-recipient pair to find a matching couple was 19/31 (61%) during a first attempt, but thereafter chances decreased to 5/17 (29%) for those participating twice and 2/11 (18%) for the couples that tried three times.

Of the 26 successfully matched recipients, 9 belonged to an originally ABO blood type incompatible combination, while 17 had positive cross matches with their intended donors (Table 3). Five times a ABO blood type incompatible pair was combined with a cross match positive one. So, 9/29 (31%) ABO blood type incompatible and 17/31(55%) cross match positive combinations were matched to new donors and recipients (p=0.11). Even some long waiting highly immunized patients could be matched to a new donor. Table 4 shows the original ABO blood type distribution of the 26 couples that were matched versus the 34 for whom no new combination was found.

	matched n = 26	not-matched n = 34
ABO blood type incompatible	9	20
Positive cross-match	17	14
Gender recipients (male/female)	11 / 15	14/ 20
Gender donors (male/female)	12 / 14	18 / 16
Age recipients (median, range)	51 (22-72)	51 (16-59)
Age donors (median, range)	54 (29-71)	52 (33-74)
PRA % historic (median, range)	11 (0-80)	20 (0-100)
Wait time months (median, range)	19 (0-69)	27 (0-84)
Donor type:		
Partner (male/female)	11 / 8	8 / 12
Child / parent	4	2 / 3
Sibling / other relative	2	3 / 2
Nonrelative	1	4

Table 3. Characteristics matched versus not-matched

Match						No-match					
	Recipient						Recipient				
Donor	A	AB	B	O	Total	Donor	A	AB	B	O	Total
A	4	1	2	4	11	A	5	-	2	12	19
AB	-	-	-	-	0	AB	2	-	-	2	4
B	2	-	-	1	3	B	-	-	1	2	3
O	5	-	3	4	12	O	2	-	-	6	8
Total	11	1	5	9	26	Total	9	-	3	22	34

Table 4. Original Blood type distribution matched (n=26) versus not matched (n=34)

All original blood type B to A and O to B combinations were matched, less successful were the O to A (71%), A to B (50%), A to A (44%) and O to O (40%) blood type combinations. For all the ABO blood type incompatible pairs with a blood type O recipient it was more difficult to find a matching couple, but it was still possible in 5 of the 21 cases (24%).

After the allocation of 26 donors to their new recipient, 24 kidney transplants were performed. The median time between the moment of enrolment in the exchange

program and the actual transplantation was 104 days (61-326). Two procedures were cancelled for medical reasons. In 22 instances the original donor and recipient underwent surgery in different centres while 2 times both operations took place in the same centre. One transplant had to be removed in the 4th postoperative week because of an irreversible rejection. The recipient was a male of 35 years old with a historical PRA of 21 % and originated from the positive cross match group. All other kidneys are functioning well after a median follow up of 8 months and none of the donors suffered from complications.

DISCUSSION

In the present report we demonstrated a successful living donor kidney exchange program in which both cross match positive and ABO blood type incompatible donor-recipient pairs participated. We were able to create new ABO blood type compatible couples with negative cross matches for 26/60 (43%) of the candidates and this resulted in 24 kidney transplants. For the next couple of years we expect an input of at least 15 new donor-recipient pairs in each match procedure. This will presumably lead to approximately 25-30 transplantations a year. This approach of donor exchange to expand the donor pool has all the advantages of living unrelated kidney donation, which is associated with excellent long-term outcome irrespective of HLA matching.

Alternative protocols have been developed to make direct donation possible within incompatible pairs, e.g. the use of plasma exchange to remove the isoagglutinins or anti-HLA antibodies in combination with the administration of i.v. immunoglobulins and anti-B cell antibodies. Disadvantages of these protocols are the demanding technique, the high financial costs and, more importantly, the high rate of rejection and graft loss (9,10).

Another alternative solution for ABO blood type or cross match incompatible pairs is the live donor-list exchange (6,11). A live donor who is incompatible with his potential recipient donates his kidney to the deceased donor wait list with the agreement that the paired recipient would receive priority for the next compatible cadaver kidney. The recipient on the wait list who receives a live kidney has the benefit of a better chance of graft survival. The recipient with the incompatible donor receives within a few days a cadaver kidney with a lower graft survival, but the benefit of decreasing his wait time. Although the "nett gain" of this type of exchange in terms of survival is probably in favour of the total pool of patients on the list, it also implies that a number of individuals have to wait longer for a deceased donor kidney. Especially the blood type O recipients will suffer from the extraction of blood type O kidneys for the benefit of blood type O recipients with a living non blood type O donor. This unfairness will not occur when the program is restricted to ABO blood type incompatible couples with non- O type recipients and

ABO blood type compatible couples with a positive cross match (12). However, this limitation, while fulfilling criteria of justice and fairness, renders the program less efficient in terms of absolute numbers of transplants. On the other hand, efficiency is not always a valid argument. The highest efficiency can be reached with one large cross-over pool including all couples irrespective of blood type or cross match. In our opinion it is unrealistic and even unethical to persuade a compatible donor to donate to a large anonymous pool in stead of directly to a relative or friend. The efficiency argument has also been used against our approach with the strict separation of the exchange donor pool from the deceased donor pool. We are aware that our program will stagnate, when the situation arises that the exchange pool exists of non-blood type O donors and type O recipients. Participation of both ABO blood type and cross match incompatible couples, which makes it possible to combine couples from these subgroups, is therefore essential for the success of the program. We were able to find new recipients for 43% of the donors and although our program did not make optimal use of the available living donor kidneys, it did not harm any of the candidates on the wait list for deceased donor kidneys. Without interference with other allocation systems we can not find any ethical argument against paired living donor kidney exchange, provided the participants are fully informed, unforced, and an independent organisation is responsible for the matching of new combinations. However, there may be legal barriers, e.g. in Germany and the United Kingdom where law forbids living unrelated donation in the absence of a close emotional relationship, or in France where even emotional unrelated donation is not allowed unless, in selected cases, a court of law rules differently. In the UK the law will change in 2006 and UK Transplant is confident to start a cross-over program that year. We encourage the various transplant organisations to embark on these programs too and, when necessary, to convince the authorities to modify transplant laws in order to make these indirect donations possible.

ACKNOWLEDGMENTS

Without the cooperation of the seven university kidney transplantation centres this program could not have been implemented. We express our appreciation to all the surgeons, nephrologists and coordinators kidney transplantation (Academic Medical Centre Amsterdam: M.M. Idu, surgeon, F. Bemelman and S. Surachno, nephrologists, S. Termeulen, coordinator. University Medical Centre Groningen: R.J. Ploeg, surgeon, J.J. Homan van der Heide, nephrologist, R. Meijer and A. Roelofs, coordinators. Leiden University Medical Centre: J. Ringers, surgeon, J.W. de Fijter, nephrologist, M. van Gurp, coordinator. Academic Hospital Maastricht: L.W.E. van Heurn, surgeon, J.P. van Hooff and E.M. van Duijnhoven, nephrologists, J. Dackus, coordinator. University Medical Centre St. Radboud: J.A.

van der Vliet, surgeon, Ph.M.M. Dooper and A.J. Hoitsma, nephrologists, D. Pilzecker, coordinator. University Medical Centre Utrecht: R.W.H. van Reedt Dortland, surgeon, R.J. Hené, nephrologist, B. Vink, coordinator. Erasmus MC University Medical Centre Rotterdam: J.N.M. IJzermans, surgeon, G. Bakker, A. Luchtenburg and W. Zuidema, coordinators).

This program was supported by the Dutch Kidney Foundation.

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Chapter 6

A highly efficient living donor kidney exchange program for both blood type and cross match incompatible donor-recipient combinations

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Transplantation, 2006, 82:1616-20

ABSTRACT
Lack of deceased donors for kidney transplant patients in the Netherlands encouraged alternative options to expand the living donor pool for recipients who have a willing donor but cannot donate directly because of a positive crossmatch or ABO blood type incompatibility. A national donor kidney exchange was considered as a possible solution. From January 2004 until June 2006, 146 couples from seven kidney transplantation centers were enrolled and participated in ten match procedures. The Dutch Transplant Foundation was responsible for the allocation and the National Reference Laboratory for Histocompatibility in Leiden performed all the serological cross matches. For 72 out of the 146 (49%) donor-recipient combinations a match was found. The success rate in the positive cross match group was significantly (p=0.0015) higher than in the ABO incompatible group (44/69 vs. 28/77); median PRA of the matched recipients in the positive cross match group was 38% (0-100) and in the ABO incompatible group 0% (0-27) (p<0.001). We were least successful for ABO blood type incompatible pairs with blood type O recipients, but for 9/53 (17%) there were possibilities. These 9 blood type incompatible pairs were coupled to 9 positive cross match pairs, which reflects the efficiency of combining the two categories of donor-recipient combinations into one program. The donor kidney exchange program in the Netherlands, in which all seven kidney transplantation centers participated, proved to be a successful program to expand the number of living donor kidney transplantations.

INTRODUCTION
The Netherlands has a population of 16 million inhabitants. Each year 1600 patients are enrolled in dialysis programs and each year approximately 800 new patients are registered on the waitlist for a deceased donor kidney. In the seventies and eighties the wait time was just under one year, but during the last two decades, the median wait time gradually increased to 4-5 years, as the number of kidneys available for transplantation has not kept pace with demand. Therefore several strategies to expand the deceased donor kidney pool have been implemented including a program for nonheartbeating donors. In the Netherlands the proportion of deceased donor kidney transplants derived from nonheartbeating donors already rose to 47% in 2005 (191/409)[1]. An alternative option is transplantation of a living donor kidney. The favourable medical outcome of living donation has attributed to the growing demand for live kidney donors. Moreover, the development of the laparoscopic donor nephrectomy increased the attractiveness of this procedure, while the excellent survival, regardless of human leukocyte antigen (HLA) matching, expanded the opportunity for living genetically unrelated donations[2]. In 2005 the seven transplantation centers in the Netherlands performed 127 kidney transplants with an unrelated and 148 with a related living donor. However, some

transplant candidates cannot identify a compatible donor because of an ABO blood type - or cross match incompatibility. For these patients protocols were developed that are aimed at the removal of isoagglutinins or donor specific HLA antibodies with plasmapheresis/ immunoabsorption combined with anti-B cell therapy and intravenous immunoglobulins (desensitization)[3,4]. Negative aspects of these protocols are their immense costs, labor intensity, the need for additional immunosuppression, and the variable response rate. An alternative strategy accepts that patients are sensitized and tries to define those HLA antigens against which the patient has never formed antibodies. These HLA antigens are then considered to be acceptable mismatches and when a deceased donor kidney with these antigens is found, it will be allocated to that patient with high priority. Claas et al reported that, within the Eurotransplant Acceptable Mismatch program, for 57 out of the 129 patients with a PRA > 85%, that were listed within a 18-month period, compatible kidneys were found resulting in a 87% graft survival at 2 years[5]. Another equally inexpensive solution, in this case for recipients with incompatible ABO blood type or positive cross match living donors, is a paired donor kidney exchange program. In the Netherlands all seven kidney transplantation centers embarked in 2004 on a common exchange program[6]. The Dutch Transplant Foundation is responsible for the allocation while cross matching is centrally performed at the National Reference Laboratory for Histocompatibility. In the present report we describe the results of this national program achieved over 30 months.

PATIENTS

From January 2004 until June 2006 146 donor-recipient pairs participated in the kidney exchange program. The recipients had a median wait time of 13 months on the cadaveric waitlist (range 0-172 months). The oldest patient in this program was 73 years, the youngest 15 years (median 51). The median age of the donors was 52 years (range 26-77). The reason to participate was a positive cross match in 69 cases and ABO blood type incompatibility in 77 cases. In contrast to the other kidney transplantation programs there were more female than male recipients in our program (79 vs. 67). This is probably due to pregnancy induced sensitization as the higher proportion of females was only observed in the positive cross match group (48 vs. 21) and not in the ABO blood type incompatible group (31 vs. 46, p= 0.0005). Table 1 shows the gender distribution of the donors and their relation to their recipients. The majority of the donors were female (79 vs. 67), but this time due to their preponderance in the ABO blood type incompatible group (48 vs. 29) and not in the positive cross match group (31 vs. 38). The largest donor group consisted of partners: 86/146, 59%. Their gender distribution was equal: there were 43 male and 43 female potential donors to their partner. However, there was a

significant (p=0.0004) difference between the ABO blood type incompatible group and the positive cross match group, with more male partner donors in the positive cross match group and more female partner donors in the ABO blood type incompatible group. The second largest subgroup (n=20) were the unrelated donors (no partners). Thus the total proportion genetically unrelated potential donors was 106/146, 73%. The blood type distribution of donor and recipients was as follows: in the positive cross match group, the most frequently encountered combinations were the 44/69 (64%) O donors with either O recipients (n=24) or with non-O recipients (n=20). As expected in the ABO blood type incompatible group the majority of recipients, 53/77, 69%, had blood type O. Twenty pairs were A to B or B to A combinations and 4 AB donors brought an A or a B recipient. There were 43 re-transplant candidates enrolled: 33 in the positive cross match group and 10 in the ABO blood type incompatible group. Median PRA of the total number of patients was 13% (0-100%): 41 % (0-100%) in the positive cross match group and 2% (0-100%) in the ABO blood type incompatible group. The median PRA of the 33 recipients who received a re-transplantation in the positive cross match group was 58% versus 36% of the 36 recipients who had never received a kidney transplant.

Donor	ABO blood type incompatible (male/female)	positive cross match (male/female)	Total (male/female)
N	77	69	
Partner	16/33	27/10	43/ 43
Unrelated	4/6	4/6	8/12
Parent	2/7	0/7	2/14
Brother/sister	2/2	4/3	6/5
Child	3/0	2/3	5/3
Distant relative	2/0	1/2	3/2
Total	29/48	38/31	67/79

Table 1. Sex distribution of the 146 donors and their relation to their recipients

METHODS

The seven Dutch kidney transplantation centers agreed on a common protocol, including medical criteria for donor and recipient, the registration procedure of participants, matching- and allocation criteria, surgical and follow-up procedures[6]. All patients and donors are molecularly typed for HLA -A,-B,-C, -DR and -DQ. Patients sera are screened for HLA alloantibodies against HLA -A,-B,-C,-DR and -

DQ, but not against -DP, with standard complement dependent lymphocytotoxicity (CDC) and ELISA. Both historic and current sera with specific alloantibodies are taken into consideration in defining unacceptable HLA antigens. The National Reference Laboratory for Histocompatibility in Leiden performs all cross matches. The Dutch Transplant Foundation is responsible for the allocation. Allocation criteria are blood type, first identical than compatible and match probability (MP)[7]. The MP takes into account the incidence of compatible ABO types, and acceptable HLA antigens for the recipient within the actual crossover donor population. The potential recipient with the lowest MP, which is the recipient with the smallest chance of finding a compatible donor in the pool, is ranked first. Further selection includes wait time counting from the first day of dialysis and donor age. The protocol prescribes that the donor travels to the recipient center and that the surgical procedures take place simultaneously. We keep a strict anonymity between the donor-recipient pairs. In 2004 the computer only matched combinations of two pairs; from 2005 it was possible to match combinations of three donor-recipient pairs. Every three months participants can be registered for a match procedure. From January 2004 until June 2006 ten match procedures were performed. The median input of new donor-recipient pairs was 14 (range 7 – 21 pairs) and the median number of couples participating in a match procedure was 37 (range 16 -56 pairs). The total input of the centers varied from 7-34 with a median of 20 participants. In the positive cross match group 87% of the couples participated 2-3 times, 38% 4-6 times and 12% 7-9 times. For the ABO blood type incompatible group the percentages were 96%, 51% and 16% respectively. For statistics the Student's-t-test and the Chi-square test with Yates correction were used when appropriate.

RESULTS

On basis of ABO blood type and unacceptable HLA antigens, 1019 match combinations were constructed for 122 couples. For the remaining 24 donor-recipient pairs no potential solutions were found. In the latter group, 18/24 were ABO blood type incompatible, which proportion was significantly (p=0.0242) higher than the 59/122 ABO incompatibles in the group with possibilities. Thereafter selection took place on the basis of Match Probability (MP), which resulted in 72 new match combinations with negative CDC cross matches in current and historic sera (8 triplets, 24 doublets) implying that 50 couples were not selected (figure 1). There was again a significant (p=0.0165) preponderance of ABO incompatible pairs in the unselected group, 31/50 vs. 28/72 in the selected group. Overall, on the basis of blood type, unacceptable HLA antigens and MP selection, the success rate in the positive cross match group was significantly (p=0.0015) higher than in the ABO blood type incompatible group (44/69 vs. 28/77). Especially the blood type

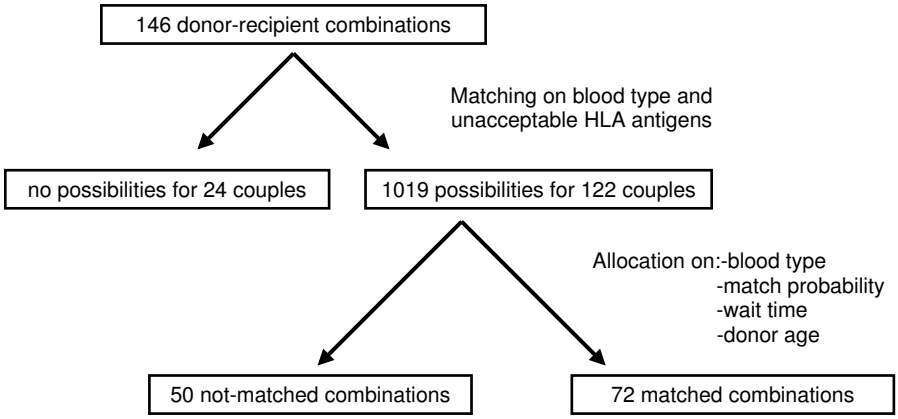

Figure 1. Matching process.

O recipients with non-O-donors were difficult to match: 9/53=17%, while the B to A and A to B combinations proved to be extremely easy to accommodate with a 100% (10/10) and 90% (9/10) success rate. Table 2 shows the characteristics of the matched versus not-matched combinations in case of positive cross match and ABO incompatibility.

	positive cross match		ABO blood type incompatible	
	matched	nonmatched	matched	nonmatched
	n = 44	n = 25	n = 28	n = 49
Gender recipients (M/F)	12/ 32	9/ 16	20/ 8	26/ 23
Gender donors (M/F)	22/ 22	16/ 9	9/ 19	20/29
Age recipient, median (range)	51(17-73)	44(15-60)	48(22-73)	52(24-73)
Age donor, median (range)	52(26-71)	50(31-60)	52(33-72)	54(35-77)
PRA% peak, median(range)	38(0-100)	60(0-100)	0(0-27)	2(0-100)
Wait time				
median months (range)	12(0-178)	25(0-96)	14(0-43)	24(0-102)
Donor type:				
Partner (M/F)	16/ 8	11/ 2	5/ 14	11/ 19
Child/ Parent	3/ 6	2/ 1	0/ 5	3/ 4
Sibling/distant relative	4/ 2	3/ 1	1/ 0	3/ 2
Unrelated	5	5	3	7

Table 2. Characteristics of matched versus nonmatched pairs in case of positive cross match and ABO incompatibility

Within the positive cross match group and the ABO blood type incompatible group we found no statistically significant effect of donor or recipient gender on matching. The overall significant difference in success rate between the positive cross match group and the ABO blood type incompatible group was only observed for female (32/48 vs. 8/31, p=0.0005) and not for male recipients (12/21 vs. 20/46, p=0.4295). Both within the positive cross match group and in the ABO blood type incompatible group the PRA of the recipients of the matched couples was significantly lower (p=0.019 and p=0.016) than that of the not-matched couples (figure 2).

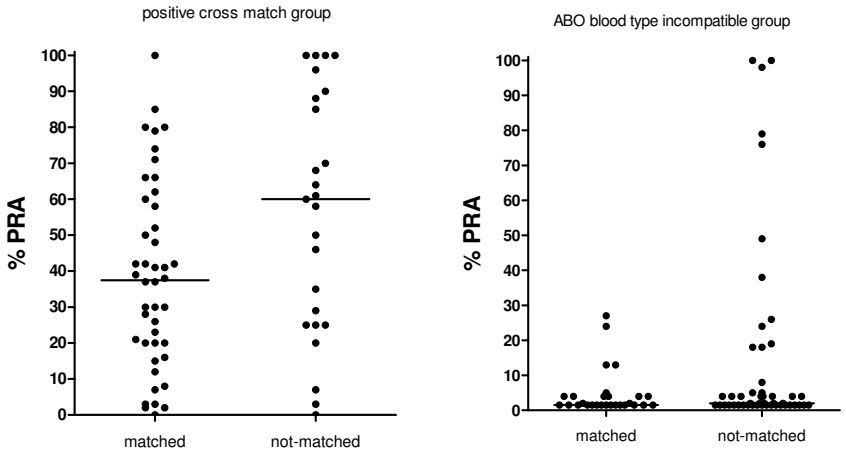

Figure 2. Peak PRA % is a determinative factor for matching both in positive cross match and ABO incompatible recipients

Wait time in the not-matched group proved to be twice as long compared to the matched group. Success rate was independent of donor/ recipient relationships: 43/86 partner combinations were successful which was comparable to the success rate of non-partner combinations. 20 of the 43 re-transplant patients were matched: 52% in the positive cross match group and 30 % in the ABO blood type incompatible group. Figure 3 shows the chances for a donor-recipient pair to find a match according to the number of allocation procedures in which they participated.

In the positive cross match group 35% of the couples were already successful in their first attempt, compared to 25% in the ABO blood type incompatible group (n.s.). After three procedures these percentages increased to 61% and 33% respectively (p=0.0008), but thereafter chances to find a match were small in both groups. From the 72 matched pairs 57 transplants are already performed and 5

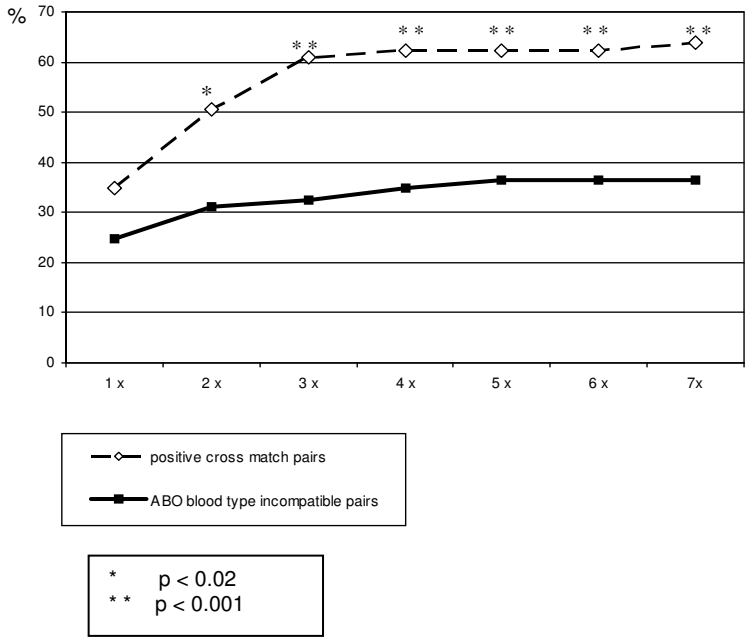

Figure 3. The chance of finding a matching couple according the number of attempts for positive cross match pairs and ABO blood type incompatible pairs

procedures are planned. One recipient died with a functioning graft (PRA 96%, waittime 5 years). We observed two graft failures despite negative cross matches): one immediate renal artery thrombosis in a patient with 0% PRA and one rejection at 4 weeks postoperatively. In 10 cases no transplantation procedure was performed because of medical or psychological problems in one of the couples that formed a selected doublet or triplet. One recipient died and three couples are currently back in the program. From the 74 not-matched pairs, 39 remained in the program while 35 others definitely left for various reasons: one recipient died, 5 recipients and 4 donors were delisted for medical reasons, 15 recipients received a deceased donor kidney, while for 10 others an alternative living kidney donor was found. Stratified for blood type, there were 10 nonmatched O recipients with O donors, 5 are still in the program, 3 couples were delisted and 2 received a kidney transplant outside the program. From the 44 O recipients with ABO incompatible donors, there are 25 in the program, 5 were delisted and 14 received another kidney transplant. Out of the 20 not-matched non-O recipients, there are 9 in the program, 2 were delisted and 9 received another kidney. Thus 25/39 (64%) of the couples that are still in the program are O recipients with non-O donors.

DISCUSSION

The present report describes the 30 months results of the successful living donor kidney exchange program in the Netherlands, in which all seven transplant centers participated. As anticipated[6], we enrolled 14-15 new donor-recipient pairs in each match procedure, which has lead to approximately 25 transplantations a year (1,6 pmp out of the 17,2 living donor transplants pmp). The majority (73%) of the potential donors were genetically unrelated which is clearly more than in the general living donor population in the Netherlands. One of the explanations for this phenomenon is the high (50%) proportion of partners in the potential donor group. While male partners dominated the positive cross match donor group, reflecting sensitization of female recipients through pregnancies, there were twice as much female partners in the ABO blood type incompatible donor group, both reflecting the positive attitude of women towards kidney donation and the higher incidence of renal insufficiency in males[8]. We were able to find new live kidney donors for almost half of the enrolled recipients and were significantly more successful for patients in the positive cross match group (64%) compared to those in the ABO blood type incompatible group (36%). In both groups PRA influenced the success rate, but still a substantial number of highly sensitized patients could be helped. In the ABO blood type incompatible group the blood type non-O to O combination was difficult to match. However, for 9/53 (17%) of these combinations we found 9 matching couples in the positive cross match group, making 18 transplantations possible. This demonstrates that combining the two categories of donor-recipient pairs increases the efficiency of a paired donor exchange program. Despite a 50% success rate we were not able to find solutions for 36% of the positive cross match couples and for 64% of the ABO blood type incompatible pairs. We observed that after three attempts the chance of finding a new donor in both categories of patients became remote. For these unlucky couples alternative solutions should be explored. The obvious first choice for the 83% unsuccessful blood type non-O to O couples is the combination of anti-B cell therapy, removal of isoagglutinins and IVIG. Especially the Karolinska protocol, which makes use of specific immunoabsorption, is patient friendly and highly successful. Unfortunately this approach is very expensive[4]. An alternative solution for the non-O to O couples is finding a blood type compatible, cross match negative, altruistic kidney donor. In this solution the incompatible non-O donor might even donate to the waitlist[9,10]. For the highly sensitized positive cross match patients the Eurotransplant Acceptable Mismatch program remains the alternative to find a deceased donor kidney. For both categories of unsuccessful donor-recipient combinations living donor list exchange is another possibility, although there is certainly no worldwide consensus on the ethical justification of such a program[11,12]. Finally desensitization protocols

using plasmapheresis, protein A columns, IVIG and anti-B cell therapy could be contemplated for those highly sensitized patients that are even unsuccessful in acceptable mismatch programs designed to find cross match negative individuals in a large deceased donor pool[5,13]. We conclude that paired living donor kidney exchange is an excellent solution and the first choice for a substantial number of recipients that cannot identify a compatible donor because of an ABO blood type – or cross match incompatibility.

ACKNOWLEDGMENTS

Without the cooperation of the seven university kidney transplantation centers this program could not have been implemented. We express our appreciation to the nephrologists, HLA-laboratories, surgeons and transplant coordinators of the University centers in Amsterdam, Groningen, Leiden, Maastricht, Nijmegen, Utrecht and Rotterdam.

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Chapter 7

Hurdles, barriers, and successes of a national living donor kidney exchange program

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Transplantation, 2008, 86: 1749-53

ABSTRACT
Living donor kidney exchange is now performed in several countries. However, no information is available on the practical problems inherent to these programs. Here we describe our experiences with 276 couples enrolled in the Dutch program. Our protocol consists of five steps; registration, computerized matching, cross matching, donor acceptation, and transplantation. We prospectively collected data of each step of the procedure. Out of the 276 registered pairs we created 183 computer-matched combinations. However, 62/183 recipients proved to have a positive cross match with their new donor, which was not predicted by the screening results of the recipient centers. Alternative solutions were found for 39 couples, resulting in a total of 160 new combinations with negative cross matches. Thereafter, due to 22 individual clinical problems, the exchange procedure had to be discontinued for 51 couples while only for 19 of them alternative solutions were found. At the end of day 128 patients had received exchange kidneys, 55 were transplanted outside the program, 59 are still on the crossover waitlist and 34 had left the program for medical or psychological reasons. A living donor kidney exchange program is a dynamic process. Many clinical hurdles and barriers are encountered that for a large part were not foreseen but should be taken into account when programs are initiated based on computer simulations. Success is dependent on a flexible organization able to create alternative solutions when problems arise. Centralized allocation- and cross match procedures are instrumental in this respect.

INTRODUCTION
Living donor kidney exchange has become an efficient solution for recipients with a blood type or crossmatch incompatible donor. In Asia (1), the USA (2) and Europe (3) several centers implemented paired exchange programs and developed computerized matching programs for that purpose. In the last year several proposals were published to expand paired kidney donation programs through optimization of algorithms or by enrolling compatible pairs (4,5). Most of these proposals are based on computer simulations and theoretical analyses, but do not take into account the practical clinical day-to-day problems inherent to these exchange programs. Examples are discrepancies in defining unacceptable HLA antigens, deteriorating clinical condition of potential recipients, and withdrawal of donor consent. In the Netherlands the seven transplant centers embarked on a kidney exchange program in 2004 according to a common protocol (6). The procedure exists of five steps: 1. registration, 2. computerized matching, 3. cross-matching, 4. acceptation of the exchange donors by the transplant centers, 5. transplantation. We here describe the hurdles and barriers we encountered during each step of the procedure.

METHODS

The Dutch Transplant Foundation performs a computer match procedure every 3 months. For registration molecular typing of HLA antigens and screening results for HLA alloantibodies using standard complement dependent lymphocytotoxicity (CDC) and ELISA were required as described before (3). In 2004 it was only possible to match combinations of two pairs; from 2005 the computer matched combinations of up to three donor-recipient pairs, while from October 2007 the computer program was able to make chains up to 17 combinations, but for practical logistic reasons we limit the number of combinations to maximally four. We selected these combinations on 6 preset conditions with the following hierarchy (7): 1. maximum number of matched pairs, 2. blood type identical before blood type compatible to be sure that blood type O donors preferentially donate to blood type O recipients, 3. difficult to match sensitized recipients first based on match probability (MP) (8). The MP takes into account the prevalence of donors with compatible ABO blood types and acceptable HLA antigens for the recipient within each actual match procedure. The recipient with the lowest MP, thus with the smallest chance of finding a compatible donor in that match run, is ranked first, 4. short chains are preferred above longer chains, for example rather two doublets than one quartet, 5. recipients preferably spread over multiple centers instead of performing all surgical procedures in one center, 6. patients with the longest wait time on the deceased donor kidney waitlist, calculated from the first day of dialysis. The final report of the computer match will be send to the National Reference Laboratory for Histocompatibility, where cross matches are performed between recipients and their new donors with the standard CDC-assay and by flow cytometry. If a crossmatch between a recipient and a new donor becomes positive, the computer program will generate alternative combinations and additional crossmatches are performed. If the computer can find no other combinations, the match procedure stops. After 4 to 8 weeks the reference laboratory reports the combinations with negative cross-matches to the Dutch Transplant Foundation. They inform the transplant centers about the match results, chain length (the number of pairs in an exchange) and the centers involved. The coordinator of each center will inform the matched donor-recipient pairs where the donation will take place. Then the donor travels to the other center for final acceptation. The serological crossmatch is repeated once more by the local tissue typing laboratory. Finally the surgical procedures will take place simultaneously. Evidently not all couples who are enrolled in our program can be matched to another pair. Moreover, even when matched, this may not always lead to a successful exchange procedure. We collected in our database the reasons for that.

RESULTS

Registration

From January 2004 until July 2008, 276 donor-recipient pairs were enrolled in our kidney exchange program. One hundred thirty-three couples participated because of a positive crossmatch, in 143 cases donor and recipient had an ABO blood type incompatibility. The median wait time on the Eurotransplant waitlist was 13 months (range 0-281) in the positive crossmatch group and 17 months (range 0-121) in the ABO incompatible group. The median age of the recipients was 51 years (range 17-73) and that of the donors 54 years (range 22-78). Spouses dominated the donor group (161/276; 58%). The second largest subgroup (n=41; 15%) were friends. Other groups like parents (10%), siblings (8%), child's (6%) or other family members (3%) were smaller. The blood type distribution of donors and recipients are shown in Table 1. In the positive crossmatch group, the majority of the donors (89/133, 67%) had blood type O with either O recipients (n=50) or with non-O recipients (n=39). As expected the most frequently encountered combination in the ABO blood type incompatible group had recipients with blood type O (99/143; 69%). The second largest group were A to B or B to A combinations (40/143, 28%).

Blood type incompatible pairs						Positive cross match pairs					
	Patient						Patient				
Donor	O	A	B	AB	Total	Donor	O	A	B	AB	Total
O	-	-	-	-	-	O	50	27	11	1	89
A	87	-	22	-	109	A	-	38	-	3	41
B	10	18	-	-	28	B	-	-	3	-	3
AB	2	3	1	-	6	AB	-	-	-	-	-
Total	99	21	23	-	143	Total	50	65	14	4	133

Table 1. Blood type distribution of the 276 donors and recipients

Median panel reactive antibody (PRA) of the recipients was 49 % (range 2-100%) in the positive cross match group and 2% (range 0-100%) in the ABO blood type incompatible group. With these 276 donor-recipients pairs 18 match procedures were performed over 4.5 years. The median input of new candidates per match run was 14 (range 7 – 22 pairs). The median number of couples participating in a match run was 47 (range 16 -66 pairs). The median input per center over the years was 34, range 17-76. Figure 1 shows the proportional input into the exchange program per center in relation to their proportional enrolment in the overall Eurotransplant waitlist.

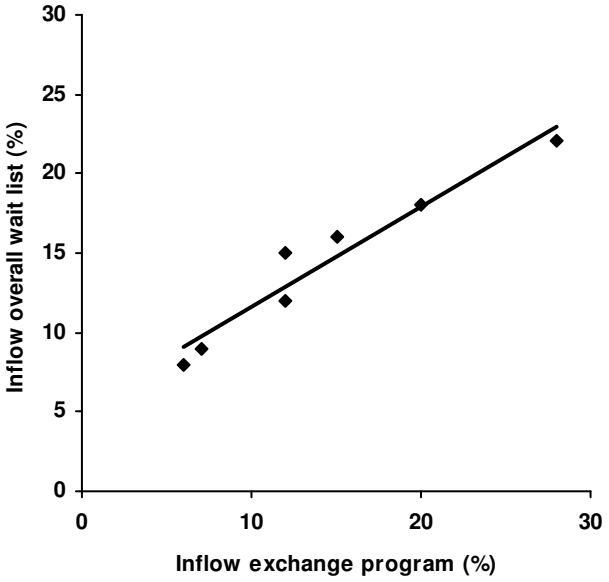

Figure 1. Proportional enrolment of patient into the exchange program by the various centers in relation to their overall waitlist enrolment

Computerized matching and crossmatching

Our computer program was able to find match possibilities for 183 couples. Of these 183 computer-matched combinations 121 pairs proved to have negative crossmatches (figure 2). Unfortunately, for 62 newly matched couples crossmatches became positive, which was not predicted by the unacceptable HLA mismatches defined by the screening results of the local tissue typing center. In case of a positive crossmatch, the reference laboratory, in collaboration with the local tissue typing center, redefined the unacceptable mismatches of the patient on basis of the HLA type of the donor, who gave the positive cross match, and additional antibody screening. For 39 of 62 pairs with a positive crossmatch alternative combinations with negative crossmatches were found, but for 23 of them this was not possible. Thus, the primary selection procedure resulted in a total of 160 (121+39) new combinations. However, for several reasons, later to be discussed, 51 of these 160 couples did not proceed to a kidney exchange. Only for 19 of them alternative solutions could be created. This required of course additional crossmatching. At the end of the day, a total of 333 crossmatches were needed to make 128 exchanges possible. Of these crossmatches 240 were negative and 93 positive.

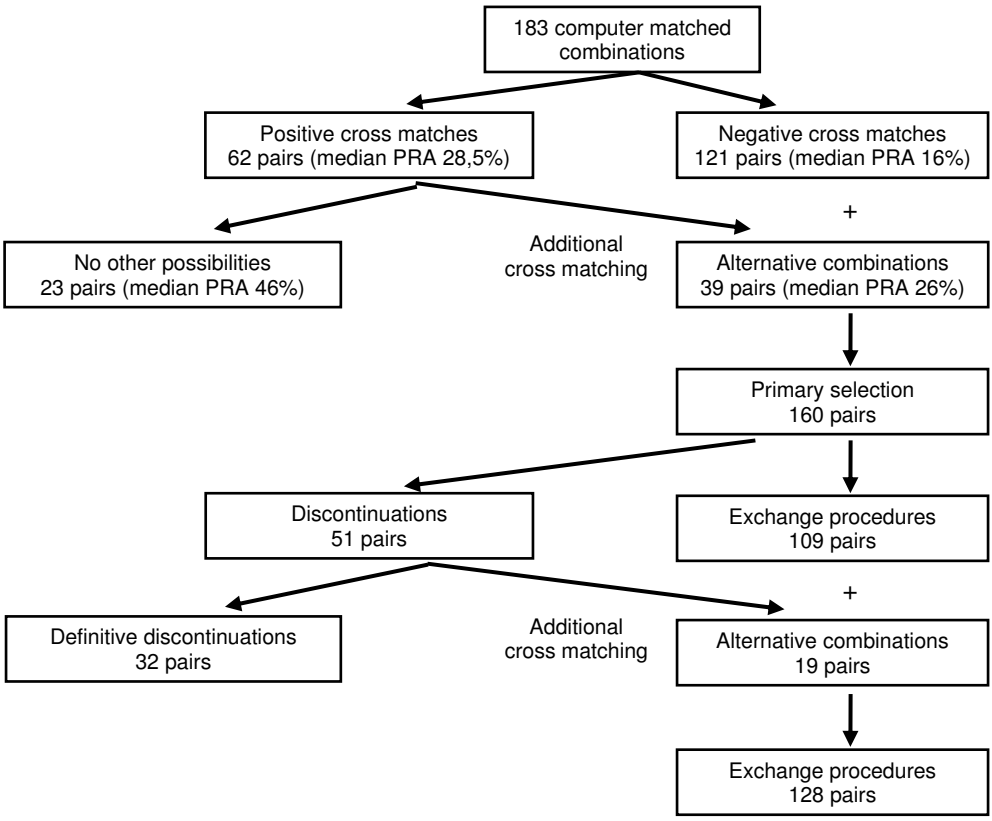

Figure 2. Cross match procedure

Discontinuation of procedures

The primary selection of 160 pairs resulted in 109 exchange procedures. However, for 51 of 160 couples, allocated to nine duets, seven triplets and five quartets, individual clinical problems resulted in discontinuation of the procedure. Reasons for discontinuation included 11 medical complications in the recipient and 11 donor-related problems. In seven instances the medical complication of the recipients was severe enough to remove them from the program definitely (cardiovascular problems in 5, malignancy in 2). Four recipients had temporary problems (peritonitis, car crash and 2 cardiovascular) and returned into the program at a later moment. Interestingly, 5 donors withdrew consent after hearing that donation was actually possible in the exchange program (median wait time in the match program 3 months). Three other donors left the program after being refused by a recipient center because of a body mass index of 34, the interpretation of renal function, and a complex vascular anatomy, respectively. In addition three extra donors were also not accepted for reasons of vascular anatomy, the classification of a Bosniak cyst and a 40% to 60% difference in function between right and left kidneys. However,

these three donors were accepted for an alternative recipient by another center. For 19 of the 51 couples in whom the exchange procedure was broken off, we found a second matching pair in the same match run (n=7), or at a later stage (n=12). This resulted in 19 extra transplants, bringing the total of exchange procedures to 128. These combinations consisted of 30 duets, 20 triplets and 2 quartets. Of the remaining 32 couples, 15 left the program immediately, 10 are still on the waitlist, 5 patients received a kidney transplant outside the exchange program, and 2 donors withdrew consent at a later moment (figure 3).

Transplant results

During follow-up 3 patients died with functioning kidney (PTLD n=1, infection n=2). Seven other failures include 2 vascular problems, 2 early and 1 late acute rejection and 2 chronic allograft nephropathy. This resulted in an uncensored all over 5 years survival of 89 % (figure 4).

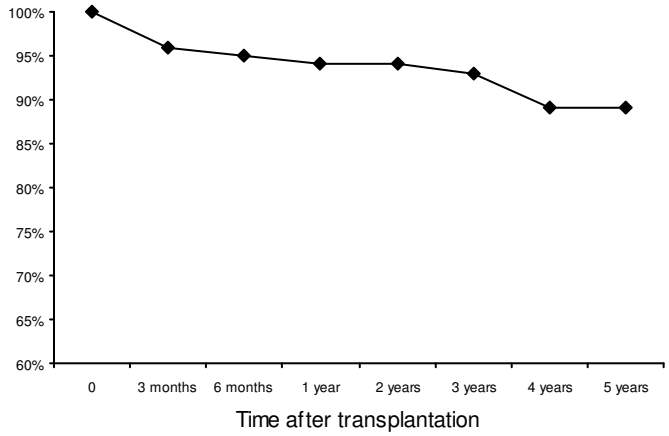

Figure 4. 5 years graft survival rates for kidney transplants performed in our kidney exchange program

Not-matched pairs

For 116 couples, we were not able to find crossmatch negative exchange solutions. Compared to the 160 matched couples, the not-matched group was dominated by ABO incompatible pairs (71% versus 38% in the matched group, $p < 0.001$). Especially the O recipients with non-O donors had a small chance to become matched (26%). In the positive crossmatch candidates, the level of sensitization was significantly higher in the not-matched (PRA 64%) than in the matched group

(PRA 42%). During follow-up 67 couples left the program: 17 of them had to be delisted for 12 medical or psychological complications in the recipient (deceased in 3, cardiovascular problems in 2, and psychological stress in 7), and 5 donor related problems (diabetes, thrombosis and withdrawal of consent in 3). The other 50 recipients were transplanted outside the exchange program: 24 patients with a deceased donor kidney and 26 with a kidney from an alternative living donor, within an ABO- blood type incompatible program or in a domino-paired program with an altruistic donor. The remaining 49 pairs are still waiting in the program (figure 3).

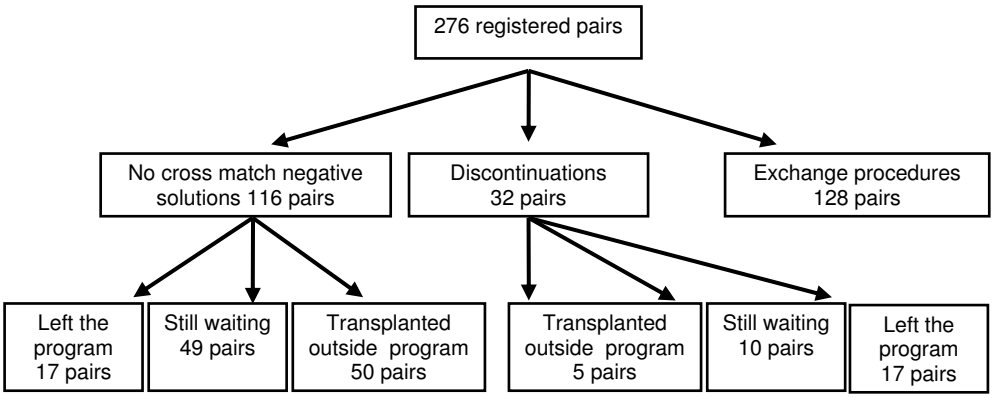

Figure 3. Follow-up of discontinued and not-matched pairs

DISCUSSION

In the present report, we describe the hurdles, barriers, and successes of a kidney-exchange program. First, we managed to cooperate closely with seven transplant centers that undertook a comparable registration activity in the exchange program. Indeed, the enrolment by the various centers paralleled their proportional input on the overall waitlist. However, it is clear that after registration a number of unforeseen problems were encountered. An important issue in the crossmatch procedure is the high percentage of crossmatches that became positive. One positive crossmatch can be responsible for breaking up triplets and quartets already containing crossmatch negative combinations. Due to the fact that all crossmatches are performed in one central HLA laboratory, we were able to continue the procedure with additional crossmatches in new combinations. For 39 of the 62 pairs, we succeeded in finding alternative combinations with negative crossmatches. However, to diminish the percentage of positive crossmatches,

more stringent criteria for the definition of nonacceptable HLA-mismatches in sensitized recipients, will be defined by the national reference laboratory. After the primary selection procedure that resulted in 160 new combinations with negative crossmatches, we observed 22 clinical problems that necessitated discontinuation of the exchange procedure for 51 couples. Reasons for discontinuation were equally divided between donor- and recipient-related problems. While recipient-related problems were all inherent to the complications of renal insufficiency, it is of interest that withdrawal of consent was a main donor-related reason for discontinuation. Although withdrawal of donor consent occasionally occurs in direct kidney donation procedures too, in the present program five selected donors and, in a later stage, five additional nonselected donors (10/276, 3.6%) left the program for that reason. Apparently, a donor kidney exchange program induces too much psychosocial stress in a relevant number of donors, because the medical excuse of incompatibility no longer existed or because of the uncertainty due to long waiting times. In theory, psychosocial evaluation might prevent donor attrition, although we have not found hard data to support this (9). There is a small chance (4%) that the recipient center will not accept a crossover donor for their patient. Some of these problems could have been prevented when centers had been given the opportunity to specify donor requirements up-front. In this way these donors would not have been offered by the computer program. However, in our program half of these donors were accepted in another center for another recipient. For 19 of the 51 couples in which the exchange procedure was discontinued we were successful in finding an alternative. Again the combination of our computerized selection algorithm and the centralized crossmatch procedure were essential for this. Alternative living donation programs, for example, ABO blood type incompatible transplants, and altruistic Good Samaritan donations allowing domino-paired procedures, may potentially interfere with a paired kidney exchange program. Indeed, 22 recipients who were enrolled in our program received a kidney, while their donors donated a kidney, in these alternative programs. However, these 22 couples had at least three times participated in crossover match runs in an attempt to be of help for other crossover candidates. Finally, it should be mentioned that this program is an additional option. Searching for other living donors should continue, while patients should also remain on the waitlist for a deceased donor kidney. At the end of the day, 183 of 276 (66%) registered patients received a donor kidney within (n=128) or outside (n=55) our program. Therefore, we feel that our program made kidney transplantations possible that were otherwise not feasible. With this report we make clear that a living donor kidney exchange program is a dynamic process. Many hurdles and barriers were encountered that were unforeseen but should be taken into account when programs based on computer simulations are initiated. Barriers may be avoided by better defining

nonacceptable HLA mismatches and by better selection of donors and recipients before each match run. Hurdles will always be there, but can be overcome by a flexible organization that is able to create alternative solutions when problems arise. Centralized allocation and crossmatch procedures are instrumental in this respect.

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Chapter 8

Justification for anonymity in a kidney exchange program

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In: Weimar W, Bos MA, Busschbach JJ (Eds). Organ Transplantation: Ethical, Legal and Psychosocial Aspects. Towards a common European policy. D-49525 Lengerich: PABST science publishers, 2008, 236-240

ABSTRACT
In January 2004 all 7 Dutch transplant centers embarked on a common living donor kidney exchange program. In the literature there is no agreement about the issue of anonymity between the couples. In 2003 we performed a pilot-study and found that potential donors and recipients preferred anonymity. We wondered whether this pretransplant preference for anonymity still existed after the exchange procedures were actually performed. Methods and patients: The study group consisted of 15 recipients and 14 donors. We used separate questionnaires for recipient and donor. Results: Only 1/14 of the donors was explicitly interested in the identity of the person to whom they had donated their kidney, while 4/15 (27%) of the recipients were interested in the person from whom they had received a kidney. 17 participants responded negatively if there would come a request from the other transplanted couple for a meeting. Finally, we asked them for their preference if they had to participate a second time in an exchange program. 69 % preferred anonymity. Conclusion: After transplantation/donation the majority of donors and recipients were satisfied with anonymity. Therefore we will adhere to anonymity in the Dutch kidney exchange program.

INTRODUCTION
In 1986 it was Rapaport who first suggested the possibility of cross-over kidney transplantation (1). His preconditions to carry out this form of transplantation included anonymity between both donor-recipient pairs. This was only a suggestion, he never materialised his ideas. The first real kidney exchange program was started in 1991 by Park in South-Korea (2). In South-Korea postmortal kidney transplants is socially nor legally accepted and thus transplantation programs are dependant on living donations. Cross-over kidney transplantation was a necessity for incompatible couples. One of Park's preconditions was a meeting between the pairs, because both operations took place in one center. In 1999 Thiel and Kirste carried out the first cross-over kidney transplantation in Europe. The two donor-recipient pairs (one German couple and one Swiss couple) had to get acquainted because of the German law (3). In the U.S.A. several small programs resulted in a total of 85 exchange procedures from 2000 – 2006, thus in 170 transplantations within seven years (4). However, still no consensus on anonymity exists. In January 2004 all seven Dutch transplant centers embarked on a common living donor kidney exchange program. In the preparation of this national endeavour we performed a pilot in 2003 in which we asked 14 potential donor-recipient pairs about their wishes to meet their exchange couple (5). All of them preferred anonymity. So in the Netherlands we decided to perform our program on an anonymous basis. Now 3 years later we wondered whether this pre-transplant preference still existed after the surgical procedures

were actually performed. Moreover, we questioned if they were curious about the identity of the other pair and their kidney function, their feelings about the indirect donation/transplantation and their interest in a meeting with the other couple.

PATIENTS AND METHODS

Study group

Our study group consisted of fifteen recipients and fourteen donors. One donor went back to Turkey after the donation and it was not possible to include him in our study. In four cases the reason to participate in the exchange program was a positive cross match and in 11 cases ABO blood type incompatibility. The blood type distribution of the donors and the recipients were diverse. The four positive cross match pairs consisted of two A to A combinations, one O to O combination and one O to A combination. For the ABO blood type incompatible pairs the A to B and the B to A combination was most frequently seen (7 pairs), followed by two B-O, one A-O and one AB-O combination. The majority of the couples were partners (n=11), there were three parent-child combinations and one time donor and recipient were good friends. Nine females and five males donated their kidney. The median age of the donors was 55 years (34 – 71 year). The group recipients consisted of eight males and seven females. Before the transplantation the kidney patients had a median wait time of 9 months on the cadaveric waitlist (range 0 – 37 months). The oldest recipient was 72 years, the youngest 22 years (median 48). The median PRA was 4 % (range 0 – 74 %).

Questionnaire

On the moment of the interview the shortest period after the surgical procedure was 1 month and the longest 3 years and 7 months (median 2 years). For the interview we used separate questionnaires for recipient and donor (Table 1). The subjects of this questionnaire were: interest in the other persons, the kidney function, agreement on a meeting with the other couple, feelings about donation via strangers and the preference for anonymity if they should have to participate a second time in an exchange program.

RESULTS

The majority of the recipients (73%) and also of donors (64%) were not interested in the identity of their cross-over donor respectively their recipient. There was only one donor interested in the person who received his own kidney, while four donors were curious about the identity of the person from which their partner received a kidney. There was only one couple of which both partners explicitly indicated their

Table 1. The questions and answers of recipients and donors

Question	Response categories	recipients n = 15	donors n = 14
1a) Do you want to know the identity of your cross-over donor/recipient?	a. yes	4	1
	b. probably yes	0	4
	c. probably no	1	3
	d. no	10	6
1b) Do you want to know the identity of the recipient/donor of your partners kidney?	a. yes	4	4
	b. probably yes	0	1
	c. probably no	2	4
	d. no	9	5
2a) Do you want to know the results of the transplantation in the recipient of the other couple?	a. yes	4	6
	b. probably yes	2	1
	c. probably no	2	3
	d. no	7	4
2b) Do you give us permission to inform the other couple about your or your partners transplantation?	a. yes	12	11
	b. probably yes	2	2
	c. probably no	1	1
	d. no	0	0
3) Do you agree to meet the other couple on their request?	a. yes	4	4
	b. yes, if my partner agree	2	2
	c. probably no	4	4
	d. no	5	4
4) You've indirectly received/ donated a kidney, while of the following descriptions suits you?	a. as if I received/donated directly	9	10
	b. a bit awkward, but minor problem	2	4
	c. a problem because another couple is involved	0	0
	d. quite comfortable to received/donated directly	4	0
5) Now you have received/donated, do you still prefer our program to be on an anonymous basis?	a. yes	10	10
	b. no	1	2
	c. doubts	4	2

preference for non-anonymity because they wanted to express their thankfulness. A number of donors (6/14) showed interest in the results of the transplantation of their own organ in the cross-over recipient, while almost no recipients or donors had objections against informing the other couple about the results of their (partner's) transplantation. However, a meeting with the other cross-over couple was denied by 9/15 recipients and 8/14 donors, while only 4/15 recipients and 4/14 donor full heartedly accepted such an offer from the other couple. Remarkably, all recipients and donors fell that indirectly receiving or donating a kidney was not a huge problem: it felt like giving or receiving in a direct way. Four kidney patients even indicated that they felt quite comfortable with the indirect way of being transplanted. Only 3/29 respondents, including one donor-recipient couple, preferred non-anonymity.

DISCUSSION

In the present study we asked the transplanted patients comparable questions about their interest in age and gender of their donors as we did in our pilot study of 2003, where we interviewed cross-over candidates. The answers were rather similar; 4/13 potential recipients in the 2003 study versus 4/15 recipients in the present study were eager to know the identity of their donor. Thus the majority of the respondents in both studies were satisfied with the anonymous character of our program. Donors were even less curious. Only one donor wanted to know more about the person to whom she had donated her kidney, but four donors (three partners and one mother) were anxious to know about the person from whom their partners/son had received a kidney. Apparently the origin of the transplant in their partner/son was more of their concern than recipient of their own kidney. The second subject in our questionnaire regarded the results of the transplant procedure in the recipient of the other couple. We asked about this issue in our pilot study in 2003 too. At that time 9 of the 13 potential donors (69%) thought that they would be interested in the function of their donated kidney. In the present study, after the actual donation, only 6 of the 14 donors (43%) responded positively. Maybe their curiosity had faded away, as donors were interviewed at a median time of two years after the procedure. Four recipients were interested in the fate of other cross-over recipient, explaining they were partners in distress. However, seven recipients did not want to be informed on the results of the transplantation in the recipient of the other couple, because they were afraid to become disappointed in case of complications. The present study is of particular interest because of the answers on the question concerning a meeting with the other pair on their request, which we compared with the answers on the question about their own explicit preference for getting acquainted. 8/29 respondents,

including three donor-recipient pairs would agree on such a meeting. 5/29 agreed on a single meeting only at the request of the other couple. 3/29 respondents, including one couple, indicated that such a meeting should take place on their own request. Another fascinating finding in our study concerned the four recipients (two partners, two children) who felt quite comfortable receiving a kidney indirectly. An explanation given was that they would not feel guilty to an unknown donor in case their graft failed. Another recipient was happy to know that an exchange procedure was able to help two patients. The latter argument could be a reason to explore the feasibility to include compatible donor-recipient pairs in an exchange program. In that way one living donor can made two transplantations possible. Finally we inquired at the preference of donor and recipient for anonymity after they had actually donated or received a kidney. Only one couple preferred non-anonymity. This is in line with the results of our 2003 interview in which all donors and recipients indicated to have no objections against anonymity. We can conclude that the majority of the kidney exchange pairs were still happy with anonymity after the transplantation. Therefore we will stick to the anonymous character of the Dutch Kidney Exchange program.

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Chapter 9

The optimal chain length for kidney paired exchanges

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Transpl Int. (in press)

ABSTRACT
Background: Living donor kidney exchange programs offer incompatible donor-recipient pairs the opportunity to be transplanted. To increase the number of these transplants, we examined in our actual donor-recipient couples how to reach the maximum number of matches by using different chain lengths.
Methods: We performed 20 match procedures in which we constructed four different chain lengths: two, up to three, up to four and unlimited. The actual inflow and outflow of donor-recipient couples for each run were taken into consideration in this analysis.
Results: The total number of matched pairs increased from 148 pairs for only 2-way exchanges to 168 for 3-way exchanges. When a chain length of 4 was allowed 5 extra couples could be matched over a period of 5 years. Unlimited chain length did not significantly affect the results.
Conclusion: The optimal chain length for living donor kidney exchange programs is three. Longer chains do not lead to significantly more transplants.

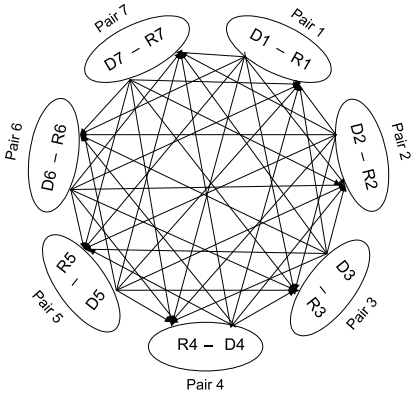
INTRODUCTION

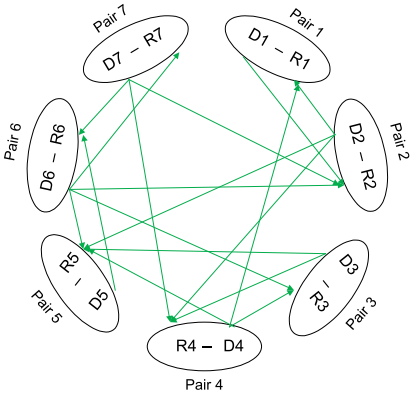
Transplantation with a living donor has emerged as the best option for patients with an end-stage renal disease. Unfortunately, some transplant candidates do not have a suitable donor due to ABO blood type incompatibility or a positive cross match. An alternative for these pairs is participation in a living donor kidney exchange procedure. In Asia, United States and Europe kidney exchange programs were developed under different conditions and with different exchange algorithms (1,2,3). In 2005 Segev et al reported their exploration to find the optimal number of new combinations based on the Edmonds algorithm theory (4). Interestingly, this theory was based on ancient Chinese calculations to minimize the lengths of routes walked by mail carriers (5). The basic principle is that an algorithm considers every feasible solution, compares these solutions, and picks the one that best meets a set of individualized priorities. The group of Delmonico reported comparable studies with an algorithm based on the theory of Edmonds. Both algorithms were tested for efficacy using simulated but not actual donor-recipient combinations opting for a kidney exchange (6,7). However in Europe, Johnson et al used an algorithm whereby all possible exchanges were selected based on a points scoring system. The criteria used in the scoring system are distance between the exchange centers, % PRA, the number of HLA-mismatches and donor age differences (8). We wondered how to optimize the Dutch kidney exchange program with an algorithm that was flexible enough to create chains of unlimited length and used the data from the 312 couples that were enrolled in our program from January 2004 till December 2008.

METHODS

Computerized matching

We embarked on a kidney exchange program in January 2004 (3). Our National protocol was based on a consensus between the seven Dutch kidney transplant centers on registration, allocation and surgical procedures. Allocation was performed by an independent organization, the Dutch Transplant Foundation, according to a computerized algorithm. Surgical procedures were performed simultaneously while the donor travelled to recipient center and a strict anonymity between pairs was kept. All cross matches between new matched donors and recipients were performed centrally by the National Reference Laboratory for Histocompatibility. By registration we collected data including name, date of birth, ABO blood type, gender and HLA typing of donor and recipient, the percentage panel reactivity antibody (PRA) and specificity of alloantibodies determined by standard complement dependent lymphocytotoxicity (CDC). Medically suitable donor-recipient pairs were registered four times a year in January, April, July and October. In January 2004 the computer program created on the basis of ABO compatibility and alloantibodies kidney exchanges between two couples, doublets. The highest possible number of doublets was manually selected from this list of possible exchanges while ensuring each enrolled couple would only be selected once. In 2005 the match program was changed making exchanges with two and three pairs possible. In October 2007 we changed the computer program algorithm once more in order to find even larger exchanges whereby a single exchange procedure consists of creating chains of couples whereby each donor donates to the recipient of the next couple and the donor of the last couple in the chain donates back to the first recipient in that chain. The program allowed unlimited chain size, although for practical reasons it was limited to a maximum of four. With the possibility of creating larger chains, the number of combinations made it impossible to manually select the exchanges to proceed with. Therefore additional steps were added to the computer program. In the first step the computer program searches for each donor in that particular match run to which recipients he can donate (Figure 1). Thereafter these separate combinations (donor with new recipient) were used to make all possible chains with different sizes (Figure 2). Then the computer program selected all possible groups of chain combinations without a couple appearing in more than one chain combination. Since the program finds all possible chain combinations, the number of results explodes even further leading to a million possibilities when 50 couples are enrolled. This is why the program ranks all these possible groups according to a preset set of conditions (Figure 3).





All combinations

D1 → R2, R3, R4, R5, R6, R7

D2 → R1, R3, R4, R5, R6, R7

D3 → R1, R2, R4, R5, R6, R7

D4 → R1, R2, R3, R5, R6, R7

D5 → R1, R2, R3, R4, R6, R7

D6 → R1, R2, R3, R4, R5, R7

D7 → R1, R2, R3, R4, R5, R6

Possible new combinations

D1 → R2

D2 → R1, R4, R5

D3 → R4, R5

D4 → R1, R3, R5

D5 → R6

D6 → R2, R3, R5, R7

D7 → R2, R4, R6

Figure 1.
Example of 7 pairs in a match run: all donor-recipient combinations are analysed resulting in possible new combinations

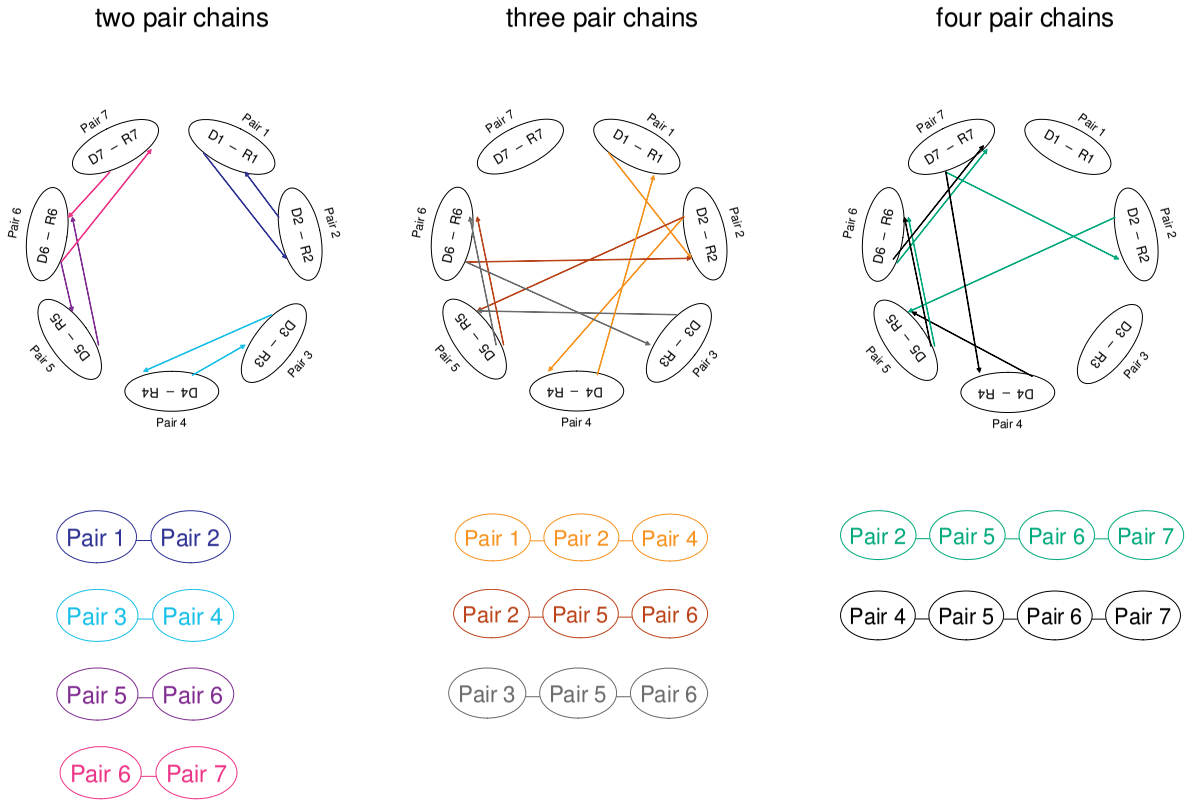


Figure 2.
With the possible new combinations chains with different sizes are constructed

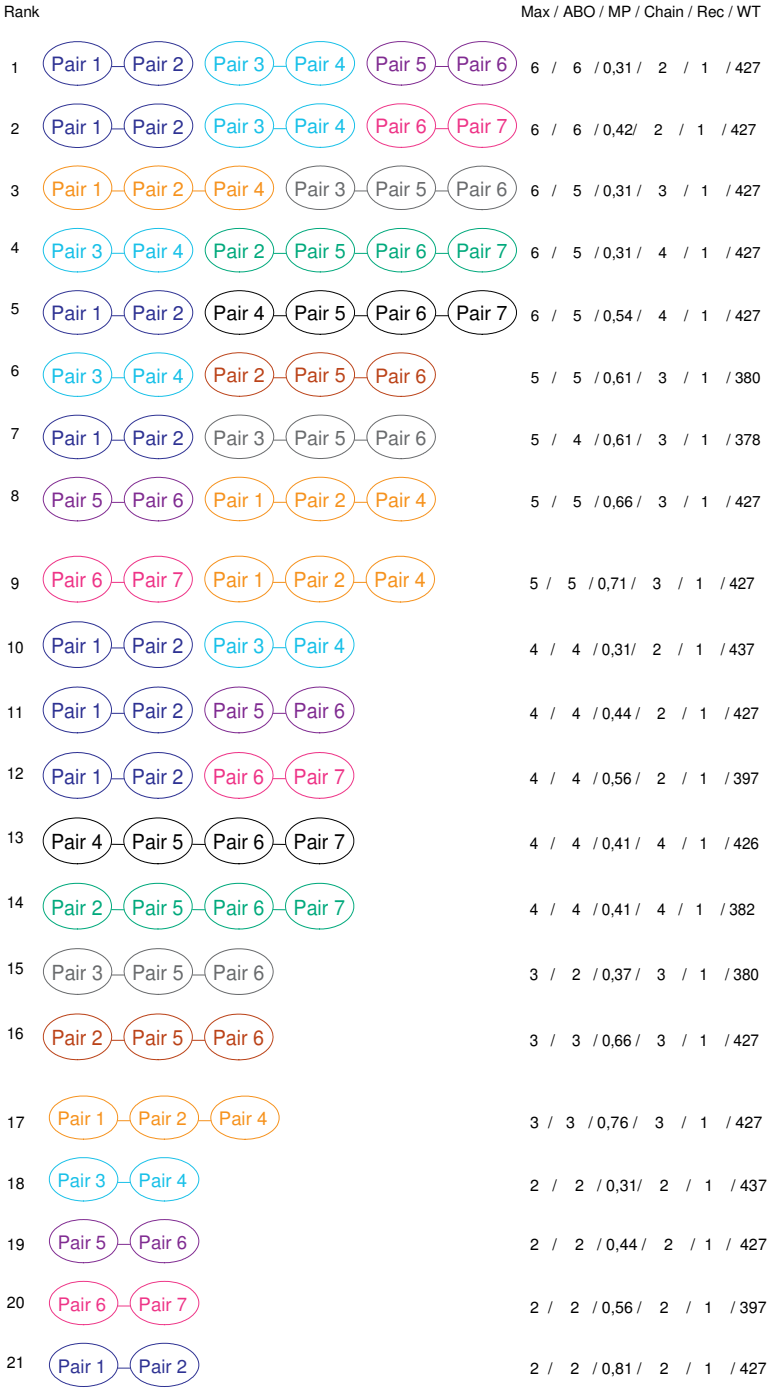


Figure 3. Groups of possible chain combinations are ranked according to preset conditions. A pair can participate only once in each group

We used 6 preset conditions for allocation, first the maximum number of matched pairs. Within the various groups with maximum number of pairs, the group with the highest number of blood type identical exchange pairs is selected. Thus blood type O donors will preferentially donate to blood type O recipients, 3. the next ranking criteria is the match probability (MP). The MP takes into account the prevalence of donors with compatible ABO blood types and acceptable HLA antigens for the recipient within each actual match procedure. The potential recipient with the lowest MP, which is the recipient with the smallest chance of finding a compatible donor in that match run, is ranked first. Thus preferences are given to difficult to match highly sensitized patients, 4. short chains are preferred above longer chains, for example rather two doublets than one quartet, 5. recipients preferably spread over multiple centers instead of performing all surgical procedures in one center, 6. patients with the longest wait time on the deceased donor kidney wait list, calculated from the first day of dialysis. There is no further prioritisation according to HLA mismatches, serology of cytomegalovirus (CMV) or donor-recipient age differences. In case of impossibilities to continue with the selected group of exchange combinations, e.g. because of a positive cross match or clinical contra indications, the next highest ranking group with the maximum number of participants is used. This can demonstrated in figure 3. When a positive cross match is found between pair 1 and pair 2, solutions 1, 2, and 3 will not be possible and the highest ranking solution is number 4. Thus there is no need to run a new computer match procedure.

Analysis

As our computer program has the flexibility to vary the maximum chain length, we have the opportunity to analyse the impact of the maximum chain length on the total number of newly created matches. We used data from the 312 actual couples that had participated in our program to compare the effect of four different maximum chain lengths: two, up to three, up to 4 and unlimited. From January 2004 till December 2008 we had performed 20 match runs with a median of 48 participants (range 16-85). The median input of new candidates per match run was 15 (range 7-22). The 312 enrolled donor-recipient pairs consisted of 169 blood type incompatible pairs and 143 positive cross match pairs. The median PRA of the 143 recipients in the positive cross match group was 50% (2-100%). Out of the 312 enrolled pairs we were able to transplant 131 patients with an uncensored all over 5 years survival of 89%. In the present analysis we again performed 20 match procedures, but with 4 different maximum chain lengths and couples were enrolled in the same match run as in reality. When temporary medical contra indications prohibited couples to participate in one or more match procedures, they were also excluded for these specific runs for this analysis. A number of donor-recipient pairs

definitely left the program because of an alternative kidney transplantation or due to recipient or donor related complications. All these factors were taken into account in the present analysis. For the recipients an up to date screening dataset with unacceptable HLA antigens was available to exclude the occurrences positive cross matches between recipients and their new donor.

RESULTS

The match results of the four different procedures are shown in Table 1.

chain length	ABO blood type incompatible pairs n = 169	positive cross match pairs n = 143	Total n = 312
2	59 (35%)	89 (62%)	148 (47%)
up to 3	63 (37%)	105 (73%)	168 (54%)
up to 4	66 (39%)	107 (75%)	173 (55%)
Unlimited	67 (39,6%)	108 (75,5%)	175 (56%)

Table 1.

New solutions for ABO blood type incompatible pairs and positive cross match pairs in various procedures

The total proportion of matched pairs per process increased from 47% for 2-ways exchanges to 56% for any size of exchanges. If only exchanges involving 2 donor-recipient pairs are allowed, a maximum of 148 pairs in the data set could exchange kidneys in 74 doublets. If the computer created matches up to 3 pairs, this resulted in a 14% (20/148) increase to 168 matches consisting of 27 doublets and 38 triplets. The procedure with a chain length up to 4 found for 173 recipients a match be made of 31 doublets, 13 triplets and 18 quartets. The increase from maximal 3-ways to maximal 4-ways is 3% (5/168). When unlimited exchanges were made possible the number of matched pairs was 175: 26 doublets, 15 triplets, 6 quartets, 5 quintets, 2 sextets, 1 septet and 1 chain with 10 pairs. This resulted in only 2 more exchanges compared to the maximal 4-way exchanges. There were 143 donor-recipients pairs who were matched in all the four different processes. Thus 5 patients were only selected in the two-ways procedure and not anymore when larger chains were created. On the other hand longer chains made 25 – 27 alternative combinations possible, resulting in a total of 20 – 27 more new pairs compared to the 2-way only system. In the total ABO blood type incompatible group we observed a 14% increase in success rate when larger chains were allowed. In the subgroup with non-O recipients an optimal chain length of four pairs

was found, while for the subgroup with O recipients the optimum was already reached with up to 3-way exchanges (Table 2a). In the total positive cross match group we found a 21% increase in success rate when larger chains were allowed. An increase was virtually restricted for the original O-O and A-A combinations (Table 2b). If we looked for the median PRA for the matched immunized patients in the positive cross match group there is a small effect of the different procedures, respectively 39%, 46%, 46% and 48%. Figure 4 shows in three different groups the chances for a couple to find a match in relation to the number of allocation procedures in which they participated. We observed that for the positive cross match group and the non-O recipients in the ABO blood type incompatible group the chance to find a match did not increase after three or four attempts. The couples with an O recipient in the ABO blood type incompatible group showed a steadily but only slightly growing success rate.

Table 2

a. New solutions for the original blood type donor-recipient pairs in the ABO blood type incompatible group

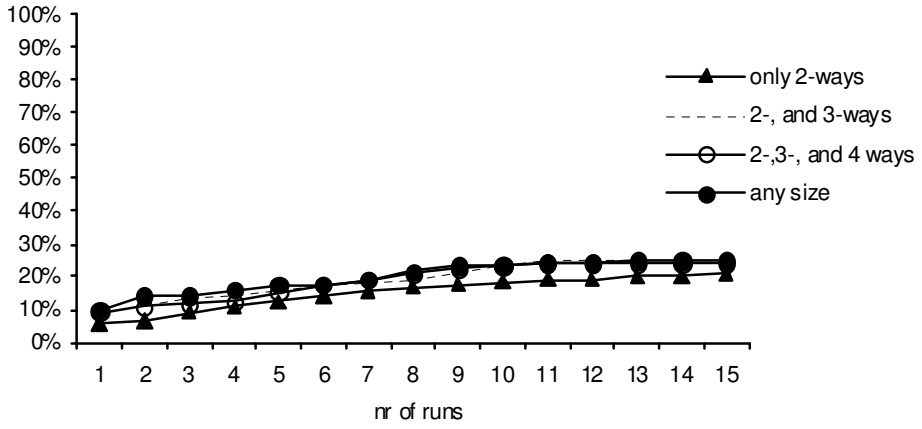
	chain length			
blood types donor-recipient pairs	2	up to 3	up to 4	unlimited
B-A,A-B,AB-A,AB-B n = 49	34 (69%)	33 (67%)	37 (76%)	37 (76%)
B-O, A-O, AB-O n=120	25 (21%)	30 (25%)	29 (24%)	30 (25%)

b. New solutions for the original blood type donor-recipient pairs in the positive cross match group

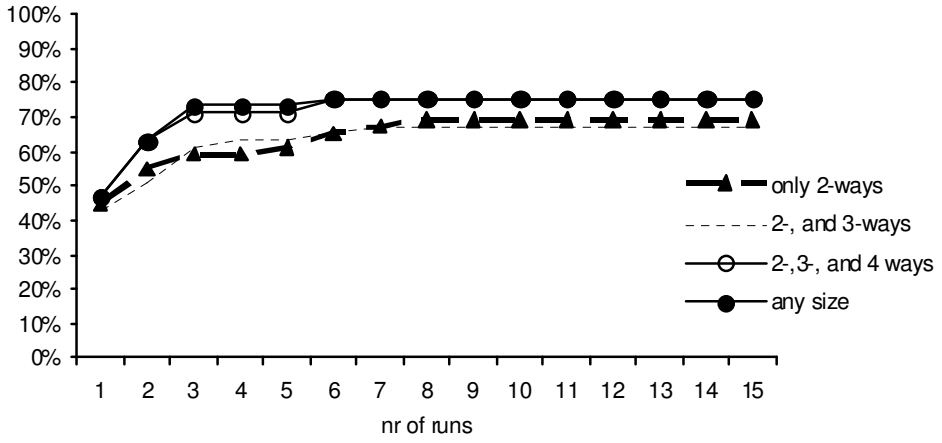
	chain length			
blood types donor-recipient pairs	2	up to 3	up to 4	unlimited
O – A n=27	25	25	24	24
O – B n=13	8	8	9	9
O – AB n=1	1	1	1	1
O – O n=55	29	37	38	38
A – AB n=3	3	3	3	3
A – A n=40	23	31	32	33
B – B n=4	0	0	0	0

Figure 4.

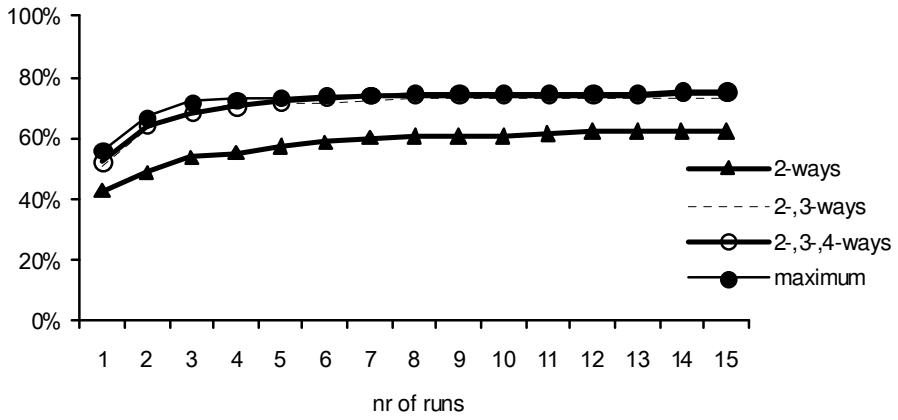
a. The chance of finding a matching pair in relation to the number of attempts for O recipients in the ABO incompatible group in all procedures.



b.The chance of finding a matching pair in relation to the number of attempts for non-O recipients in the ABO incompatible group in all procedures.



c. The chance of finding a matching pair in relation to the number of attempts in the positive cross match group in all procedures.



DISCUSSION

The present analysis shows that it is possible to increase the success rate of a kidney exchange program by constructing longer chain lengths. Our analysis is not based on computer simulations. We used actual donor-recipient data taken into account all the hurdles and barriers that were encountered in real life. Examples are comorbidity of the patient necessitating temporary or definitely leaving the program, withdrawal of consent by the donor, and alternative kidney transplants (9). Our results are also based on the actual median input of 15 combinations every 3 months during a period of 5 years with a median of 48 enrolled couples in 20 match procedures compared to 2-way exchanges only. We were able to find 18% more new combinations when chains of unlimited sizes were constructed while at the same time we even noted a 9% increase in median PRA of the matched patients. However, the biggest proportional increase both in numbers (14%) and PRA (7%) was already reached when 3-way exchanges were allowed. Enlarging the potential chain length to 4 gained only 3% extra possibilities while unlimited chain length compared to up to 4 resulted in just 1% more new combinations. Thus only a small number of couples may profit from unlimited chain lengths. This observation has to be balanced against the logistic burden of longer chains. In our analysis the difference between 3-way and 4-way exchanges was only 5 extra couples over 5 years time, i.e. one extra couple a year. Therefore we feel that the optimal maximal chain length for all practical purposes is 3, especially for newly starting exchange programs. Multiple simultaneous surgeries can stretch the capacities of several centers and requires a great deal of careful coordination.

However, it should be noted that the results of this analysis is based on a Caucasian population, with a blood type distribution of 45% O, 40% A, 11% B and 4% AB. Another point for discussion is that not only chain length, but also the preset conditions will effect the number of successful matches. Our main goal was to find the maximum number of exchanges, which then formed our leading preset condition. Thereafter blood type identity, difficult to match patients, logistics and wait time were taken into account. However when other factors e.g. differences in age between original and exchange donors or between exchange donors and recipients would be considered, the number of potential solutions would decrease. The number of HLA-mismatches and distance between donor and recipient center would likewise influence the success rate. These factors might be implemented for good medical reasons, but will result in less transplants, longer wait time on the deceased donor wait list and thus in higher morbidity in a patient group without alternative living donors. So limitation of allocation criteria is essential for the success of a kidney paired exchange program and is associated with excellent uncensored survival. Especially recipients with high PRA in the positive cross match group profited from our program. The vast majority of the successful couples were already matched within 3 procedures. Thereafter their chances became small. For them domino-paired kidney transplantation triggered by Good Samaritan donors is the next alternative (10). Thereafter desentization programs may function as last resort.

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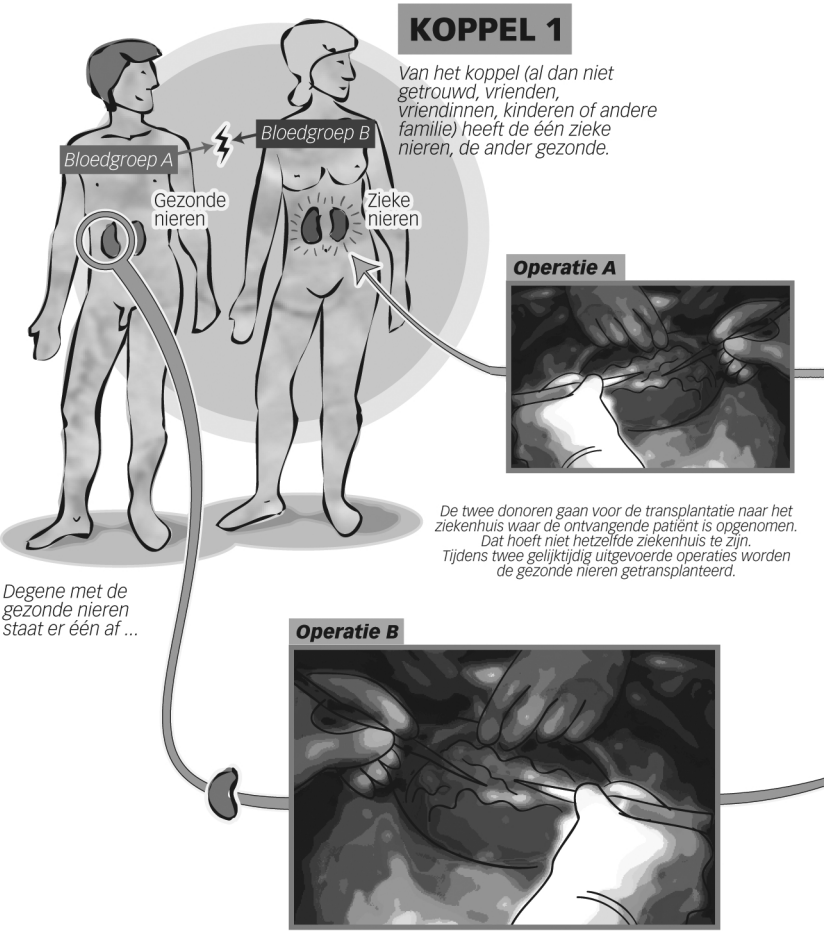
Chapter 10

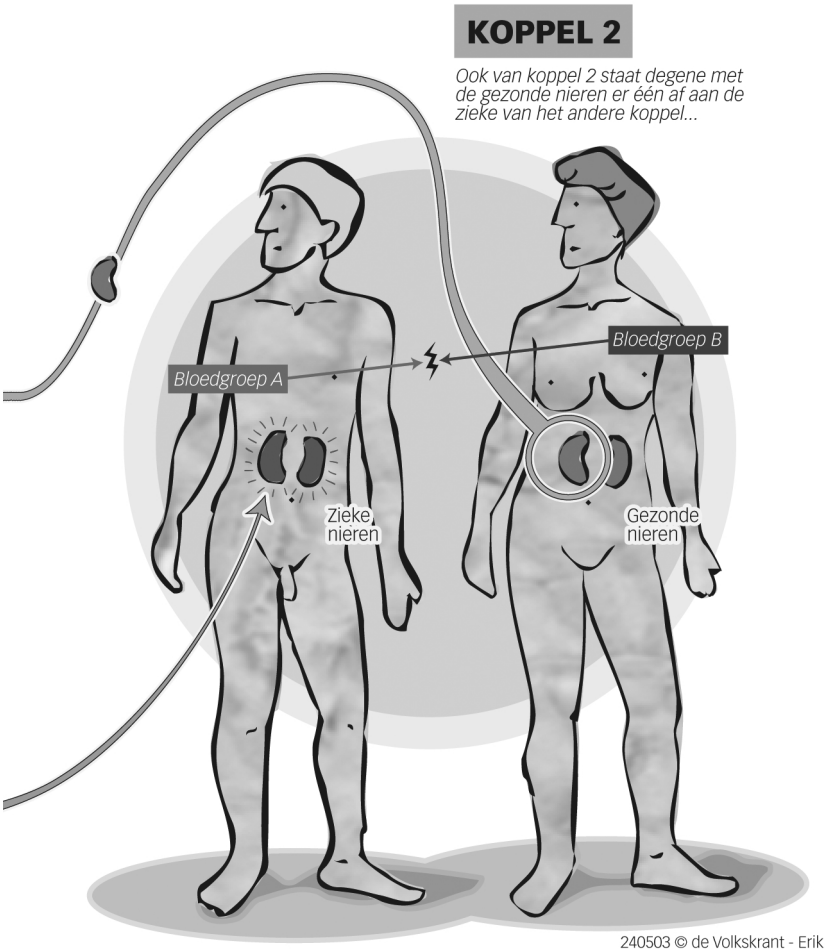
Summary in English and Dutch

Koppels helpen elkaar bij ruil-transplantatie

Het valt niet mee om een nierdonor te vinden. Koppels (partners, vrienden, familie) kunnen vaak niet bloedgroep hebben. Twee koppels met dit probleem kunnen door een ruil-transplantatie vaak twee van bestanden in een donor-database is de zoektocht naar deze koppels simpel.



helpen doordat ze bijvoorbeeld een verschillende problemen tegelijk oplossen. Door het vergelijken



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SUMMARY
In this thesis we describe the realization of the largest living donor kidney exchange program in the world.

Chapter 1 describes the developments in the field of kidney transplantation. It took until the early sixties, after the discovery of azathiopirine, that deceased donor kidney transplantations became possible. Since that time the success rate of organ transplantation has significantly improved which attracted large numbers of transplant candidates. As the number of deceased organ donors did not increase, the wait time on the list steadily grew to more than 4 years. A strategy to expand the donor pool included the use of non-heart beating donors. However, this had no effect on the shortage of donor kidneys. Therefore a revival of the use of kidneys from living donors was undertaken. Initially transplantations with living genetically related donors were performed successfully, but it became clear that the graft survival of genetically unrelated donor was also excellent. Unfortunately not all willing donors were able to donate directly, due to a positive cross match or an ABO blood type incompatibility. In these cases, exchanging donors could be a solution. For example the recipient of pair A receives a transplant of the donor of pair B and the recipient of pair B receives the donor kidney from pair A.

In 2003 we started with the preparation of a national living donor kidney exchange program. In **chapter 2** medical and logistic aspects were described, also psychological and ethical considerations. We felt there was no difference in the medical indications and contra-indications between directed and in directed living donation for recipients and donors. A successful kidney exchange program requires a large pool of donors and patients. Therefore, this has been organised in a national program. An independent organisation like the Dutch Transplant Foundation has been made responsible for the allocation of the exchange kidneys. The donor will travel to the recipients center and the donation procedures start at the same moment to minimize the chance that the donor withdrawn of the program. For psychological and ethical reasons we should be sure that there is not too much pressure on potential donors because due to our exchange program there are no medical reasons not to donate. In the literature there is no consensus about anonymity between donor-recipient pairs. Remarkably in our pilot study with 14 potential donor-recipient pairs all participants preferred anonymity.

In **chapter 3** we describe this pilot study. There were separate questionnaires for recipient and donor. All questions were multiple-choice questions. The subjects of this questionnaire included a. the willingness of the donors and recipients to participate in an exchange program, b. under what conditions they would

participate e.g. under strict anonymity or after getting acquainted, and c. questions about the results of the surgical procedures.

Chapter 4 describes how we organized our program. The protocol consisted of four different steps the registration procedure for participants, allocation – and matching criteria, cross-match procedure in our National Reference Laboratory and surgical and follow-up procedures.

In January 2004 the seven transplant centers embarked on a kidney exchange program. In **chapter 5** we reported our 1-year experiences. Participation of both ABO blood type and cross match incompatible couples, which makes it possible to combine couples from these subgroups, is essential for the success of the program. We were able to create new ABO blood type compatible couples with negative cross matches for 26/60 (43%) of the candidates and this resulted in 24 kidney transplants.

After 30 months the Dutch living donor kidney exchange program became the most successful program in the world with a success rate of almost 50% (**chapter 6**). Participation of all the seven transplantation centers made it possible to expand the total number of living donor kidney transplantations in the Netherlands with 10%. Two important factors influenced the success rate; immunization of the patient (PRA) and the specific blood type combination of the enrolled donor-recipient pair. Patients in the positive cross match group were significantly more successful (64%, 44/69) compared to those in the ABO blood type incompatible group (36%, 28/77). However the B to A and A to B combinations in the ABO blood type incompatible group proved to be extremely easy to accommodate with a 95% success rate. In particular, the blood type O recipients with non-O-donors were difficult to match (17%, 9/53).

In **chapter 7** we make clear that a living donor kidney exchange program is a dynamic process. An important issue in the cross match procedure is the cross matches positively between a recipient and a newly matched donor. One positive cross match can be responsible for breaking up triplets and quartets. Because of the fact that all cross matches are performed in one central HLA laboratory, we were able to continue the procedure with additional cross matches in new combinations. However, in the period between the results of the cross matches and the actual surgical procedure medical and psychological problems were encountered that were unforeseen and lead to temporary or permanent discontinuations. Fortunately, our computer program is able to create alternative solutions.

In **Chapter 8** the preference of anonymity between donor-recipient pairs is evaluated in a pilot study. The study group consisted of 15 patients who received a kidney and 14 donors who already donated in our living donor kidney exchange program. After transplantation and donation the majority of donors and recipients were satisfied with anonymity, therefore we will continue to ensure anonymity in the Dutch kidney exchange program.

In **Chapter 9** we describe the evaluation of the computer match program in which we examined in our actual donor-recipient couples how to reach the maximum number of matches by using different chain lengths. In conclusion, the optimal chain length for living donor kidney exchange programs is three. Longer chains do not lead to significantly more transplants.

SAMENVATTING

Dit proefschrift beschrijft het tot stand komen van het grootste gepaarde donorruil programma voor nierdonatie bij leven in de wereld.

In **hoofdstuk 1** is de ontwikkeling van de niertransplantatie beschreven. In de begin jaren zestig na de ontdekking van Azathiopirine werden succesvolle niertransplantaties uitgevoerd met nieren afkomstig van overleden personen. Dit succes kreeg echter een keerzijde. Aangezien steeds meer patiënten voor een niertransplantatie werden aangemeld en het aantal postmortale nierdonaties stabiel bleef, ontstond er een wachttijd voor een postmortale nier van ruim 4 jaar. Het postmortale niertransplantatie programma werd uitgebreid met non-heart beating donoren. Er bleef echter nog steeds een tekort aan donornieren bestaan. De alternatieve oplossing om dit orgaantekort te bestrijden is een niertransplantatie met een nier van een levende donor. Kwamen aanvankelijk alleen directe familieleden in aanmerking voor nierdonatie, inmiddels is gebleken dat transplantatie van nieren van niet-verwante donoren even goede resultaten oplevert. Helaas is het niet altijd mogelijk om een nierdonatie bij leven uit te voeren bij een beoogd donor-ontvanger paar. Zowel bloedgroepincompatibiliteit als de aanwezigheid van tegen de donor gerichte antilichamen bij de ontvanger maakt deze procedure op immunologische gronden onmogelijk. Gepaarde donorruil kan in deze gevallen een oplossing bieden. Hierbij doneert de donor van patiënt A een nier aan patiënt B, terwijl tegelijkertijd de donor van patiënt B een nier afstaat aan patiënt A.

In 2003 is de voorbereiding gestart voor het opzetten van een landelijk programma voor nierdonatie bij leven, gepaarde donorruil. In **hoofdstuk 2** worden de medische en logistieke overwegingen besproken. Daarna volgen de psychologische en ethische aspecten. Op medisch gebied bestaan er geen verschillen in de medische indicaties en contra-indicaties voor donor en ontvanger tussen directe en indirecte nierdonatie bij leven. Logistiek gezien is voldoende participatie alleen mogelijk wanneer het programma op nationale basis wordt georganiseerd. De allocatie van de indirect te doneren nieren kan dan door een onafhankelijke nationale organisatie worden uitgevoerd: de Nederlandse Transplantatie Stichting. De gezonde donor zal worden verwezen naar het transplantatiecentrum van de beoogde ontvanger. Het gelijktijdig uitvoeren van beide donatieprocedures is een vereiste om de kans te minimaliseren dat één van de twee donoren zich op het laatst bedenkt en zich terugtrekt uit de procedure. Op psychologisch en ethisch gebied dient ervoor gezorgd te worden dat er niet een te grote druk wordt uitgeoefend op potentiële donoren, aangezien voor dit programma medisch argumenten om af te zien van donatie komen te vervallen. In de literatuur

is er geen consensus over de wenselijkheid van anonimiteit tussen donor-ontvanger paren. Opmerkelijk was dat de 14 donor-ontvanger paren uit onze pilotstudie zonder uitzondering van mening waren dat de procedure anoniem moet blijven.

Deze pilotstudie is beschreven in **hoofdstuk 3**. Er werd gewerkt met aparte vragenlijsten voor donor en ontvanger met daarin multiple-choice vragen aangaande de volgende onderwerpen: bereidheid tot deelname aan een donorruil programma, voorwaarden tot deelname ten aanzien van anonimiteit tussen de paren of kennismaking en nieuwsgierigheid naar de herkomst van de nier of het resultaat van de gedoneerde nier.

Voor de verdere logistieke uitwerking wordt in **hoofdstuk 4** het protocol beschreven ten aanzien van de registratie van deelnemende donor-ontvanger paren, de allocatie en matching procedure, de centrale uitvoering van de kruisproeven tussen ontvanger en zijn nieuwe donor in het Nationaal Referentie Laboratorium, de chirurgische uitvoering en de na controle van donor en ontvanger.

In januari 2004 is het gepaarde donorruil programma voor nierdonatie bij leven daadwerkelijk van start gegaan. In **hoofdstuk 5** worden de korte termijn resultaten beschreven. Na 1 jaar leverde dit voor 26 donor-ontvangercombinaties ruilmogelijkheden op met negatieve kruisproeven. Er werden uiteindelijk 24 patiënten getransplanteerd, waarmee het gepaarde donorruil programma een succespercentage van 43% heeft. De participatie van zowel bloedgroep incompatibele paren als positieve kruisproef paren leidde tot dit succes.

Na 2½ jaar is het Nederlandse programma wereldwijd verreweg het grootste geworden en met een 50% slagingspercentage ook het meest succesvolle (**hoofdstuk 6**). Het Nationale gepaarde donorruil programma is met succes geïmplementeerd in alle zeven niertransplantatie centra en er bestaat bij patiënten en hulpverleners een gedegen draagvlak voor een dergelijk programma. Dit mag blijken uit het feit dat 10% van alle levende nierdonaties wordt uitgevoerd via een gepaarde donorruil procedure. Er zijn twee belangrijke factoren die het slagingspercentage beïnvloeden. De mate van immunisatie van de nierpatiënt, af te lezen aan de PRA waarde, en de specifieke bloedgroep combinaties van ontvanger en donor. De kans op selectie voor de 69 positieve kruisproef combinaties bedroeg 64% (44/69) ten opzichte van de 77 bloedgroepincompatibele combinaties voor wie de kans op selectie 36% bedroeg (28/77). Echter bloedgroep A ontvangers met een bloedgroep B donor en het spiegelbeeld hiervan, de

bloedgroep B ontvangers met een bloedgroep A donor hadden de grootste kans op een ruilmogelijkheid, namelijk 95% (19/20). Voor de ontvangers met bloedgroep O met een bloedgroep A, B of AB donor is het succes percentage beduidend lager namelijk 17% (9/53).

Bij de evaluatie van de 4½ jaar resultaten (**hoofdstuk 7**) bleek dat het centraal uitvoeren van de kruisproeven tussen ontvanger en zijn nieuwe donor een belangrijke bijdrage leverde voor het succes van het programma. Echter in de periode tussen het uitvoeren van de kruisproeven en de werkelijk donatie-transplantatie procedure kwamen ook medisch- en psychologische problemen bij de nieuwe donor-ontvanger paren aan het licht die tot tijdelijke of definitieve ontkoppelingen leiden. Gelukkig konden een aantal ontkoppelingen weer opnieuw gematcht worden met behulp van ons computer match programma.

In **hoofdstuk 8** wordt de voorwaarde anonimiteit tussen donor-ontvanger paren geëvalueerd in een studie met 15 getransplanteerde cross-over patiënten en 14 donoren die hun nier doneerde in het gepaarde donorruil programma. De meeste paren waren tevreden met de anonimiteit, dus daarom zullen wij ervoor blijven waken dat anonimiteit in ons gepaarde donorruil programma gehandhaafd blijft.

In **hoofdstuk 9** beschrijven we de evaluatie van het computer match programma waarbij we gekeken hebben naar de optimale ketenlengte en we tot de conclusie zijn gekomen dat een ketenlengte van maximaal 3 paren in een match combinatie optimaal is.

Appendices

ACKNOWLEDGEMENTS / DANKWOORD

Het Nederlandse donorruil programma voor niertransplantaties is door de inzet van vele mensen een succes geworden. Ik wil iedereen die zowel voor als achter de schermen een bijdrage heeft geleverd hiervoor hartelijk danken. Een aantal mensen wil ik in het bijzonder bedanken.

Mijn promotor Prof.dr. W. Weimar, beste Willem, hartelijk dank voor het in mij gestelde vertrouwen en voor alle ruimte en mogelijkheden die ik heb gekregen om te groeien en te bloeien. Ondanks dat ik nog maar enkele maanden op de afdeling werkte, liet je me de interviews afnemen bij de potentiële cross-over kandidaten. Hierdoor wist je mij te stimuleren en te enthousiasmeren, maar tevens gaf je me het vertrouwen dat ik het kon. Dit heb ik zeer gewaardeerd. Het was fascinerend om te zien hoe je het donorruil programma onder de aandacht van de media wist te brengen. De internationale belangstelling die hieruit voortvloeide heeft voor leuke bijkomstigheden gezorgd. Dank!

Prof.dr. F.H.J. Claas, Prof.dr. J.N.M. IJzermans en Prof.dr. J.J. van Busschbach, beste Frans, dank dat je vanaf het prille begin het donorruil programma een warm hart hebt toegedragen. Vele malen was je bereid om een tekst van advies te voorzien. Je reactiesnelheid was steeds hoog, ondanks je zeer drukke agenda. Ook je steun vanaf rij zeven in vele congreszalen waardeer ik zeer. Hierdoor zag ik mijn presentaties met nog meer vertrouwen tegemoet. Beste Jan IJ, dank voor je chirurgisch enthousiasme voor het uitvoeren van vele donorruil procedures. Eén zak snoep brengen op de operatie afdeling bij de eerste cross-over procedure in 2003 was blijkbaar al voldoende. Vele jaren geleden heb jij me voor het eerst kennis laten maken met de wereld van de niertransplantatie, dat is blijkbaar een goede basis geweest voor mijn verdere ontwikkeling, dank.
Beste Jan B, dank dat je het destijds aandurfde om als co-auteur bij mijn eerste artikel te staan. Samen hebben we aan het begin gestaan van een nieuwe samenwerking tussen de afdeling niertransplantatie en psychologie. Ik hoop dat er nog veel wetenschappelijke resultaten uit deze samenwerking mag voortkomen. Dank voor je bijdragen aan mijn proefschrift.

Prof.dr. R. Zietse, Prof.dr. A.J. Hoitsma, Prof.dr. R.J. Ploeg en Dr. M.T. Hilhorst, beste Bob, dank voor je inspirerende gesprekken en discussies die we veelal in de ochtend hadden over de meest uiteenlopende onderwerpen. Ik ben daarom zeer benieuwd naar je vraag op de dag van mijn verdediging, dank voor je steunende en stimulerende woorden. Beste Andries, dank voor je bijdrage als nefroloog, maar ook als opmerkzaam werkgroep lid van het cross-over programma. Voornamelijk

wil ik je bedanken voor je adviezen tijdens de opstartfase van het programma en tijdens alle werkgroepvergaderingen, onafhankelijk van het tijdstip waarop ze plaatsvonden. Beste Rutger, dank voor je chirurgische inbreng in de cross-over werkgroep. Vanaf de start van het programma ben je steeds bereid geweest mee te denken tijdens de werkgroepbijeenkomsten. Beste Medard, dank voor het luisteren en de opbouwende kritiek tijdens mijn allereerste Engelse presentatie over het donorruil programma. Deze presentatie was als voorbereiding op de echte presentatie die ik ging geven tijdens mijn allereerste symposiumbezoek in München. Dank voor je hulp.

Marjan Vliegen en Willij Zuidema, Marjan, zonder jouw deskundige en analytische bijdragen zou dit proefschrift er nooit zijn geweest. Dank voor al je snelle reacties die ik mocht ontvangen op mijn per email toegestuurde, in lekentaal geformuleerde, vragen. Geduldig probeerde je vervolgens te achterhalen en te ontcijferen wat mijn echte vraagstelling was. Nog leuker en gezelliger zijn je persoonlijke bezoekjes aan Rotterdam. Dat humor een mens op de been houdt, daar ben jij een zeer inspirerend voorbeeld van. Met jou als paranimf zie ik de verdediging met vertrouwen tegemoet.
Willij, ruim acht jaar geleden kwam ik je per toeval in de gangen van het Erasmus MC tegen. Als oud-collega's hebben we bij gekletst over de jaren dat we beiden betrokken waren bij het niertransplantatie programma, jij vanuit de afdeling niertransplantatie en ik vanuit de afdeling Chirurgie. Je wist me in enkele minuten enthousiast te maken om bij jullie op de afdeling te komen werken. Ons gesprek, destijds, is het startpunt geweest voor mijn fantastische loopbaan op de afdeling niertransplantatie. Ik dank je voor de mogelijkheden die je me hebt geboden in de afgelopen jaren, maar nog meer voor alle gezelligheid.

Marc en Lotte van Delft, enkele jaren geleden heb ik jullie voor het eerst ontmoet tijdens een afdelingsdag georganiseerd door de VWA (werkgever van Marc en Fred) in Den Haag. Zijdelings kwam ook mijn werk ter sprake en vanaf dat moment is jullie interesse voor het computer match programma blijven bestaan. Op een oude laptop hebben jullie het eerste model gebouwd. Heel veel dank voor de vele uurtjes die jullie er aan gewerkt hebben. Inmiddels is de jaarlijkse afdelingsdag van de VWA uitgegroeid naar gezamenlijke familie-uitjes naar sprookjesachtige parken waar vooral Lizan en Eline mooie herinneringen aan hebben. Eline droomt er nog steeds van dat Lizan en zij ooit naast elkaar gaan wonen.

Wilfred van der Deijl, enkele jaren geleden herschreef je het computer match programma tot een zeer efficiënt en volgens mij zeer uniek programma. Jouw kennis is van groot belang geweest voor het succes van het donorruil programma.

Hartelijk dank voor je fantastische bijdragen. Tijdens de ontwikkelfase was jij telkens weer bereid om op mijn verzoek aanpassingen aan te brengen. Dank voor de vele telefoongesprekken, waarbij je me op fantastische wijze en met veel geduld door het match programma heen loodste, als ik weer eens de weg kwijt was. Jouw talent om ingewikkelde programmeertaal om te zetten in lekentaal heeft mij geïnspireerd tot enkele kleurrijke figuren in dit proefschrift. Het computer match programma kreeg uiteindelijk ook veel internationale belangstelling. Ten slotte wil ik ook Martin Suijs bedanken voor zijn hulp in het afgelopen jaar.

Bernadette Haase-Kromwijk, Beste Bernadette, dank voor je steun en vertrouwen die ik vanuit de Nederlandse Transplantatie Stichting heb mogen ontvangen, waardoor ik op een fantastische en uitdagende wijze aan dit mooie samenwerkingsprogramma heb kunnen werken. Door jouw Europese contacten en uitgebreide netwerk is het donorruil programma ook in Europa op de kaart gezet. Tevens dank ik je voor de middelen die je menigmaal beschikbaar stelde om het donorruil programma te kunnen laten uitgroeien tot een succes. Je bereidheid om aan nieuwe suggesties en ideeën mee te werken was onuitputtelijk. Ook wil ik Karin Keizer en Debby Lappenschaar bedanken, die samen de eerste stappen hebben gezet om dit unieke programma tot ontwikkeling te brengen. Onvergetelijk is daarbij de altijd bereidwillige ondersteuning van Marlies Broxterman. Dank je wel Marlies voor je interesse en secretariële ondersteuning. Tevens dank aan je collega's die dit met evenveel enthousiasme van je over hebben genomen. Verder wil ik Erwin de Buijzer nog bedanken die nieuw leven blies in het onderwerp algoritme en te allen tijde bereid was hierover te discussiëren. Uiteindelijk heeft dit geleid tot een prachtig artikel waarbij de bemiddeling van Aline Hemke met de computer afdeling van groot belang is geweest. Aline, bedankt voor je interesse en je belangstelling in het cross-over programma.

Marian Witvliet, Thérèse Prins, Sophia Stein, Dave Roelen en alle andere medewerkers van het Nationale Referentie laboratorium. Beste Marian en Thérèse, jullie betrokkenheid bij het donorruil programma is hartverwarmend. Ondanks dat jullie alleen de namen kennen van vele cross-over paren en geen gezichten, was voor jullie iedere goede kruisproef een mogelijkheid tot transplantatie voor een nierpatiënt. Ik dank jullie voor de flexibiliteit en bereidheid op ieder willekeurig moment in het proces om nog een extra kruisproef uit te voeren. Verder bewonder ik jullie zorgvuldige, intensieve, maar ook zeer belangrijke werk, dat ik vaak naar patiënten toe heb uitgelegd met de termen: klontering en vechtende bloedcellen. Dank voor jullie fantastische samenwerking. Tevens wil ik Sophia, Dave en alle andere medewerkers die vanaf het begin of in een later stadium bij het donorruil programma betrokken zijn geweest hartelijk danken voor hun inzet en hun

interesse in het cross-over programma. Verder wil ik Ilias Doxiadis bedanken, beste Ilias, dank dat je me ooit geïntroduceerd hebt bij je Canadese en Amerikaanse collega's in Toronto. Het was mijn eerste ervaring om als genodigde spreker een presentatie te geven in het buitenland. Dank voor je gezelschap en discussies onderweg in bus en vliegtuig.

De nefrologen, chirurgen, urologen, immunologen, anaesthesisten, maatschappelijk werkers, verplegend personeel en secretariële medewerkers van het Academisch Medisch Centrum Amsterdam, Vrije Universiteit Medisch Centrum Amsterdam, Universitair Medisch Centrum Groningen, Leids Universitair Medisch Centrum, Universitair Medisch Centrum Maastricht, Universitair Medisch Centrum St. Radboud en Universitair Medisch Centrum Utrecht wil ik hartelijk danken voor hun inzet. Dankzij jullie inspanningen en aanhoudend enthousiasme zijn er vele gepaarde donorruil procedures uitgevoerd. Het onderlinge vertrouwen heeft een belangrijke rol gespeeld in dit unieke samenwerkingsprogramma.

Beste Regien Meijer, Annemarie Roelofs (UMCG), Sylvia ter Meulen (AMC), Carla Schrauwers (VuMC), Bep Vink, Anne Moazzeni, Liesbeth Berendsen (UMCU), John Dackus, Philip Ulrichts (UMCM), Simone Mooren, Desiree Pilzecker, Yvonne Hooghof (UMCN), Marijke van Gurp (LUMC) en Ruth Dam (LUMC) dank voor jullie fijne samenwerking in de afgelopen jaren. Jullie waren een geweldig team met een open karakter waardoor we goed met elkaar konden discussiëren en we veel van elkaar geleerd hebben. Ik dank jullie voor jullie inbreng. Jullie organisatorische talenten en flexibiliteit hebben vele doubletten, menig triplet en zelfs ingewikkelde kwartetten mogelijk gemaakt. Het is een plezier om met jullie samen te werken, hiervoor dank!

Leonieke Kranenburg, beste Leonieke, jij was één van de eerste die de psychologische aspecten van het cross-over programma beschreef. Je mooie artikelen waren een goede stimulans voor mij. Dank dat je later ook co-auteur bij mijn artikelen wilde zijn. Jouw promotie is inmiddels verleden tijd, nu ik nog.

De nefrologen, dialyse-verpleegkundigen, capd-verpleegkundigen en secretaresses van het Albert Schweitzer Ziekenhuis, Franciscus Ziekenhuis Roosendaal, Maasstad ziekenhuis, Oosterschelde ziekenhuis, Sint Franciscus Gasthuis en het Vlietland ziekenhuis wil ik hartelijk danken voor de gastvrijheid die ik heb mogen ontvangen wanneer ik jullie ziekenhuis bezocht voor klinische lessen of voor een gezamenlijk georganiseerde voorlichtingsbijeenkomst voor patiënten. Dank dat jullie potentiële cross-over paren enthousiast maakten en hen doorstuurden naar het Erasmus Medisch Centrum.

Beste Madelon van Agteren, Michiel Betjes, Marien Fieren, Teun van Gelder, Marcia Kho, Iris Noorlander, Joke Roodnat, Ajda Rowshani, Jan van Saase, Jacqueline van de Wetering, Arjan van Alphen, Dennis Hesselink en Marieke Wabbijn, dank voor jullie belangstelling en interesse in het donorruil programma. Tevens wil ik jullie bedanken voor jullie inspirerende vragen tijdens de vele besprekingen waardoor ik met een verfrissende blik naar het cross-over programma kon blijven kijken.
Beste dialyse-verpleegkundigen, capd-verpleegkundigen, verpleging afdeling 4 Noord en dames van de polikliniek niertransplantatie van het Erasmus MC, dank voor jullie interesse in het donorruil programma en jullie goede verzorging van alle cross-over patiënten. Verder wil ik jullie bedanken voor de ontvangen gastvrijheid op jullie afdeling en voor jullie inbreng tijdens de klinische lessen. Beste dames van de polikliniek, dank voor jullie inzet en coördinatie om ook de anonimiteit tijdens de polikliniek bezoeken te blijven behouden.

Ian Alwayn, Khe Tran, Turkan Terkivatan en Frank Dor, jullie chirurgische talenten zijn een belangrijke bijdrage geweest voor het succes van het cross-over programma. Dankzij jullie coördinatie konden vele procedures in samenwerking met twee, drie of zelfs vier ziekenhuizen gelijktijdig beginnen. Tevens wil ik Ingrid Mertens zur Borg van de afdeling anaesthesie bedanken voor de samenwerking, de goede voorbereiding en voor het mogelijk maken van de eerste cross-over procedure in ons ziekenhuis op 15 april 2003. Dankzij de inzet van de medewerkers van de afdeling anaesthesie zijn nog veel geslaagde cross-over procedures uitgevoerd.

Verpleegkundigen van afdeling 9 Zuid, dank voor jullie hulp en gastvrijheid wanneer ik de cross-over paren kwam bezoeken. Jullie inzet heeft er voor gezorgd dat de anonimiteit tussen de vele cross-over paren gewaarborgd werd. In het bijzonder wil ik Jolanda Dijkstra en de dames van het opname bureau bedanken voor hun hulp bij het inplannen van de cross-over donatie-transplantatie procedures. Jullie flexibiliteit is zeer belangrijk geweest voor het uitvoeren van alle doubletten, tripletten en kwartetten met de diverse centra. Nico Tronchet, medisch maatschappelijk werker, beste Nico, dank voor de fijne samenwerking en je interesse en je goede begeleiding van de cross-over paren.

Patiënten. Vanwege de anonimiteit kan ik helaas geen namen noemen, maar alle patiënten en donoren die ik heb mogen interviewen en mogen bezoeken op de afdeling tijdens hun opname wil ik hartelijk bedanken voor hun bijdragen en het vertrouwen dat zij hebben gehad in het donorruil programma.

Collega's; Marian van Noord, Annemarie Geel, Judith Kal, Mirjam Tielen, Annemarie Luchtenburg, Sandra Middel, Nazli Altintas, Marleen van Buren, Louise Maasdam, Nelly de Leeuw van Weenen, Monique Cadogan, Frederike Ambagtsheer, Mirjam Laging, Tessa Royaards, Jantine van Driel, Magda Bron, Emma Massey en Saida Ibrahimi. Beste dames, dank voor jullie gezelligheid op de afdeling maar ook daarbuiten. Dank voor de aangename lunchafspraken en de vele, versgezette kopjes koffie. Het was me een waargenoegen om met een aantal van jullie een hotelkamer te delen en congressen in het buitenland te bezoeken. Tijdens deze congresbezoeken waren er vele leermomenten, maar ook momenten om elkaar beter te leren kennen. Verder dank ik jullie voor de ruimte die ik kreeg om dit proefschrift te schrijven. Vooral op de momenten dat ik afwezig was en jullie de cross-over procedures in goede banen moesten leiden en tevens de cross-over paren moesten begeleiden. Tevens wil ik jullie bedanken voor de inbreng en adviezen bij de verschillende proefpresentaties die ik gehouden heb. Dank voor al jullie hulp, steun en luisterend oor. Jullie zijn geweldig en het is zeer prettig om met jullie samen te werken.

Tot slot mijn familie, lieve pa, dank voor alles wat jij en ma me hebben meegegeven, waardoor ik geworden ben, wie ik nu ben. Lieve Janny, Ton, Leendert, Suzie, Lisanne, Marlotte, Cris, Anne en Thomas, dankzij jullie hebben we een fantastische familie. Dank voor al jullie hulp en steun, speciaal op de momenten wanneer ik weer een congres in het buitenland ging bezoeken. Janny, bedankt dat je mijn paranimf wilt zijn.

Fred, we leerden elkaar kennen in de keuken van Janetta en Maarten en ontdekten onze gemeenschappelijke liefde voor koken. Inmiddels delen wij zo veel meer met als grootste geluk onze dochter Eline. Eline, je bent een geweldige, lieve meid met verrassende beschouwingen, opmerkelijke vragen en vaak uiterst functionele oplossingen. Wat is het leven toch eenvoudig en mooi. Ik hoop dat we met z'n drieën nog veel moois mogen beleven.

Marry

CURRICULUM VITAE

Marry de Klerk werd op 27 oktober 1965 geboren te Ridderkerk. Van 1978 tot 1985 volgde zij het V.W.O. aan de Christelijke scholengemeenschap Farelcollege te Ridderkerk. Haar eerste kennismaking met de geneeskunde volgde in september 1985 toen zij als doktersassistente werkte bij Drs. R.E. Barnard, huisarts te Ridderkerk. Zij behaalde haar doktersassistente diploma in 1986. In augustus 1987 stapte zij voor het eerst het Erasmus Medisch Centrum binnen, het toenmalige Dijkzigt, en ging zij werken als polikliniekassistente op de afdeling Inwendige Geneeskunde (Maag-Darm-en-Leverziekten). In 1989 maakte het specialisme Inwendige Geneeskunde plaats voor het specialisme Chirurgie en ondersteunde zij Dr. R. den Toom en Dr. H.G.T. Nijs bij hun onderzoek naar de effectiviteit van schokgolfvergruizing (ESWL) van galblaasstenen. Zij behaalde haar diploma medisch secretaresse in 1990. Van april 1991 tot januari 1992 werkte zij enkele maanden als secretaresse Hoogleraar Heelkunde voor Prof.dr O.T. Terpstra. Vervolgens zette zij haar werkzaamheden voort op de afdeling Heelkunde als secretaresse van het Levertransplantatieteam en tevens als secretaresse van de in 1992 aangestelde lever- en transplantatiechirurg Dr. J.N.M. IJzermans. Tot haar werkzaamheden behoorde het ondersteunen van het spreekuur van Dr. J.N.M. IJzermans waarbij zij regelmatig gesprekken voerde met leverkanker- en levertransplantatiepatiënten. Deze intensieve patiëntencontacten zijn voor haar aanleiding geweest om de opleiding HBO Maatschappelijk werk en Dienstverlening te gaan volgen. Gedurende haar studie zette zij haar werkzaamheden bij Dr. J.N.M. IJzermans op parttime basis voort en werkte zij tevens op parttime basis als maatschappelijk werker bij de afdeling Sociale Psychiatrie van de Stichting Pameijer te Schiedam. In deze functie bood zij ondersteuning aan thuiswonende volwassenen en ouderen met een psychiatrische problematiek. Tijdens haar afstudeeronderzoek verdiepte zij zich in de integratieproblemen in de maatschappij voor mensen met een psychosociale handicap onder leiding van Christel van der Pol. In 1997 behaalde zij haar diploma HBO Maatschappelijk Werk en Dienstverlening aan de Hogeschool Rotterdam & Omstreken te Rotterdam. Zij vervolgde in 1998 haar loopbaan op de afdeling Plastische en reconstructieve chirurgie in het Erasmus MC – Sophia Kinderziekenhuis. Zij werkte daar als coördinator en begeleidde ouders en kinderen met aangeboren schedel- en aangezichtsafwijkingen. Een belangrijk facet van de werkzaamheden betrof het inrichten van het multidisciplinaire spreekuur. Sinds april 2002 is zij werkzaam op de afdeling Inwendige Geneeskunde - Niertransplantatie als coördinator nierdonatie bij leven (Afdelingshoofd Prof.dr. W. Weimar). In 2003 raakte zij betrokken bij de voorbereidingen voor het Nederlandse donorruil programma voor niertransplantatie. Sinds 2005 werkt zij op deeltijd basis voor de Nederlandse

Transplantatie Stichting als nationaal coördinator van het cross-over niertransplantatie programma. In de afgelopen jaren heeft Marry het Nederlandse donorruil programma voor niertransplantatie onder de internationale aandacht gebracht. Voor transplantatiecentra in Canada, Australië, Londen en Parijs was dit een reden om haar uit te nodigen voor aanvullende informatie met het doel om een dergelijk programma in het eigen land op te starten.
Marry is getrouwd met Fred de Klerk en samen hebben zij een dochter Eline van 5 jaar oud.

PHD PORTFOLIO

Name PhD student	Marry de Klerk – Nugteren
Erasmus MC Department	Internal Medicine – Transplantation
PhD Period	January 2004 – December 2009
Promotor	Prof. dr. W. Weimar

1. PhD Training

English Communication, Erasmus MC, Rotterdam, 2005

Academic English for lecturers and staff, Erasmus MC, Rotterdam 2006

(Inter)national conferences and workshops

Workshop Living kidney donation, Agence de la Biomédicine 2009, Paris	invited
Organ Donation Congress/European Transplant Coordinators Organization 2009, Berlin	oral
National Paired donation workshop, NHS Blood and Transplant 2009, London	invited
European Society of Organ Transplantation Congress 2009, Paris	oral
Symposium Dutch Society of Transplantation 2009, Zeewolde	oral
Seminar Transplant Forum 2008, Brussel	invited
Symposium National Workgroup Transplantation Nurses 2008, Utrecht	invited
XXII International Congress of the Transplantation Society 2008, Sydney	invited
Regional meeting Nephrology Western Australia 2008, Perth	invited
American Transplant Congress 2008, Toronto	oral
Symposium Dutch Society of Transplantation 2008, Zeewolde	oral
European Society of Organ Transplantation Congress 2007, Praque	poster
American Transplant Congress 2007, San Francisco	oral
Ethical Legal and Psychosocial Aspects of Transplantation congress 2007, Rotterdam	oral
British Transplantation Society 2007, Manchester	invited
Meeting of the European Society of Transplantation Urology 2007, Berlin	invited
International Transplant Nurses Society congress 2006, Rotterdam	invited
Workshop Kidney exchange program, Belgian Transplantation Society 2006, Luik	invited
World Transplant Congress 2006, Boston	oral
European Transplant Coordinators Organization 2006, Wroclaw	invited
Symposium Dutch society of Nephrology 2006, Veldhoven	oral
Symposium Dutch Society of Transplantation 2006, Zeewolde	oral
International Society of Organ Donation and Procurement 2005, Gramado	oral
Canadian Council for Donation and Transplantation Task Force 2005, Toronto	invited
International Transplant Nurses Society congress 2005, Orlando	oral
European Dialysis & Transplant Nurses Association 2005, Vienna	invited
American Transplant Congress 2005, Seattle	oral
Symposium Dutch Society of Transplantation 2005, Kerkrade	oral

American Society of Nephrology 2004, St. Louis	poster
International Transplant Nurses Society congress 2004, Vancouver	oral
European Transplant Coordinators Organization 2004, Leuven	oral
International Symposium on Living Donor Organ Transplantation 2004, Essen	oral
Symposium National Workgroup Transplantation Nurses 2004, Utrecht	invited
European Transplant Coordinators Organization 2003, Venice	oral
International Transplant Nurses Society congress 2003, Scottsdale	oral
American Transplant Congress 2003, Washington	poster
International Congress on Ethics of Organ Transplantation 2002, Munich	oral

2. Teaching activities

Lecturing

Albeda College Training Dialysis Nurses, 2004 – 2009, Rotterdam

International Congress of the Transplantation Society, Postgraduate Course 2008, Sydney

World Transplant Congress, Postgraduate course 2006, Boston

European Federation for Immunogenetics - Education Day, 2005 Leiden

Training national children dialysis nurses 2004, Utrecht

Training national surgical assistants 2003, Rotterdam

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Starting a cross-over kidney transplantation program in The Netherlands: ethical and psychological considerations.
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de Klerk M, Keizer KM, Claas FHJ, Witvliet M, Haase-Kromwijk BJJM, Weimar W.
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Het Nederlandse donorruil programma voor nierdonatie bij leven.
Ned Tijdschr Geneeskd. 2007, 151(2): 130-3

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A flexible national living donor kidney exchange program taking advantage of a central histocompatibility laboratory: the Dutch model.
In: Cecka JM, Terasaki PI (Eds). Clinical Transplants 2008, 69-73, Terasaki Foundation Laboratory, Los Angeles, California 90064. ISBN 1-880318-17-2

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