LIVE KIDNEY DONATION: INFORMED CONSENT RELATED ASPECTS

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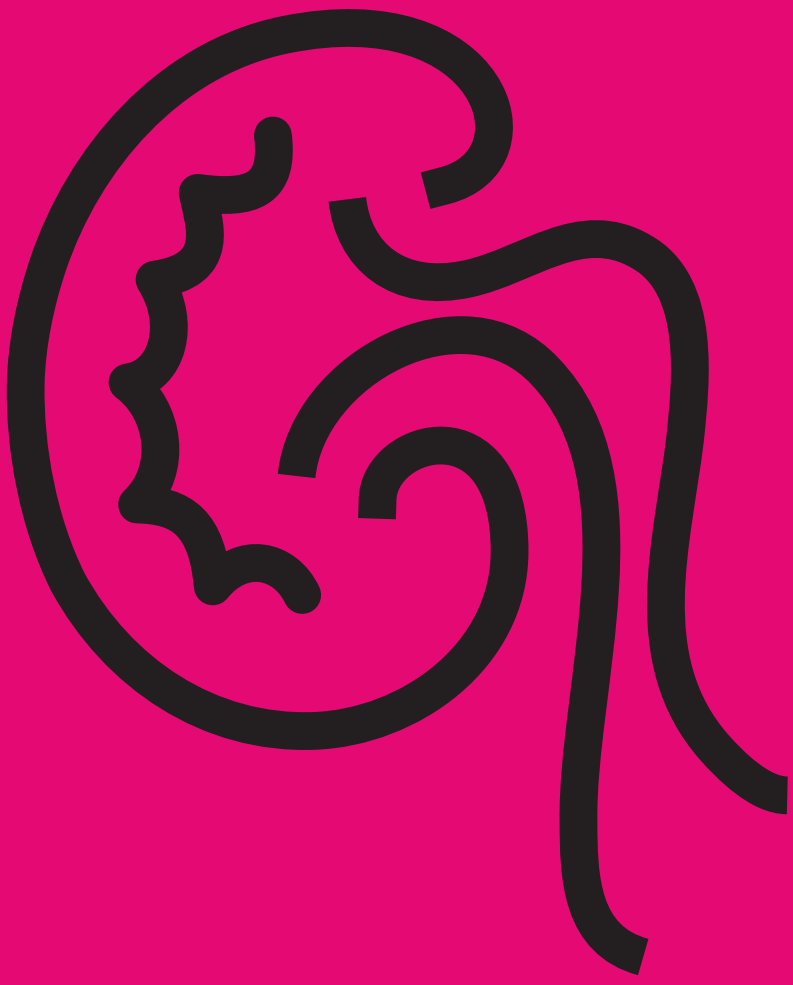

Chapter 1

Introduction

INTRODUCTION

End stage renal disease (ESRD) is the final stage of chronic kidney disease, which can be caused by a multitude of factors. The ultimate treatment is a kidney transplant, but unfortunately, to date, demand exceeds supply. In 2015, 544 patients with ESRD were on the waiting list for a kidney transplant in the Netherlands[1]. These patients are in need of dialysis, they are transplantable, meaning that they are medically fit to undergo a surgical procedure and there are possibilities for the implantation of a donor kidney. The patients on the waiting list usually do not have a potential living donor, and are dependent on deceased donation. This is unfortunate, first of all, because not enough deceased donor kidneys are available to treat every patient on the waiting list, but more importantly, living kidney donation is associated with significantly better recipient outcomes[2].

Aside from the patients on the waiting list, there is a large number of patients with renal disease who are still preemptive, *i.e.*, they are not yet undergoing dialysis, but their renal function is declining towards ESRD stadium. A key priority in the treatment of these patients is the prevention of dialysis by means of a preemptive kidney transplantation. In the Netherlands, patients are eligible to undergo preemptive kidney transplantation when estimated glomerular filtration rate (eGFR) reaches 20% or less of normal function. Preemptive kidney transplantation has been amply proven to improve recipient outcome, with regard to lifespan of the transplant, a lower rejection rate, a lower rate of perioperative cardiovascular mortality, and a lower overall rate of cardiovascular complications[3-7]. Preemptive kidney donation is mainly performed in patients with living donors, but in selected cases this is also possible with a deceased donor kidney, such as in patients with a PD catheter or AV fistula who have not yet started dialysis or in patients with rare blood types.

In some cases, a living donor is available, but not a match for the intended recipient due to incompatible AB0-bloodtypes or the presence of anti-donor HLA antibodies. To enable these recipients to get a transplant, and to realize more transplantations, paired kidney exchange programs (PKE) were created[8]. The Dutch PKE program was developed in 2004 between all eight Dutch transplant centers with the aim to facilitate cross-over kidney transplantations[9, 10]. In 2015, 21 kidneys were donated within the PKE program. Aside from helping patients with non-matching living donors receive a donor kidney, the PKE program also helps to shorten the waiting list. If a non-matching donor cannot be paired to another couple's recipient, the possibility to include an anonymous donor ("unspecified donor") in the equation was introduced in 2014, and in 2015, an additional nine kidneys were transplanted in a so-called "altruistic exchange transplantation"[1]. The recipient with the non-matching donor receives a kidney from the unspecified donor, and the recipient's donor donates a kidney to a matching patient from the national

waiting list. Since the start of the PKE program in 2004, a total of 263 patients have been transplanted through this program[11].

If the paired-exchange program does not result in a suitable match,improvements in immunosuppressive medication in the recipient, advanced possibilities for immune-absorption and plasma-pheresis, allowing AB0-incompatible transplantation, and even the availability of a new generation of monoclonal antibodies to allow HLA-incompatible transplantation have facilitated donation, even if blood type("AB0-incompatible donation") or HLA type ("HLA-incompatible donation") does not match.

These are, in a nutshell, the possibilities for kidney transplantation. Although living donation is regarded to be a safe and feasible operation, and it has been demonstrated to significantly improve recipient outcome, it has one major disadvantage: a living donor is needed who is exposed to a surgical intervention with no direct medical benefit. Performing this procedure goes against the Hippocratic oath ("primum non nocere" - first, do no harm), and the decision must be carefully considered and justifiable in each individual case. It is therefore of the utmost importance that the transplant community can guarantee the highest quality of the procedure itself, but also of every aspect of donor education, preparation and follow-up.

Live Donor Nephrectomy – History and Development

The very first successful donor nephrectomy (and the following transplantation) took place at the Peter Bent Brigham Hospital in Boston, USA, in 1954[12]. The procedure was performed by Joseph E. Murray, and John Hartwell Harrison. At this stage, the procedure was nowhere near the minimally invasive techniques employed today: it was done through a large incision, resecting one or more ribs to gain access to the retroperitoneally located kidney. On February 8th, 1995 the first laparoscopic living donor nephrectomy was performed by Lloyd Ratner and Louis Kavoussi at the Johns Hopkins Bayview Medical Center in Baltimore, USA[13]. Since then, the live donor nephrectomy has evolved enormously. More and more procedures were performed using the laparoscopic technique, and by now this has become the gold standard in many transplant centers [14-17]. Over the years, many modifications have been made to the laparoscopic technique to further improve its safety and efficacy. In 1998 the hand-assisted approach (HAL) was first described by Wolf [18]. This technique allowed for the introduction of the surgeon's hand, mainly through the pfannenstiel incision used to retrieve the kidney. Advantages of the hand-assisted technique include the ability to use tactile feedback, to achieve less blood loss, shorter warm ischemia times, and reduction of overall operative time[19]. A disadvantage could be that HAL is more invasive, and patients may experience more postoperative pain and a longer convalescence period, as compared to those operated purely laparoscopically. However, a number of studies comparing these two procedures found no substantial differences in warm-ischemia time, blood loss, hospital stay or

complication rate[20-25], and currently both techniques are employed, and preference varies per center. In addition to the laparoscopic, transperitoneal technique, the retroperitoneoscopic technique was first described in 1995 by Yang *et al*[26]. Although this was still somewhat of a hybrid procedure between open- and minimally invasive surgery, the technique seemed promising, and was further modified and described by other authors with good results[27, 28]. An advantage of this technique is that during the entire procedure, the peritoneum remains intact. The risk of damage to for instance bowel, spleen or other intraperitoneal organs is thus minimized. As with every laparo- or endoscopic procedure, there is a learning curve, and ample experience with laparoscopic procedures is vital. Hand-assisted retroperitoneoscopic donor nephrectomy (HARP) is an excellent alternative, developed and described by Jonas Wadstrom providing more control whilst still performing minimally invasive surgery[29]. Advantages of the HARP technique have been recently described in two randomized controlled trials (RCT), being a shorter warm ischemia time, shorter skin-to-skin time and fewer intraoperative events[30, 31]. These four techniques are all used on a fairly regular basis, and preferences vary per surgeon or center. In addition, the mini-open donor nephrectomy is used, and can be considered as a minimally invasive approach as well [32]. In the last decade, even more specialized techniques have become available. The most frequently employed is the single port donor nephrectomy (Laparoendoscopic Single Site, LESS). Positive results have been reported in a number of articles[33-35], but whether it will prove to have significant advantage over "traditional" techniques remains to be seen. Other modifications that have been introduced are the robot assisted donor nephrectomy[36-41], which is currently mainly used in trials, and the natural orifice donor nephrectomy (NOTES). Of the latter, only a handful of case reports have been published[42-44], and whether this technique will eventually be implemented as common practice is debatable.

Donor Selection, Extended Criteria Donors and Additional Possibilities

As the laparoscopic donor nephrectomy evolved and became a fully implemented surgical procedure, practice began to change with regard to the selection and approval of potential donors. When first introduced, only genetically-related donors (first degree) were allowed to donate a kidney, but this was later expanded to include more distant genetically related donors, spouses, and friends. Although this is still true for some countries (*e.g.* Germany [45]), in others anonymous donation, nowadays called unspecified donation[46], has been legalized[47-49].

Also, medical criteria for the acceptance of potential donors have changed enormously. On its introduction, almost every comorbidity was one too many and donors were more often rejected than accepted. But since much more information on the actual short- and long term risks of live kidney donation has become available the procedure has been generally considered to be safe. Therefore, so-called "extended criteria living donors" are

increasingly being accepted as living kidney donors[50]. The term "extended criteria living donors" comprises a multitude of (medical) conditions in which donation is considered a possibility, even though opinions still vary among transplant professionals. Examples of these conditions/circumstances are hypertension[51, 52], obesity[51, 53-55], vascular multiplicity[56, 57] and women of childbearing age[58]. It has to be underlined that each donor has to be regarded as an individual, and the decision whether to accept a donor or not has to follow a tailored approach. Technical considerations also play a part in the acceptance of potential donor, and some of these factors can also be described under ECD. During the implementation of the laparoscopic technique, it was quite custom to only retrieve the left kidney, mainly because of the longer renal vein. Multiple authors have since demonstrated that the right kidney can in fact be safely retrieved, and functional outcomes in the recipient were comparable to those who had received a left donor kidney [59-61], and may be even preferable because it is easier to recover than the left kidney, and the risk of splenic lacerations is decreased[62]. Vascular multiplicity (*i.e.* more than one renal vein and/or artery) has been a reason for rejection in many cases. But again, it has been demonstrated repeatedly that the retrieval and implantation of a donor kidney with one or more veins or arteries is not associated with a negative outcome in either the donor or the recipient[50, 56, 57].

Complications and Adverse Events

Complication rates after live donor nephrectomy are relatively low, and the most devastating one, mortality, is reported to occur only sporadically[63, 64]. A recent study reporting on nearly 15,000 live donor nephrectomies (96% laparoscopic) found an overall complication rate of 16.8%. Clavien Dindo grade II and higher events were encountered in 8.8% of donors, grade III or higher in 2.5%, and grade IV or higher in only 2.5%[65]. The most common complications were gastrointestinal (4.4%), bleeding (3.0%), respiratory (2.5%) and surgical/anesthesia-related injuries (2.4%). The in-hospital mortality in this study was reported as 0.007% (one donor).

Although it has been established that short-term complications after live kidney donation are mostly mild in nature, and severe complications are rare, this cannot be stated with the same certainty for long-term complications. It is challenging to present long-term risks since many uncertainties and different views exist regarding this matter. Although much research has been done to assess the absolute risk of End Stage Renal Disease (ESRD), the opinion among health care professionals regarding this risk still varies [66-69]. It used to be believed that kidney donors had no increased risk of ESRD[70]. Then, new data became available presenting a high relative, but low absolute risk of ESRD[66, 69]. Recent research suggests that in specific populations, the risk of ESRD is indeed significantly increased after donation, in one study even up to 5.3 times higher than the general population[71-73]. Even though these are qualitatively well designed

studies with large sample sizes, there's a methodological problem that is not easy to overcome: choosing the perfect control group. It is debatable whether living donors should be compared to the general population, since they are a highly selected subgroup in near-perfect health. The ideal control group would be made up out of people who were approved for living kidney donation, but did, for a non-medical reason, not donate. But these individuals are sparse, and not always easy to find. Still, it has been demonstrated that specific donor characteristics are indeed associated with a greater long-term risk of ESRD, when compared to individuals from general population studies with the same characteristics: in one large model-based study, the highest risk was estimated for young, black kidney donors. Male donors had a slightly higher risk than female donors, and so had current smokers[71]. In addition, other long-term risks need to be further investigated, for instance, risk of gestational hypertension in female kidney donors[50, 58, 74, 75]. Future research and long-term follow-up of living kidney donors will eventually shed more light on this topic.

Live Donor Nephrectomy in the Netherlands – Facts and Figures

All in all, living kidney donation has gained in popularity over the last years, and with good reason. Every patient with a living donor means one less patient on the waiting list, and the recipient will greatly benefit from a living donor kidney.

In 2015, 983 kidney transplantations were performed in the Netherlands: 470 kidneys came from a deceased donor, 513 transplantations were performed using a living donor (52%) [1]. At the Erasmus MC, University Medical Center in Rotterdam, harboring the largest live donor kidney transplant program in Europe, 45% of all living donor kidney transplantations are performed preemptively.

This high percentage of living kidney donations in The Netherlands is unique in the world[76]. In the United States, 41% of all transplanted kidneys in 2015 came from living donors[77]. Although living kidney donation has been legalized and implemented in nearly all countries, and numbers have increased over the last years, the Netherlands still have a leading role when it comes to this procedure (31 living donors per million of population[76], with more than half of all kidney transplants involving a living donor. The described Dutch PKE program is one of the most successful paired kidney exchange programs worldwide[9, 10], and many trials assessing the surgical procedure for the live donor nephrectomy have been initiated in the Netherlands[31, 59, 78, 79].

Informed Consent

Although live kidney donation has been widely accepted, because the benefits for the recipients far outweigh the risks for the donors, we need to keep in mind that donors are not patients. They are healthy individuals, undergoing a surgical procedure for the benefit of others. If for whatever medical or psychological reason donation seems

contraindicated, the potential donor should be rejected. But not only medical or psychosocial factors play a role in the selection process of living kidney donors. Every medical professional, legalist or ethicist agrees that the decision to donate (consent) should be voluntary, free from coercion and informed. The first two are not always easy to prove, but efforts should be made to ensure these criteria are indeed met. The last item, informed, is the one item that we can, at least partly, control.

There are great differences in informed consent procedures between different countries, and even between different regions within a country. These differences begin with national legislation practices[80-82]. Spanish law for example, dictates that consent for live donation has to be obtained, documented and signed in the presence of a judge [83], while in Greece at least two witnesses have to sign a declaration of consent[84]. In the Netherlands, the law on organ donation stems from May 1996 and is quite lenient on the matter of live organ donation. Consent has to be obtained in writing, signed and dated[85]. This is further documented in the EU Directive (EU Directive 2010/53/EU for Living Organ Donation Practice)[86, 87].

But differences in practice also exist on more local levels. There are many discrepancies in the procedure itself, provided information and the manner in which consent is obtained between different countries, transplant centers and even transplant professionals within one center[68, 88]. To deliver the highest quality of care in live kidney donation, more uniformity in the informed consent procedure is mandatory. This first and foremost regards the contents, but it also includes timing, and documentation. Who should obtain informed consent? The information provision process is a team effort of the whole transplant team, so who should be in charge? Since the surgeon is the one responsible for the actual procedure, it makes sense that consent is obtained áfter the donor has been seen by him. On the other hand, the screening process itself may reveal unwanted information, which may also warrant informed consent. Maybe the informed consent process should indeed be a process, with different "stop-or-go" moments along the way, which should all be properly documented, dated and signed. "Who" and "how" are mainly logistic items, and these should be quite easy to arrange. The "what" part is more complex, and deserves some additional attention. As medical professionals involved in the education of and care for living donors, we have an obligation to fully inform them about the details, risks and possible complications of the live donor nephrectomy, and the long-term consequences of the donation itself, so that they can make a balanced decision, but also, to prepare them for the procedure and the post-operative course. But when are donors optimally informed? There are many uncertainties when it comes to information provision and informed consent, in patients in general, let alone in living kidney donors. What information do they need, which details are vital in their educational process? And at what stage during this educational process should the actual informed consent be obtained?

According to a national guideline on information provision for elective surgical procedures, those complications with an incidence of 1% or more and those with severe consequences have to be disclosed[89]. But does this suffice for living donors? Seen in light of the fact that donors are healthy at the start of the procedure, every complication or adverse event is one too many. Obviously, it is impossible to prevent each and every complication from happening, even with the strictest safety precautions. But the least we can do is inform donors of the possibility of these complications. Some infrequent complications may be quite disconcerting to a donor who has no idea these adverse events are in fact quite "normal" (*e.g.* testicular pain, neuropathy).

There is, however, another aspect of informed consent that has to be taken into account when it comes to living kidney donors. Some studies have demonstrated that donors do not always use the same decision-making strategy as patients. Instead of carefully weighing risks and benefits of a procedure, and then deciding whether to go through with it or not, many donors decide to donate upon the first moment of hearing of the possibility[90-92]. Most of them do not change their mind, regardless of the information provided during the educational process. More importantly, it has been suggested that they do not really hear the details about complications or risks, they only use provided information to confirm their decision[93], although more recent studies do bring some nuance to this statement[94].

A handful of studies that have been performed regarding donors' knowledge about the donation procedure in general indeed show deficits, especially regarding (long-term) complications[95]. In addition, a number of authors published self-reported donor experiences with the informed consent procedure, which also demonstrated a substantial lack of understanding, especially of possible complications[96, 97]. But whether these deficits in knowledge are due to lack of education or lack of comprehension remains to be debated. Either way, the transplant team should make an effort to reduce these knowledge deficits. Some steps have already been taken, by introducing a home-based educational program for a selected donor population, which has shown to improve general knowledge regarding living donation and willingness to donate (up to five times more)[98]. Standardization of the informed consent procedure is another way to further improve donor education, and many authors believe that this is a crucial step in the process of refining the quality of care for living kidney donors.

AIMS AND OUTLINE OF THIS THESIS

Part I – The Informed Consent Procedure

The first aim of this thesis was to assess the current situation regarding the informed consent procedure for live donor nephrectomy. What strategies are currently being

employed with regards to donor education, disclosed information, timing of informed consent, and documentation? In the first part of this thesis, these aspects of the informed consent procedure in live donor nephrectomy are evaluated.

First of all, a systematic review of the available literature was performed to summarize the available information on the informed consent procedure for live donor nephrectomy. Information was extracted regarding the procedure itself, details about the contents of provided information, timing, legal framework and donor experience (**chapter 2**). There are some guidelines regarding informed consent for surgical procedures. As previously stated, general consensus is that every complication with an incidence of >1% should be disclosed, in addition to those complications with severe consequences[89]. So, which complications would that be for the live donor nephrectomy? In **chapter 3**, a meta-analysis was performed assessing all possible short-term complications after minimally invasive live donor nephrectomy. The first part consisted of a descriptive systematic review, providing an overview of all encountered complications after minimally invasive live donor nephrectomy. The second part depicts the results of the actual meta-analysis, comparing the different techniques currently employed for minimally invasive live donor nephrectomy with regards to short-term complications. To gain insight in which complications were actually mentioned to potential living donors by kidney transplant surgeons across the country, a web-based survey was created (**chapter 4**). All surgeons involved in live kidney donation in the Netherlands were invited to complete this survey, which contained questions regarding personal experience, operative technique, disclosure of short- and long term complications, and the informed consent procedure employed in the different transplant centers.

Part II – Donor- and Patient Knowledge & Satisfaction

The second aim of this thesis was to assess donor- and patient knowledge of provided information during the educational process leading up to informed consent, and their satisfaction with the informed consent procedure.

The first thing to keep in mind when testing donor knowledge is the hypothesis that donors may not go through the same decision-making process as patients. Instead of carefully balancing all risks and benefits of a surgical procedure and then deciding whether or not to proceed with it, it has been proposed that donors use moral, or emotional reasoning, and make up their mind upon the first moment of hearing of the possibility to donate[90-93]. Many do not change their mind regardless of the waiting period, or which information they receive; they rather focus on positive aspects to reaffirm their decision[93]. The latter aspect is indeed confirmed by some donors reporting the postoperative realization that they were "blinded", or "heard what they wanted to hear", and not quite as informed as they had believed to be prior to surgery[96].

The first chapter of the second part of this thesis describes the results of the pilot study on donor knowledge (**chapter 5**). This study consists of 46 living kidney donors, whose preoperative surgical outpatient visits were observed and scored by means of a preset checklist. Informers (attending surgeons, surgical fellows and specialized nurses) received an informer score of a maximum of 20 points. Donors were asked to complete a pop quiz-style questionnaire directly after the consult, and again on the day of admission for the donor nephrectomy. Questions regarded the surgical technique, short- and long term complications, duration of admission and duration of convalescence. They could also score a maximum of 20 points. Additional baseline characteristics were collected and used for correlation purposes. Six to twelve weeks postoperatively, all donors received an evaluation and satisfaction questionnaire. After completion of the pilot study, a nationwide prospective study was initiated to further assess donor knowledge. The protocol for this study is outlined in **chapter 6**. The protocol was created in a multidisciplinary working group, including surgeons, nephrologists, urologists, and a psychologist, all involved in living donor kidney transplantation. The study was designed as an inventory project, and had multiple aims. First of all, we wanted to assess whether the differences reported in our survey study were indeed present, or whether it was just a matter of reporting bias. If the first was true, something might have to change. Uniformity should be pursued, especially seen in light of the successful paired kidney exchange program (PKE) in the Netherlands (5.1% of all live donor nephrectomies are within the PKE program)[11]. Standard policy involves donors traveling to the recipient's center for surgery, but receiving education in their own center. Most donors visit the outpatient clinic of the other center prior to surgery, and are seen by the local surgeon on the day of admission for donor nephrectomy. If information received in their own center differs greatly from information received on in the "new" center this could be quite troubling for the donor. To evaluate current practice in informed consent procedures, 378 potential kidney donors were recruited prior to receiving any information in one of the eight Dutch transplant centers. A second cohort of 226 donors (including 29 donors who had also already been included in the first cohort)was included on the day of admission for donor nephrectomy. Both were asked to complete the pop-quiz with questions regarding surgical technique, short- and long-term complications and duration of admission and convalescence, providing extensive information about donor comprehension. **Chapter 7** describes the results of the nationwide inventory- and donor knowledge study.

Finally, a general discussion on the contents of this thesis is presented in **chapter 8**. **Chapter 9** outlines future perspectives with regard to informed consent procedures in live donor nephrectomy, but also in other (elective) surgical procedures. A summary is provided in English and Dutch in **chapter 10** . **Chapter 11** comprises a list of

publications by the author of this thesis, her Curriculum Vitae, PhD portfolio, and the acknowledgements.

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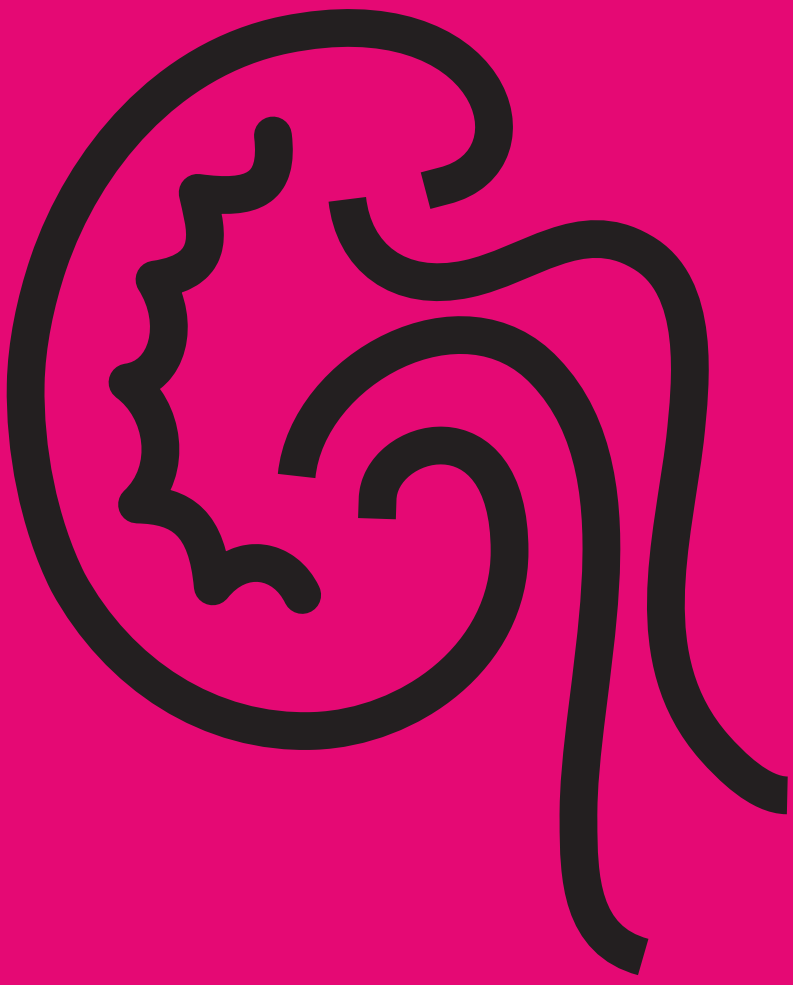
"So perhaps the best thing to do is to stop writing Introductions and get on with the book"

~ AA Milne



Chapter 2

The Need for a Standardized Informed Consent Procedure in Live Donor Nephrectomy: A Systematic Review

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ABSTRACT

Background Informed consent in live donor nephrectomy is a topic of great interest. Safety and transparency are key items, getting increasingly more attention from media and healthcare inspection. Since live donors are not patients, but healthy individuals undergoing elective interventions, they justly insist on optimal conditions and guaranteed safety. Although transplant professionals agree consent should be voluntary, free of coercion and fully informed, there is no consensus on which information should be provided, and how donors' comprehension should be ascertained.

Methods Comprehensive searches were conducted in Embase, Medline OvidSP, Web-of-Science, PubMed, CENTRAL (The Cochrane Library 2014, issue 1) and Google Scholar, evaluating the informed consent procedure for live kidney donation. The methodology was in accordance with the Cochrane Handbook for Interventional Systematic Reviews and written based on the PRISMA statement.

Results The initial search yielded 1009 hits from which 21 papers fell within the scope of this study. Procedures vary greatly between centers and transplant professionals vary in information they disclose. Although research has demonstrated that donors often make their decision based on moral reasoning rather than balancing risks and benefits, providing them with accurate, uniform information remains crucial, as donors report feeling misinformed about or unprepared for donation. Although a standardized procedure may not provide the ultimate solution, it is vital to minimize differences in live donor education between transplant centers.

Conclusion There is a definite need for a guideline on how to provide information and obtain informed consent from live kidney donors, to assist the transplant community in optimally preparing potential donors.

INTRODUCTION

With very low complication and mortality rates, live donor nephrectomy is a safe, low-risk surgical procedure. In contrast to patients, living donors are (generally) healthy individuals in whom a vital organ is removed for the benefit of others. It is of the utmost importance that any patient is correctly informed about the specific details, risks and alternatives of a procedure, but the unique character of the live donor nephrectomy may warrant an extra vigilant approach to the informed consent process. Relevance further increases since extended criteria donors (*e.g.* overweight/obese donors, older donors, donors with hypertension and/or vascular multiplicity/anomalies) are increasingly being accepted. These individuals could be more prone to complications, and potential donors must be well aware of the risks involved with their upcoming procedure [1].

Every physician, ethicist or legalist will agree that a person giving consent should be "fully informed", "free of coercion" and "competent"[2], but there is no consensus on details to be provided during the process, nor the manner in which these should be delivered and documented. In 2011, the Advisory Committee on Organ Transplantation (ACOT) released a document with recommendations for the informed consent procedure in living organ donors in the United States (US). Although not legally binding, the committee recommended that each hospital involved in live organ donation should use a standardized informed consent form, adjusted to regional legislation. The document also provides a list of items that should be included in the educational process [3]. These forms have not yet been implemented in all transplant centers, but at least written and signed consent is mandatory in many [4]. Unfortunately, the European situation differs from the American one. There are no European or nationwide guidelines, nor are there legal documents providing structured details on the informed consent procedure. Although there are many different policies and guidelines outlining matters that should be disclosed to potential donors, details are often not specified [5, 6]. The actual documentation of consent also differs regionally; Spanish law for example, dictates that consent for live donation has to be obtained, documented and signed in the presence of a judge [7], while in Greece at least two witnesses have to sign a declaration of consent[8].

These differences make it impossible for healthcare professionals to practice a uniform strategy and it is challenging to determine which patient has received which information. Recent data from our group demonstrate that when tested on their knowledge, a large number of living kidney donors underestimate the complications and risks of live donor nephrectomy. Surman *et al.* published similar findings in renal and liver transplant patients, revealing significant conceptual limitations to their knowledge about their postoperative situation, underlining the importance of adequate preoperative education [9]. Comparable results are demonstrated in other studies, where donors report varying degrees of (dis)satisfaction with and misunderstanding of provided information

[10]. The question is raised whether the necessary information has not been provided correctly, whether donors simply not understand or remember it, or, as has been proposed by some, whether they selectively filter information and thus miss particular risks associated with donation. Standardizing the informed consent procedure will help us better understand and address this. In light of ever-growing demands for safety, transparency and documentation within the healthcare system, it can be expected that a standardized procedure will be legally mandatory in the near future.

The aim of this systematic review is to make an assessment of the informed consent procedure as it is described in the available literature, with regards to disclosed information, timing, documentation and donor comprehension of, and satisfaction with provided information. We hereby hope to address shortcomings and create the basis for a standardized procedure. In addition we will propose a concept to confirm donors' comprehension of the provided information.

METHODS

All aspects of the Cochrane Handbook for Interventional Systematic Reviews were followed, and the paper was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[11]. No review protocol was written in advance.

Literature search strategy

A comprehensive search was performed on January 17th 2014 in Embase, Medline OvidSP, Web-of-Science, PubMed, CENTRAL (The Cochrane Library 2014, issue 1) and Google Scholar. No date limits were used, so that no potentially relevant articles would be missed. Detailed search strings for each database are provided in Appendix 1, no other limits were applied. All references were screened by two independent reviewers (KK, JAL). If any discrepancies in inclusion or exclusion occurred, a senior investigator was consulted (FJMFD). Study selection was accomplished through three phases of screening. During the first phase, the following types of studies were excluded: published conference abstracts and articles not presenting empirical research or reviews (*e.g.* personal commentary, letters to the editor). During the second phase, abstracts were reviewed for relevance, and the full-text articles were obtained. In the last ~~next~~ phase, full-text articles were reviewed; requirements for inclusion were a description of the informed consent procedure in live donor nephrectomy. Manual reference checks were performed to search for potentially missing studies. No authors were contacted to provide full-text articles, since all included articles were obtained in full-text. Articles not written in English were excluded to prevent translational bias.

Data extraction and critical appraisal

Data extraction was performed by two authors (KK, JAL). Again, if any discrepancies occurred, consensus was reached after consulting a senior investigator (FJMFD). The level of evidence of each paper was established using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool[12]. The GRADE approach defines the quality of a body of evidence by consideration of risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias.

RESULTS

Out of 1009 papers identified in the initial search, 21 studies fell within the scope of the search protocol, consisting of 13 original articles and eight reviews. No additional studies were included after manually scrutinizing reference lists. The PRISMA flow diagram for systematic reviews is presented in Figure 1. Unfortunately, the quality of the

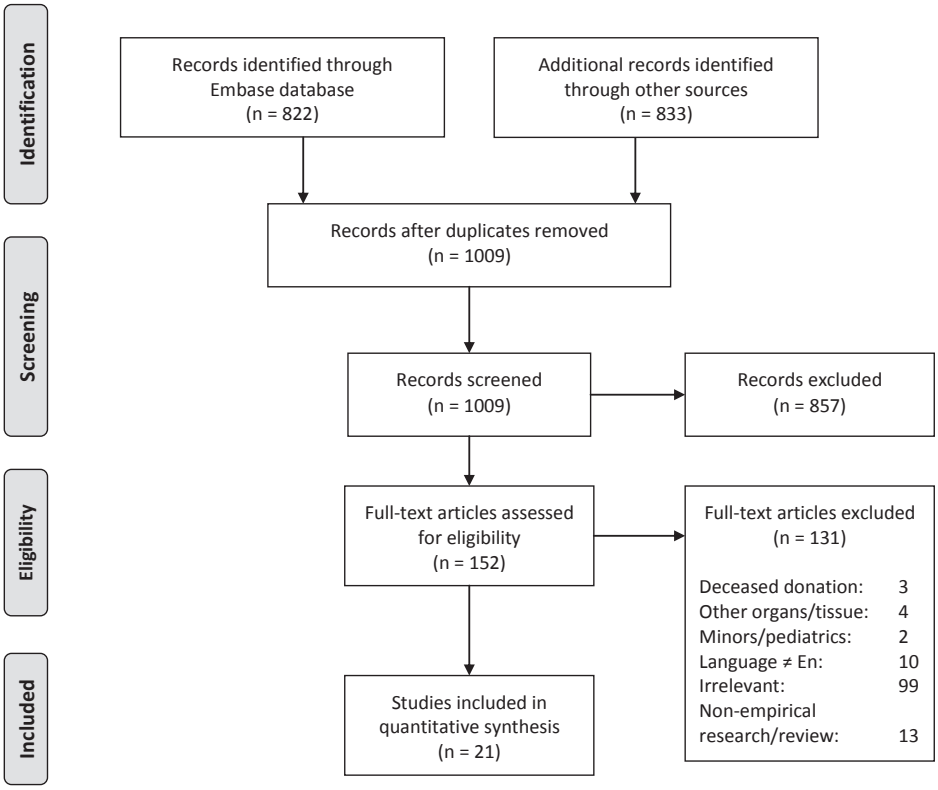

Figure 1- PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the systematic literature search.

included articles ranges from low to very low which can be explained by the fact that our systematic review consists of observational studies, automatically downgrading the level of evidence. The detailed assessment of the quality of the available evidence using the GRADE tool is presented in Figure 2.

Informed Consent Procedure in Live Donor Nephrectomy

Patient or population: Live Kidney Donors
Settings: Several types of studies as listed below
Intervention: Informed Consent

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)
Donors Surveys/Interviews Follow-up: 42 years[1]	496 (5 studies[2])	⊕⊖⊖⊖ **very low**[3,4]
Medical professionals Surveys Follow-up: 2 years[5]	551 (3 studies[6])	⊕⊖⊖⊖ **very low**[3,7]
Informed Consent contents/procedure Follow-up: 9 years[8]	493 (5 studies[9])	⊕⊕⊖⊖ **low**[10]
Reviews Follow-up: 41 years[11]	0 (8 studies[12])	⊕⊖⊖⊖ **very low**

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Five studies, publication range 1970-2012
[2] Five survey/face to face interview studies
[3] Subjective information in surveys and interviews
[4] Great variations between donors
[5] Three surveys, publication range 2007-2008
[6] Three survey studies
[7] Great variations between practitioners/centers
[8] Five observational studies, publication range 2004-2013
[9] Three detailed analyses of informed consent forms/written information, two local process descriptions
[10] Objective analysis/description of materials or procedures
[11] Eight reviews, publication range 1971-2012
[12] Reviews

Figure 2 - Summary of findings table of included evidence about the informed consent procedure in live donor nephrectomy, generated by the GRADE tool.

Informed consent process

Reviews

Table 1 summarizes the results of eight reviews published between 1971 and 2012[10, 13-20] including the country of origin and year of publication.

The main concern with informed consent in live organ donation is that hardly any research has been performed on the subject. Despite the importance of informed consent emphasized by all authors and the advice to implement standardized procedures documenting donors' understanding of all risks and benefits, most hospitals have not yet done so, nor are there mandatory statutes issued by governments to ensure that

Table 1. Results of eight review articles investigating informed consent in living kidney donation

Author, year, Country, LKD rate (%)[a]	General contents	Key topic	Conclusion
Gordon, 2012 USA (43%)	Informed consent procedure	Living kidney and liver donors	Deficiencies in disclosure resulting in unmet information needs and poor comprehension of risks Variability in transplant centers Greater efforts are needed to improve the informed consent procedure
Ciszek, 2012 Poland (4%)	Ensuring donor safety	Living kidney donors	Standardized informed consent form should be introduced, expressing donors' full recognition of risks and benefits. It should enumerate types of info to be provided. Both verbal and written consent should be mandatory. Include non-medical specialists in process of information provision. Mismanaged communication may result in serious misconceptions and risks for donors and team members.
Petrini, 2010 Italy (NK)	Informed consent	Living kidney donors	Comparison of research subjects with donors can improve informed consent procedure Rigorous framework is crucial Absolutely free and informed consent is illusory but continuous efforts have to be made to improve current situation Validation of informed consent should be rigorous yet not overburdening
Valapour, 2008 USA (45%)	Understanding and validity of informed consent	Living kidney donors	Small number of empirical studies Donors may not be fully informed at time of giving consent Donor understanding of consequences of donation is an important area of investigation to improve informed consent process
Mazaris, 2006 United Kingdom (32%)	Ethical issues in kidney donation	All aspects of kidney donation	Only thoroughly informed donor can make voluntary decision Intense debate on ethical issues in transplant community Agreement would protect potential donors and ensure future of living kidney donation
Kallich, 1994 USA (38%)	Informed consent procedure, law, policy and ethics	Living organ donors	Transplant community needs to implement a series of policies and procedures that protect donors' right to make informed choice
Adams, 1987 USA (NK)	Informed consent, liability, medical ethics	All living organ donors	Donors should have all information a reasonable person would want plus any individual specific needs Consent obtained based on misrepresentation or nondisclosure is invalid and may be seen as battery, but these days failure to disclose nature, risks or alternatives is mainly seen as professional negligence Organ donor should enjoy as much protection as medical research subject

Table 1. Results of eight review articles investigating informed consent in living kidney donation (continued)

Author, year, Country, LKD rate (%)[a]	General contents	Key topic	Conclusion
Fellner, 1971 USA (NK)	Psychological aspects of donor selection	Living kidney donors	Discrepancy between what the medical profession assumes the kidney donor experiences during the screening period and the actual perception. Most donors decide to donate immediately after being asked, special situation that cannot be compared to normal decision making Initial decision has to be defended throughout waiting period for surgery

[a]Living kidney donation rates in country of origin at time of publication
LKD – live kidney donation; NK – not known

hospitals live up to certain standards. Various authors compare living organ donors to medical research subjects[17-19, 21]. Although they are essentially not that different in undergoing a medical procedure for the benefit of others, for the latter, strict rules and regulations apply and every research project is subject to extensive analysis by an independent Institutional Review Board (IRB)[17, 19]. It can be assumed that no IRB would ever approve kidney removal as part of a research trial[21]. Multiple authors state that donors, contrary to research subjects, may not make a decision by carefully weighing risks and benefits but rather by emotional or moral reasoning[13, 15, 22, 23]. Fellner describes that there seems to be a discrepancy between what the potential kidney donor experiences during the screening period and what the medical team generally assumes. Instead of a deliberate balancing of risks and benefits, a simple yes-or-no decision is followed by an extensive waiting period and a feeling of having to defend the decision[13]. Some authors believe that donors do not actually perceive all the information given to them, but rather focus on positive aspects to reaffirm their decision[15]. The question has been raised whether they actually understand all information provided to them, and it is argued that potential donors may not be fully informed at the time of consent[10, 14, 15, 17, 20]. Although this theory is somewhat confirmed by donors retrospectively reporting that they did not feel adequately informed about (some) aspects of kidney donation[10, 17], it has to be taken into account that the concept of live kidney donation has changed drastically since the 1970s. The live donor nephrectomy itself has been fully implemented in the general practice and much more information has become available regarding outcome and possible peri- and postoperative complications. Due to these developments live kidney donation has gained ground over the past decades, and numbers are increasing worldwide; this merits a revisited opinion on information disclosure and consent. Although the informed consent process has evolved alongside the surgical procedure in an attempt to incorporate the most up to date knowledge and transfer it to potential donors in an understandable fashion, it still has to be brought to perfection. In addition,

authors worry that psychosocial and financial aspects are neglected in the informed consent procedure, which is often led by medical specialists[16, 17]. More research is needed to gain insight in what information should be provided to potential donors, by whom and in which manner to ensure optimal support in the decision making process, thereby safeguarding their autonomy[10, 17].

Original papers

Thirteen original papers were identified (1970 – 2013). Table 2 provides an overview of the main characteristics and results of these studies, as well as the country of origin. Only a few studies have been performed assessing the informed consent procedure in live kidney donation. Most are surveys (N=5) among either medical professionals (N=3) or donors (N=2), or material (*i.e.* educational information, consent forms) or procedure analysis (N=4). In accordance with the reviews, considerable variations were observed between transplant centers and in some centers information provision was even deemed inadequate[24]. In one survey, a little over half of the respondents reported mentioning a certain risk of developing kidney failure but another 42% told donors that this risk was none-existent or left it out completely[25]. Similar differences were encountered by other authors[26], highlighting once again the need for a standardized procedure. Although these differences can be at least partially attributed to lack of evidence regarding the medical risks donors are exposed to after nephrectomy, it is alarming that potential donors receive different information in different centers.

Gordon showed that some donors did not feel accurately informed about the post-operative risks and possible complications by the transplant team[21]. Fellner however, reported that all donors felt the information-giving process was more than adequate[23]. Valapour *et al.*[27] described that although some donors did report a lack of understanding of especially long-term (*i.e.* 48%), psychological (31%) and financial risks (68%), this did not influence their theoretical willingness to donate again or negatively affect their experience, supporting Fellner's earlier conclusion that the decision making process in donors may differ from that in patients[22, 23, 27], which was later confirmed by Simmons *et al.* [28].

Contents of informed consent

Authors agree that whilst medical aspects of donation are usually well covered, psychosocial and financial aspects are much less frequently discussed[24, 25, 29]. Worsened familial relations associated with live kidney donation are reported in a small number of cases and up to 25% of donors deal with adverse financial effects[30]. The possibility of positive psychological outcomes are mentioned in about three quarters of centers, whereas negative aspects are often neglected[25]. Parekh *et al.* describe that informed consent in US centers is mainly obtained by surgeons (74%). In non-US centers surgeons

Table 2. Results of 13 original articles investigating informed consent in living kidney donation

Author, Year, Country, LKD rate (%)[a]	Study design	Topic	Study group	Main study parameter	Results/Conclusion
Thiessen(4), 2013 USA (43%)	Inventory	Consent forms	143 unique forms (RR 87%)	Inclusion of elements in consent forms	99% Obtains written consent Need for uniform process
Gordon(31), 2012 USA (43%)	Inventory	Consent forms	332 forms (RR 36%)	Reading levels of consent forms	Average reading level freshman college Most transplant centers have failed to incorporate evidence based practices in informed consent forms
Gordon(21), 2012 USA (43%)	Interviews	LD experience	LD in post-operative period	Experience in general	LD felt uninformed about (rare) complications, although most had a positive experience
Valapour(27), 2011 USA (44%)	Survey, retrospective	LD understanding	262 2-40 months after donation (RR 74%)	Understanding of short- and long term risks	Good understanding recipient outcome, screening process and short term medical risks, less understanding of psychological risks, long term medical risks and financial risks 94% Would donate again
Sites(36), 2008 USA (45%)	Descriptive	IC process	One US hospital	Educational process	Extensive informed consent procedure, repetitive information provision, check of understanding, two week cooling off period.
Parekh(25), 2008 United Kingdom (36%)	Survey	Communication of risk factors	216 Health care professionals 40 countries, 177 centers	Methods and contents of risk conveying	Considerable variation in communication of risks between centers worldwide 69% Written consent form >90% Convey specific risk factors, great variation in contents
Rodrigue(29), 2007 USA (44%)	Survey	General practice	132 US centers (RR 64%)	IC process	30% Written consent prior to screening 95% Written consent prior to surgery, other 5% verbal consent 11% Cooling off period Community would benefit from standardized process, improve public opinions and recipient access to living donation

Housawi(26), 2007 Worldwide	Survey	Long term medical risks of kidney donation	203 transplant professionals worldwide	Communication of risk factors, surgeons vs nephrologists	66% Written consent >80% discusses hypertension, proteinuria, kidney failure; actual information varies (increased vs not increased) Surgeons less convinced of long term risks than nephrologists
Lennerling(24), 2004 Zweden (36%)	Inventory	Written LD information	16 information brochures from 14 countries	Provided information in brochures	Many brochures lack crucial information Emotional decision making; adequate information provision even more important Great variation in hospital stay and sick leave, financial terms.
Wright(43), 2004 Canada (58%)	Descriptive	Donor evaluation process	One Canadian hospital	Donor evaluation/IC process	Process of confirming capacity to understand and consent, disclosure of information about the proposed procedure, donor understanding Transparency of process and procedures & reflection on practice may encourage debate and permit openness and clarity
Cabrer(30), 2003 Spain (NK)	Survey	LD experience	22 LDs from Spain six months after donation	Evaluation of quality of process perceived by LD	88% Understood evaluation period in retrospect 95% Confirmed received information concurred with actual experience
Fellner(23), 1976 USA (NK)	Interviews	LD experience	12//22//148 (potential) LDs	Decision making process and overall experience	Decision making process immediate, prior to information gathering. Information-giving process more than adequate Experience satisfying and meaningful, All would repeat process
Fellner(22), 1970 USA (NK)	Interviews	LD experience	20 LDs after donation, 10 planned LDs prior to donation	Decision making process and overall experience	23 LDs made decision immediately upon getting asked, before receiving all information. None opted-out after a long and repetitive information period Decision making in donation is an early event preceding all information gathering and clarification

[a]Living kidney donation rates in country of origin at time of publication

LKD – Live Kidney Donation; RR – response rate; LD – living donors; IC – informed consent; NK – not known

are responsible for approximately 50% of cases[25]. Housawi *et al.* presented similar rates with surgeons obtaining consent in 70% of donors[26]. Table 3 demonstrates items that should, according to current literature and our own experience, be incorporated in a standardized informed consent procedure for live donor nephrectomy, and by whom they should be provided.

Table 3. Elements to be included in a standardized informed consent procedure

Category	Information	Details
Surgical information	Mortality	
	Major complications	Organ damage
		Bleeding
		Infectious complications
		Thromboembolic complications
	Minor complications	Pain
		Minor infectious complications
	Duration of hospital stay	
Medical information	Screening procedure	
	Long term effects	Chronic pain
		Hypertension
		Proteinuria
		Kidney failure
		Cardiovascular disease
	Risks of living with one kidney	Risk of malignancy in remaining kidney
		Kidney trauma
	Follow up	
Psychosocial information	Inflicted stress	
	Depression	
	Benefits	
	Potential impact on lifestyle	
Financial information	Expenses to be borne by donor	
	Potential impact on ability to obtain health- and life insurance	
	Potential impact on ability to future employment	
Other information	Voluntary nature	
	Legitimate ways out	
	Recipient benefits	Better quality kidney
		Shorter waiting time
	Risk of graft loss in recipient	
	Alternative donation procedures	
	Sick leave duration	

Many brochures and informed consent forms appear to be quite difficult to read. Gordon *et al*[31] assessed 332 informed consent forms demonstrating an average college freshman reading level. This stands in marked contrast to recommendations that patient education materials should be written at an average of 5th-8th-grade primary school reading levels. Seeing this in perspective of our own living donor population, this may seem a bit harsh. The median age of our population is currently 53 years, and a recent cohort

demonstrates that 56% of our donors have received further education after primary school (Timmerman *et al.*, unpublished data)[1]. Still, every donor needs to understand all provided information, and if nearly half of the population has only gone to primary school, college reading levels may be too difficult.

Timing of information and consent

Authors agree that information should be repetitive and provided at an early stage [10, 17].

Although most centers use presumed consent for the evaluation process, the Centers for Medicare and Medicaid Services (CMS) require programs to have two separate informed consent processes; one for the screening period and one for the actual donor nephrectomy, the latter already being employed in most centers [25, 29]. Many donors report that they decided to donate a kidney the first moment they heard about the option [22, 23], prior to receiving any information about the risks of the procedure. It is even more striking that none of them changed their mind after going through the extensive screening process. It is recommended that specific details of provided information are carefully documented upon each donor-contact. Although donor understanding is still not guaranteed, there will at least be more insight into the information-giving process.

Legal aspects

The manner of providing information to (potential) donors and the method of acquiring informed consent is dependent on the local legal situation. Policies and laws vary enormously between different countries [32, 33], and in the US even between different states[29]. In some regions, the donor's signed informed consent is sufficient[29], while others require witnesses or even a public authority to be present at the time of consent[7, 8, 33]. Even though informed consent is a standard requirement for live organ donation in most countries, some require additional justification[33]. In the Netherlands, the law on organ donation stems from May 1996 and is quite lenient on the matter of live organ donation. Consent has to be obtained in writing, signed and dated. This is further documented in the EU Directive (EU Directive 2010/53/EU for Living Organ Donation Practice)[34] which requires Member States to adhere to minimum standards in live organ donation (van Assche *et al*, submitted)[2].

Donor experience

Few studies discuss donors' experience with the informed consent procedure [21, 27, 30] and most are descriptive, retrospective studies or surveys. Fellner reports very positive results in early studies dating back to the seventies, with all interviewed donors reporting the experience to be "the most meaningful of their lives" [22, 23]. More recent studies demonstrate that donors generally feel well informed and most of them would be willing to donate again with the information at hand [27, 30]. Nonetheless, some donors

do report various degrees of dissatisfaction with and misunderstanding of provided information. Gordon *et al.* [21] published numerous living donor experiences. For some donors, it was the most meaningful experience of their lives; others look back on the ordeal with mixed feelings. Many donors felt, at least to some degree, unprepared for (adverse) postoperative events. Two donors reported a negative experience with donor education and informed consent: complication and mortality rates and long term risks were inadequately described as were life style adjustments and risks for the recipient. Another donor reports a similar experience, where she feels that "everything she learned about live kidney donation, she learned after her surgery", and regrets the blind trust she put in the transplant team. Yet another donor criticizes the media and medical industry for "only promoting the happily-ever-after stories", failing to investigate or share negative donor experiences. Another recurring statement in the donors' narratives was the postoperative realization that they were 'blinded' and thereby not quite informed at the time of giving consent: "I acknowledged my understanding, but never actually believed the rules applied to me", or: "I thought my consent was informed, but I eagerly heard what I wanted to hear – that I was eligible to donate".

DISCUSSION

With regulations in health care becoming ever more strict, transplant teams are forced to reevaluate current practice concerning patient safety and informed consent, especially in living organ donors undergoing surgery for the benefit of others. Donor education, leading up to informed consent, needs to be carried out according to certain standards.

We performed a systematic review of the available literature to assess the existence and contents of these standards and whether transplant centers have actually implemented such procedures in their daily practice. We have included original articles as well as other reviews, thus creating a "meta-review" of the available literature. To the best of our knowledge, ours is the first article that actually bundles all available evidence on the informed consent procedure in live kidney donation. This is therefore the first overview article that can serve as a basis for creating a standardized procedure. Although many authors touch on the subject, most do not actually describe the contents of the informed consent procedure. Little research has been performed, and available data shows a great deal of variation in practice between different hospitals [25, 26], and even between different team members within one organization. Similar results were encountered when information brochures and informed consent forms from different centers were analyzed. In addition, these forms proved to be of an average college freshman reading level, which is much higher than the recommended level of 5th-8th grade primary school [31].

The most alarming finding however was the fact that, although a minority, some donors reported feeling misinformed, in some cases to such a degree that they felt the transplant team had lied to them regarding possible complications, long-term results and recipient outcome [21]. These donor experiences are unacceptable and pose a threat to the success of a living donor transplant program. It is our responsibility to safeguard the informed consent procedure for live kidney donation by ensuring that potential donors are well educated and prepared for their upcoming procedure and postoperative course.

Although standardizing the informed consent procedure is a noble aim, there will inevitably be variations due to cultural, religious and educational differences between donors. Still, a standardized procedure will serve as a guideline, and alterations can be made according to the local population. Additional features can further support the educational system, and adjustments can be made according to local needs. Appointing independent donor advocates or involving a home-based educational team in the process could be of great value [35-37].

Another point of interest is the fact that we cannot change the way donors perceive the information laid upon them. Fellner was the first to demonstrate that most donors made the decision to donate upon the first moment of hearing of the option, and none of the interviewed donors had changed their mind after learning about all the risks associated with donating a kidney [22, 23]. At the time these studies were conducted, live donation was performed only in family members. Donors may therefore have felt more pressure to donate because there were fewer options for their loved ones. Still, more recent studies confirm Fellner's earlier findings and although much more knowledge is available regarding the nephrectomy, its outcomes and possible adverse events it is again suggested that donors do not actually use the provided information to make a deliberate decision, carefully weighing risks and benefits in a process eventually leading up to consenting or declining, but rather to reassure them that they have indeed made the right call [15].

There are, unfortunately, few studies reporting on donor experience regarding education and consent in live kidney donation. In the field of live liver donation a little more information is available, but results vary: some studies report donors' knowledge of the risks and benefits to be "good to very good", while some others report significant gaps in their knowledge [38]. Available information on kidney donors is anecdotal and no reliable conclusions can be drawn, but it does give some insight in their perception of the information process. Although most donors considered donating to be a positive and meaningful experience and the main proportion would repeat the procedure if given the chance, quite a large percentage of donors report not being fully informed about (certain aspects of) the procedure [21, 27]. Some donors report being well informed but simply thinking that the mentioned risks would not apply to them [21]. This not only

further underlines the importance of adequate documentation to determine whether all donors have indeed received all the necessary information, it also warrants a new strategy to confirm donor comprehension. To assess whether the provided information has actually reached donors, a pop-quiz could be administered to them at different moments in their screening process. A prospective trial using short questionnaires with open questions is currently being conducted in our center, to assess whether this provides accurate information regarding donor comprehension. This will give us more insight in which items of the informed consent process are covered adequately, and which need more specific attention. This then will guide us in creating a standardized procedure.

One of the foreseen problems with the incorporation of a standardized information- and consent process is the heterogeneity of the potential donor pool. Striving for a worldwide standard format will therefore be virtually impossible, in light of political, cultural and religious differences between countries and even populations within one geographical area. A standardized format can serve as a basis and alterations can be made according to the local situation. Another objection physicians may have to the implementation of a standardized procedure is the extra labor that mandatory documentation will add to their workload. However, 82% of surveyed transplant centers worldwide would be willing to adopt centralized consent templates, with US centers being slightly more willing than non-US centers (79% vs 84%, $p<0.001$) [25].

Limitations

A limitation and one of the major issues of this review, is the fact that the available evidence is rather subjective and descriptive. Since donation procedures vary between regions, countries and centers[39], as do informed consent procedures, published data is subject to interpretation in light of local practice. The contents of the informed consent procedure, and the manner in which information is provided, is dependent on local legislation and opinions on for instance ethics and religion. These opinions vary over time and per country, or even per region within a country[39, 40]. Since the included studies comprise a wide time range and geographical area, results must be seen in perspective of these differences. In addition, local statistics on live donation, especially live donor nephrectomy complication rates and success rates in recipients may influence not only the way medical practitioners inform potential donors, but also the way that donors perceive this information, and how they experience the donation process in general.

For this systematic review we have only included living kidney donors, opposed to including all potential donors (*i.e.* liver, lung). While the process of informed consent in live liver- or lung donation is in many aspects similar to live kidney donation, complication rates in the former two are far greater than those in live kidney donation.

In addition, the geographical distribution of live liver and lung donation is different from live kidney donation. Although there are significant differences between countries regarding live kidney donation rates, this is still a much more common procedure. Live kidney donation was the first form of live donation to be performed, and informed consent procedures for the other organs may even be based on the procedures developed for kidney donation. Even so, the (also scarce) literature on informed consent in organ donation other than kidney similarly concludes that there are many variations in policy, opinions and donor comprehension, and consensus on best clinical practice is lacking[38].

There are obviously many more ethical issues that should be addressed regarding live kidney donation, and may deserve attention during donor education and the informed consent procedure, but which are not included in this systematic review. Medical practitioners should ascertain themselves that there are no signs of coercion, and that the decision to donate is indeed voluntary. There is also the matter of paid donation, a currently much debated issue, on which opinions differ greatly [41, 42]. However, these issues do not quite fall within the scope of this review and are therefore not pursued any further.

Looking at the assessment of the quality of the included studies, using the GRADE tool, we conclude that the evidence of each included study ranges from very low to low. Since the GRADE tool is primarily useful for assessment of interventional studies, the evidence scale is automatically downgraded since the published literature consists only of observational studies. Creating a protocol for a randomized controlled trial regarding the informed consent procedure is difficult and at risk for bias, and this has to the best of our knowledge not yet been initiated. It would, however, drastically improve the quality of evidence regarding this procedure.

In conclusion, it is clear that a standardized informed consent procedure for live donor nephrectomy is much needed to ensure donor safety and satisfaction. It is to be expected that this will become legally mandatory, thereby protecting donors as well as physicians. It will further aid the transplant community in systematically providing and documenting information that will optimally prepare potential donors for the procedure and postoperative course. Once implemented it will serve as a basis in donor education and greatly benefit donors as well as medical practitioners.

The success of implementing a standardized procedure relies on input from transplant professionals from different centers and preferably different countries involved in live kidney donation. If an international working group were to be set up, local and regional protocols and guidelines could be combined to form a solid concept. The authors would like to invite those interested in participating in such a working group to contact us, preferably through email correspondence.

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APPENDIX I – SEARCH STRINGS USED IN DIFFERENT DATABASES

Embase.com

('informed consent'/de OR (((inform* OR form*) NEAR/3 consent*) OR ((duty OR duties) NEAR/3 warn*)):ab,ti) AND ('living donor'/de OR ((living OR live OR related OR altruist*) NEAR/3 (donor* OR donation* OR transplant*)):ab,ti)

Medline OvidSP

("informed consent"/ OR (((inform* OR form*) ADJ3 consent*) OR ((duty OR duties) ADJ3 warn*)).ab,ti.) AND ("living donors"/ OR ((living OR live OR related OR altruist*) ADJ3 (donor* OR donation* OR transplant*)).ab,ti.)

Cochrane

((((inform* OR form*) NEAR/3 consent*) OR ((duty OR duties) NEAR/3 warn*)):ab,ti) AND (((living OR live OR related OR altruist*) NEAR/3 (donor* OR donation* OR transplant*)):ab,ti)

Web-of-science

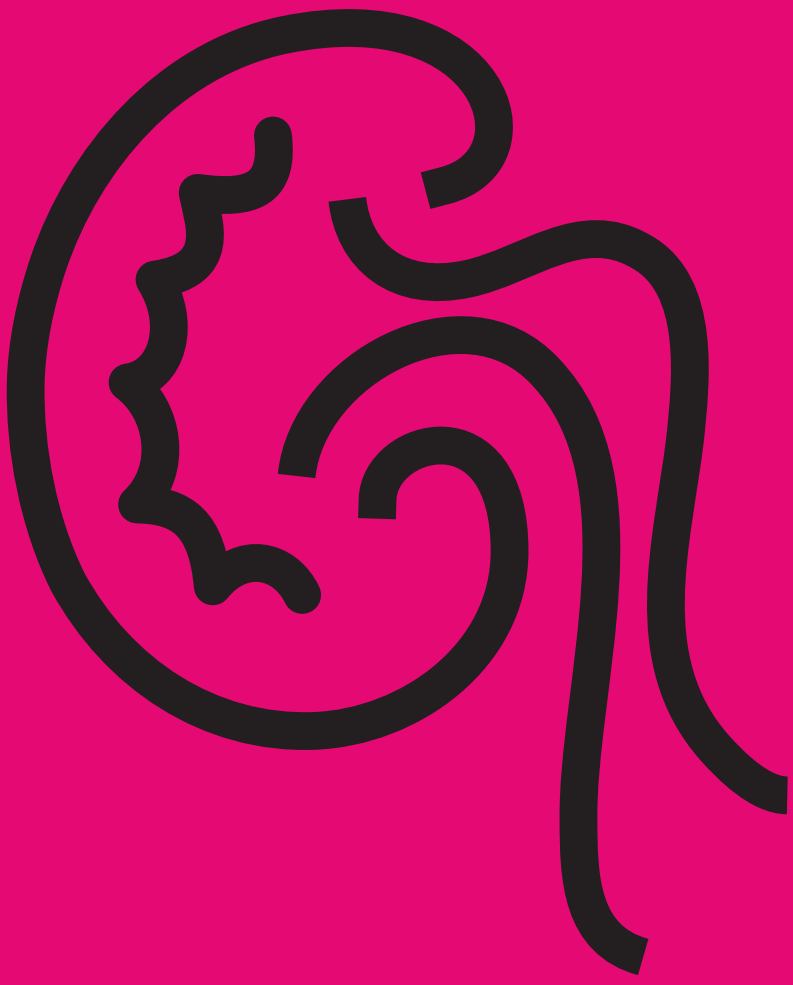
TS=(((((inform* OR form*) NEAR/3 consent*) OR ((duty OR duties) NEAR/3 warn*))) AND (((living OR live OR related OR altruist*) NEAR/3 (donor* OR donation* OR transplant*))))

PubMed as publisher

((((inform*[tiab] OR form*[tiab]) AND consent*[tiab]) OR ((duty[tiab] OR duties[tiab]) AND warn*[tiab]))) AND (((living[tiab] OR live[tiab] OR related[tiab] OR altruist*[tiab]) AND (donor*[tiab] OR donation*[tiab] OR transplant*[tiab]))) NOT medline[sb]

Google Scholar

"informed consent"|"duty to warn" "living|live|related|altruistic donor|donation|transplantation"|"living|live|related|altruistic kidney donor|donation|transplantation"



Chapter 3

Peri-operative Events and Complications in Minimally-Invasive Live Donor Nephrectomy. A Systematic Review and Meta-Analysis

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ABSTRACT

Background Minimally-invasive live donor nephrectomy has become a fully implemented and accepted procedure. Donors have to be well educated about all risks and details during the informed consent process. For this to be successful, more information regarding short-term outcome is necessary.

Methods A literature search was performed, and all studies discussing short-term complications after minimally-invasive live donor nephrectomy were included. Outcomes evaluated were intra- and postoperative complications, conversions, operative and warm ischemia times, blood loss, length of hospital stay, pain score, convalescence, quality of life and costs.

Results 190 Articles were included in the systematic review, 41 in the meta-analysis. Conversion rate was 1.1%. Intraoperative complication rate was 2.3%, mainly bleeding (1.5%). Postoperative complications occurred in 7.3% of donors, including infectious complications (2.6%), of which mainly wound infection (1.6%) and bleeding (1.0%). Reported mortality rate was 0.01%. All minimally-invasive techniques were comparable with regard to complication- or conversion rate.

Conclusion The employed techniques for minimally-invasive live donor nephrectomy are safe and associated with low complication rates and minimal risk of mortality. These data may be helpful to develop a standardized, donor-tailored informed consent procedure for live donor nephrectomy.

INTRODUCTION

Live donor nephrectomy is considered to be a safe, low risk procedure, fully implemented in many transplant centers worldwide. There are many different surgical techniques for this procedure, and preference differs between centers[1, 2]. Although the traditional open technique is still employed, minimally-invasive procedures should be recommended as the gold standard, since morbidity is reduced and quality of life improved[3-5]. Modifications to the laparoscopic technique have been introduced, including the retroperitoneoscopic approach (RDN), hand-assistance (HALDN/HARP) and robot-assisted approach as well as the single incision laparoscopic donor nephrectomy (LESS). More recently, the first cases of natural orifice transluminal endoscopic surgery (NOTES) live donor nephrectomy have been reported, with transvaginal kidney extraction[6-8]. With the introduction of these techniques, a great number of studies, including randomized controlled trials, have been performed to assess their value, safety and efficacy. Still, there doesn't seem to be one technique that evidently stands out from the rest, and preferences vary among surgeons and centers (as seen in a recent survey among kidney transplant surgeons, Kortram *et al*, unpublished). Overall, complication rates are low and mortality occurs only sporadically [9, 10]. However, if a healthy donor is not well informed and experiences complications related to the procedure anger and distress may occur, negatively affecting the outcome for this patient as well as the living donation program. Therefore, donors must be well educated during the informed consent process. A key condition for the successful employment of donor education and informed consent is the availability of a complete overview of the specific details and risks of the operative techniques.

Little research has been performed regarding the specific contents of the informed consent procedure, and there are no well-designed studies on how donors experience the informed consent and the educational process[11]. Available evidence is quite subjective, and if anything, suggests that some donors report feeling misinformed, in a single incidence to such a degree that the donor felt the transplant team had withheld the truth about possible complications, long-term results and recipient outcome[12]. On the other hand, providing more information doesn't necessarily improve donors' comprehension of details and risks of the procedure[13-15].

The current project has two major objectives. First, to provide a systematic review of all available evidence on informed consent including all information regarding short term outcome of minimally-invasive live donor nephrectomy focusing on the incidence of individual complications. Second, to conduct a meta-analysis comparing the different procedures for live donor nephrectomy and complications. By creating a clear overview of the incidence of complications and (serious) adverse events, evidence-based infor-

mation can be provided to potential donors, thereby further optimizing our educational and informed consent process for the live donor nephrectomy.

MATERIALS AND METHODS

All aspects of the Cochrane Handbook for Interventional Systematic Reviews were followed and the study was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[16] for Randomized Controlled Trials and the Meta-analysis of Observations Studies in Epidemiology (MOOSE) guidelines[17] for observational studies. The initial review protocol was registered in the PROSPERO database with number CRD4201404170 (www.crd.york.ac.uk/PROSPERO/).

Literature search strategy

A comprehensive search was performed with the help of a biomedical information specialist on September 24th 2014, and updated on March 8th 2016, in Embase, Medline OvidSP, Web-of-Science, PubMed, CENTRAL and Google Scholar (Figure 1). No date limits were used. Search strings for each database are provided in Appendix 1, no other limits were applied during the search. During screening, only articles written in English were included to prevent any misinterpretations of data. All references were screened by two independent reviewers (KK, FJMFD). If any discrepancies occurred, a third investigator was consulted (JNMI). Study selection was accomplished through two phases. During the first phase, titles and abstracts were reviewed for relevance, and full-text articles were obtained. Published abstracts were included if they contained detailed information regarding complications. During the second phase, full-text articles were reviewed. Case reports, commentaries and letters were excluded. Survey studies and studies describing results from national databases were excluded to prevent double inclusion of donors. Studies mentioning short-term complications after minimally invasive live donor nephrectomy were eligible for inclusion. If a full text article corresponding to a published meeting abstract was available, the abstract was disregarded. The same strategy was employed for preliminary results of which definitive results were also available. If data was unclear or pooled for different techniques or indications the authors were contacted to provide source data. Authors were also contacted when study cohorts of two or more publications seemed to overlap. If no response was obtained after two reminders, articles were excluded if data was pooled for different nephrectomy indications, or if the classic open technique was included in their cohort. In some articles, with evident overlapping cohorts, inclusion was based on a number of criteria. Preferably, the most recent publication or the largest cohort of patients was included. However, in some cases a dated publication contained more details and it was therefore decided to include the paper

with the greatest evidential value. If operative techniques were pooled, articles were included in the systematic review but not in the meta-analysis. Systematic reviews and meta-analyses were carefully screened for already published/background information but were not included in the data-analysis process. All references of included full text articles were manually scrutinized to ensure that no relevant articles were missed.

All articles were used for the systematic review part of this project; only those that compared (or mentioned, within one cohort) two or more different minimally-invasive live donor nephrectomy techniques were included in the meta-analysis.

Data extraction and critical appraisal

Data extraction was performed by two authors (KK, FJMFD). Again, if any discrepancies occurred, consensus was reached after consulting a third investigator (JNMI). Data was collected on study design, population, operative technique, procedural details and complications. A list of all possible complications was created prior to the start of data extraction, and if complications came up that weren't included these were added to the checklist. All intra- and postoperative complications and conversions were scored, as well as mortality. Conversions from LESS to multiport laparoscopy or a hand-assisted procedure or from pure laparoscopy/retroperitoneoscopy to hand-assisted were not scored in this analysis. If an article only described specific complications, all other complications were scored as "unknown". If however the description of complications was detailed (for instance split to minor and major) but some "common" complications were not listed in an article, it was assumed these did not occur in that specific population and were scored as "zero". Less frequently mentioned complications like (but not limited to) testicular pain and thigh numbness were scored as unknown. Mortality was scored as "none" or the number of fatalities, when this was literally stated. It was scored as "none assumed" when for instance "no (other) major complications occurred", or when no donors were missing in follow-up data. All other cases were scored as "unknown". A number of other outcome measures were scored, namely operative time, estimated blood loss, warm ischemia time, length of stay, readmissions, length of convalescence, pain score, analgesic requirement, quality of life and costs.

The level of evidence of each paper included in the meta-analysis was established using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool[18]. The GRADE approach defines the quality of a body of evidence by consideration of risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (supplementary figure 1).

Statistical analysis

For the systematic review individual complications were presented as absolute values and percentages. Continuous factors were provided in means and range.

A meta-analysis was performed using Review Manager version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). Random effects models were used to account for possible clinical heterogeneity. Results were presented in forest plots with risk ratios (RR). Overall effects were determined using the Z-test, and results were presented in risk ratios. Ninety-five percent confidence intervals (CI) of these values were given and P-values <0.05 were considered statistically significant. Heterogeneity between studies was assessed by three methods. First, a Tau^2 test and an X^2 test were conducted for statistical heterogeneity, with $P<0.1$ being considered statistically significant. In addition, I^2 statistics were used to assess clinical heterogeneity, using a cut-off point of 35%. The number of donors in each study group weighted group means. Sensitivity analyses were performed for all outcome measures per comparison, first isolating only randomized trials, then excluding all retrospective studies. Studies with substantially more weight than others were also left out to assess different effects.

RESULTS

Out of 2168 unique articles identified in the search, 205 fell within the scope of our predetermined search. However, there were substantial issues with 20 of these publications; *i.e.* evidently overlapping cohorts, no specification of complications (*i.e.* only overall percentages or grades) or pooled data for different nephrectomy indications. Five authors provided us with source data, and the other articles were excluded according to the criteria stated in the methods section. A total of 190 articles remained for the systematic review[19-208]. There were a great number of publications that addressed two or more operative techniques but pooled complications. Two authors provided us with source data, and the other articles were excluded from the meta-analysis part of this review. Forty-one remained for inclusion in the meta-analysis. Supplementary figure 1 depicts the flowchart of the literature search.

The included articles originated from transplant centers worldwide. A table providing an overview of the number of included articles per country is included as supplementary table 1.

Part 1 – Systematic Review of Complications after minimally-invasive live donor nephrectomy

The studies comprised a total of 32.038live donor nephrectomies. Table 1 shows the distribution of these donors over the different techniques.

For this part of the review, complications were not divided over the different operative techniques. The purpose was to provide an overview of which complications occur, and in which frequency.

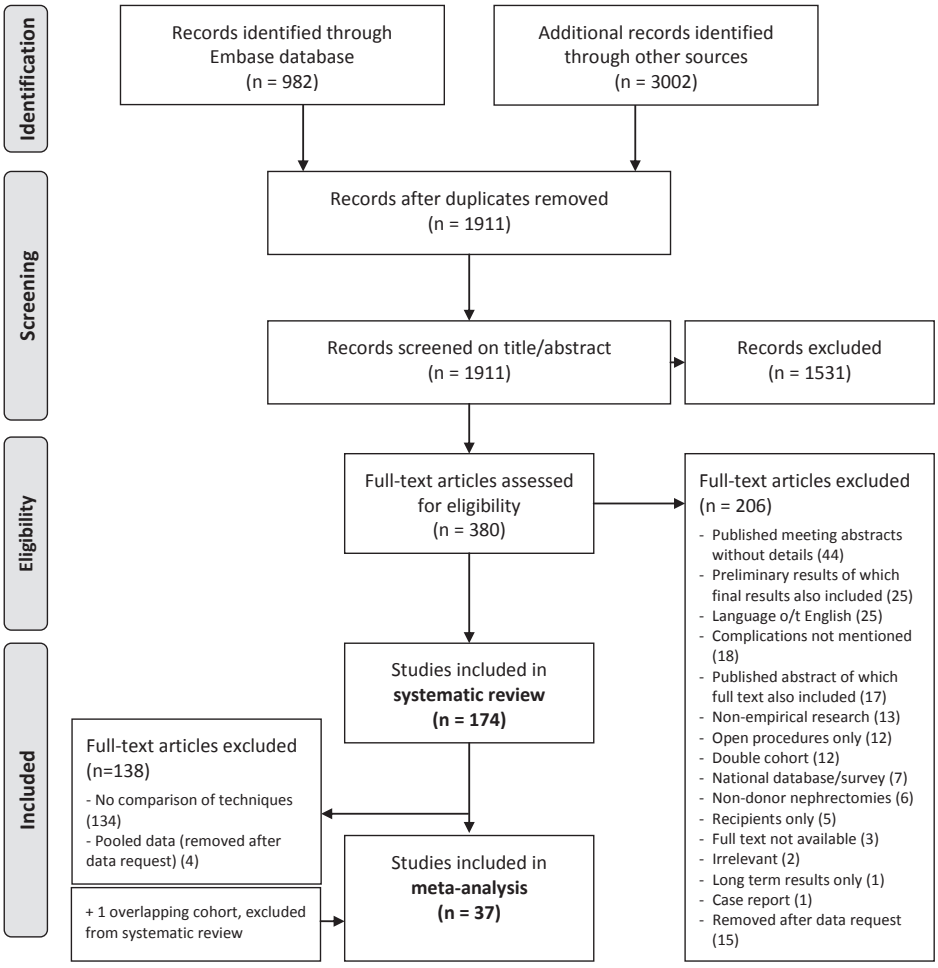

Figure 1 – PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the systematic literature search.

Table 1. Distribution of 32.038 live donors over the different operative techniquesa

Procedure	N (%)
Laparoscopic	18.374 (57.4)
Hand-assisted laparoscopic	8.112 (25.3)
Retroperitoneoscopic	1.107 (3.7)
Hand-assisted retroperitoneoscopic	1.300 (3.8)
Single-port laparoscopic (LESS)	1.214 (3.8)
Robot-assisted laparoscopic	417 (1.3)
Mini-open	1.436 (4.5)
Natural orifice transluminal endoscopy (NOTES)	78 (0.2)

a. Although we know the exact numbers for each of the procedures, results are, unfortunately, not always split over the different operative techniques

Conversion

Conversion to a traditional open technique was mentioned in 160 articles (84%). The overall conversion rate was 1.1% (table 2). The reason for conversion could not be determined in all cases; reasons were provided in 288 of a total of 316 conversions (91%). Elective conversions for adhesions, vascular anomalies or failure to progress were scored, although these were not considered to be complications. Conversions for bleeding or injury to other organs were also scored as intra-operative complications.

Table 2. Conversions, intra- and postoperative complications, reinterventions and mortality after minimally-invasive live donor nephrectomy.

	N° of articles	**N° of nephrectomies**	**N° of events**	**%**
Conversion (ALL)	160	28.376	316	1.1
Emergent	149	27.694	189	0.7
Bleeding	145	27.694	185	0.7
Injury other organs	149	27.694	4[a]	0.01
Intraoperative Complications (ALL)	173	27.776	612	2.2
Bleeding	175	27.776	391	1.5
Injury other organs	153	26.440	221	0.8
Spleen	151	26.440	97	0.4
Bowel	153	26.440	49	0.2
Bladder	151	26.440	12	0.05
Liver	151	26.440	14	0.05
Adrenal gland	151	26.440	22	0.08
Other	151	26.440	27[b]	0.1
Postoperative Complications (ALL)	187	30.970	2174	7.0
Bleeding (ALL)	176	30.443	290	1.0
Requiring transfusion	175	29.443	128	0.4
Requiring intervention	173	29.878	60	0.2
Injury to other organs (ALL)	170	28.562	26	0.09
Bowel	170	28.562	14	0.05
Spleen	167	28.074	6	0.02
Bladder	167	28.074	3	0.01
Pancreas	167	28.074	3	0.01
Infectious complications (ALL)	163	26.729	697	2.6
Wound infection	158	25.650	405	1.6
Abscess	152	25.910	19	0.07
Urinary tract infection	141	23.573	105	0.4
Pneumonia	153	25.808	148	0.6
Thoracic Empyema	104	19.845	1	0.01
Infectious – other[c]	111	19.785	12	0.06
Fever e.c.i.	55	11.095	71	0.6
Cardiopulmonary complications				
Cardiovascular	148	25.431	18	0.07
Cerebrovascular	149	25.475	1	0.004
Pneumothorax	150	25.842	36	0.1
Pulmonary – other[d]	113	20.436	71	0.3
Thromboembolic complications	146	23.574	39	0.2

Table 2. Conversions, intra- and postoperative complications, reinterventions and mortality after minimally-invasive live donor nephrectomy. (continued)

	N° of articles	**N° of nephrectomies**	**N° of events**	**%**
Gastro-intestinal complications				
Ileus	138	24.958	187	0.7
Small bowel obstruction	58	13.854	30	0.2
Chylous ascites	78	17.564	81	0.5
GI-bleed	88	16.022	5	0.03
GI-other[e]	62	12.399	115	0.9
Other complications				
Fascial defect	121	22.532	3692	0.2
Testicular swelling/pain/epididymitis	63	14.390	32	0.6
Thigh numbness	51	11.235		0.3
Pain	61	12.062	95	0.8
Remnant kidney function disorder	41	8.681	24	0.3
Urinary retention	100	19.537	100	0.5
Drug reaction	38	7.065	2	0.03
Other general complications[f]	101	20.030	194	1.6
Mortality	142	25.116	3	0.01
Surgical Reinterventions	163	28.516	165	0.6

a. Injury to other organs included spleen (2), bowel (1), mesentery (1)
b. Other organs/structures include: , pancreas (4), gallbladder (1), diaphragm (18), mesentery (4)
c. Other infectious complications included sepsis (3), pyelonephritis (1), phlebitis (8)
d. Other pulmonary complications included atelectasis (35), respiratory distress (13), pulmonary edema (8), pleural effusion (10), hypoxia (5)
e. Other GI complications included gastroenteritis (58), pancreatitis (11), constipation (13), liver function disorder (24), appendicitis (4), cholecystitis (2), gastric ulcer (3)
f. Other general complications included: Seroma (68), neuropathy/neurapraxia (23), subcutaneous emphysema (18), ocular complications (16), rhabdomyolysis (12), skin complications (16), electrolyte disorder (8), urethral injury (12), headache (4), ear haematoma (1), parotitis (1), depression (5), vertigo (1)

Complications

Table 2 provides an overview of all encountered complications and their incidence. There were many different definitions for intra-operative bleeding. Some authors regard it as a complication only if total blood loss exceeded 500 ml while others set the limit at 300 ml. Some studies only listed bleeding as a complication when an additional intervention (*i.e.* extra clip, suture or even conversion) was necessary and some authors did not specify at all. The need for blood transfusion was stated in 168 articles. Injury to other organs was stated in most articles, however the action taken to repair this remained unclear in the majority thereof. Table 3 sums up the postoperative complications. The reported complications vary between studies. While some authors report every adverse event from nausea to severe complications requiring surgical reintervention, others only mention specific types of- or major complications.

Table 3. Overview of additional intra- and postoperative parameters during and after minimally-invasive live donor nephrectomy.

Parameter	Population (n)	Value
Intra-operative parameters		
Operative time (minutes, mean, range)	22.594	194.3 (78 – 320)
Warm ischemia time (minutes, mean, range)	18.544	3.7 (0.7 – 8.7)
Blood loss (milliliters, mean, range)	17.489	147 (15 – 545)
Postoperative parameters		
Length of stay (days, mean, range)	22.898	3.8 (0.6 – 13)
Pain (VAS-score, mean, range)		
Day 1	1.004	4.1 (0.37 – 8)
Discharge	757	2.2 (2 – 5)
Outpatient clinic[a]	488	1.3 (0.8 – 1.25)
Readmissions	3.084	95 (3.1%)
Duration of convalescence (days, mean, range)	2.363	24.1 (4 – 60)
Postoperative Quality of Life (SF36, mean, range)[bc]	787	68.2 (34,5 – 90.5)

a. Values are reported at a time interval of 14-30 days postoperatively
b. Quality of life was assessed at a time interval of 1 – 6 months. The majority of studies assessed this between 4 and 6 weeks, one study at 3 months and one at 6 months postoperatively.
c. One additional study used the WHOQOL instead of the SF36 (n=50 donors), reporting a mean value of 72.8, range 69.4-76.2.

Mortality

Mortality within 30 days is very rare after live donor nephrectomy. Of the 190 included studies, mortality was reported in 65 (34%, N=16.604 nephrectomies). In 77 additional articles (8.512 nephrectomies), it was assumed that no mortality occurred based on complication rates and follow up. In the remaining 46 articles (24%, 6.922 nephrectomies) the occurrence of mortality couldn't be reliably deduced. In the remaining population of 27.816, only three deaths were reported, adding up to an overall reported mortality rate after live donor nephrectomy of 0.01%.

Surgical Reinterventions

A total of 165 surgical reinterventions were reported (0.6%). But as with mortality, not every article clearly stated it; in 27 articles reinterventions were not mentioned (N=3.522 procedures). In addition, 4% of studies (N=6, 12 cases), that did mention reoperations did not specify the indication therefor, and some other studies provided indications for some, but not all reinterventions (N=14 cases). Whether reoperation was done via laparoscopy or laparotomy was unclear in the majority of studies. Most reoperations were due to bleeding or to evacuate a hematoma (N=61, 37%). Small bowel obstruction due to internal or port-side hernia, or entrapment in a suture was the reason for reintervention in 26 cases (16%). Other indications for reintervention were wound infection or dehiscence (9), bowel injury (7), fascial dehiscence (7), splenectomy (5), appendectomy (4), , orchidectomy due to torsion or ischemia (3), chylous ascites (3), pancreatic injury (2), retrieval of corpus alienum (2), abscess drainage (1), bladder injury (1), ovariectomy

(1), perforated duodenal ulcer (1), vocal cord injury (1).. In addition, five laparotomies were performed due to abdominal pain, but no abnormalities were encountered during surgery.

Other outcome measures

Intraoperative parameters were described in nearly all articles. Unfortunately, operative time, warm ischemia time, blood loss, length of stay and duration of convalescence were provided in means and medians, as was the visual analog scale for postoperative pain. Since the majority of data was given in means (80%), those in medians were disregarded. Table 3 provides an overview of these extra parameters. Convalescence was defined differently in the included articles, ranging from return to daily activities to full physical function. These definitions were combined. Analgesic use, although described with fair regularity, was documented in many different ways, regarding drugs, dosage or days or even hours of use.. Overall costs were not often reported, but if so these varied enormously. The broad spectrum of inclusion dates and countries may very well account for this.

Part 2 - Meta-analysis

Forty-one articles were included in the meta-analysis. Comparisons were made between pure laparo- and retroperitoneoscopic procedures and hand-assisted procedures, laparoscopic procedures and retroperitoneoscopic procedures, multiport and single-port procedures, and all of these together versus mini-open donor nephrectomy. Two retrospective, small-populated studies comparing the robotic technique with any of the other techniques were found in our search, and one RCT. Unfortunately; complications in the RCT were only mentioned in Clavien-Dindo scales, and the individual complications could not be determined[209]. This technique was therefore left out of the meta-analysis.

The main finding was that there were only few significant differences between the minimally-invasive techniques.

Hand-assistance

Nineteen articles compared laparo- and/or retroperitoneoscopic procedures with and without hand assistance; three randomized controlled trials (RCT)[30, 64, 99], four prospective[43, 65, 69, 208] and eleven retrospective studies[38, 41, 54, 92, 116, 117, 139, 151, 152, 177, 179]. A total of 777 procedures were performed with, and 1465 without hand assistance, but since not all studies mentioned every outcome, total numbers vary per outcome measure. Conversion rate (1.5 versus 2.1%), and overall intra- (6.2 versus 5.7%) and postoperative (9.9 vs 10.3%) complication rates and surgical reinterventions (0.6 versus 0.7%) were comparable between the two groups. The only difference, although not statistically significant, found between these two techniques was intraoperative bleeding (defined as every

bleeding mentioned by the author that exceeded "normal expected blood loss"), which was more frequently encountered after hand-assisted procedures: 4.0 versus 3.9%, RR 1.52 (95% CI 0.95-2.43), p=0.08 (Figure 2).

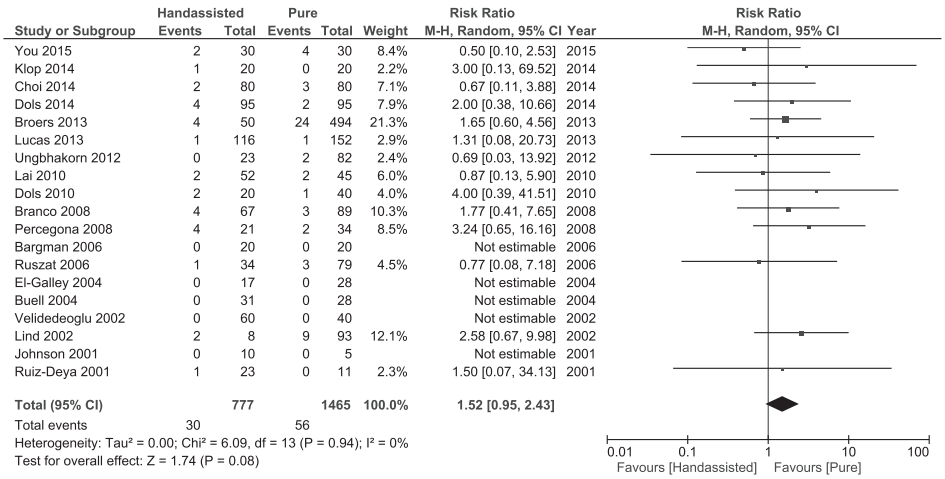

Figure 2 - Intraoperative bleeding compared between handassisted and pure laparoscopic/ retroperitoneoscopic procedures.

Laparoscopic versus retroperitoneoscopic donor nephrectomy

Seven articles compared laparoscopic with retroperitoneoscopic techniques, two RCTs[64, 99], two prospective[65, 132] and three retrospective studies[41, 152, 163]. A total of 311 procedures were retroperitoneoscopic, 1159 laparoscopic. Conversion (1.6 versus 2.0%), overall intra- (4.5 versus 5.6%) and postoperative complications (9.6 versus 12.2%) were again comparable between techniques. None of the individual intra- or postoperative complications showed statistically significant differences.

Multiport versus single port donor nephrectomy

Ten studies were identified comparing single- with multiport procedures; three RCTs[27, 107, 149], one prospective study[194], and six retrospective series[20, 31, 47, 144, 183, 205]. In total, 764 single port procedures were compared to 1214 laparoscopic procedures. Conversions were rare in these studies; only 2 occurred (0.1%), both in multiport donor nephrectomies, of which one was elective and one emergent due to bleeding. Intra- (0.9% in both groups) and postoperative (6.5 versus 5.2%) complications were again comparable, as were reinterventions (0.1 versus 0.9%). Postoperative pain was slightly more often described after LESS donor nephrectomies (2.7 versus 0.8%, RR 3.56, 95% CI 0.90-14.11, p=0.07). , other pulmonary complications (*i.e.* pleural effusion, atelectasis,

respiratory distress, pulmonary edema or hypoxia) were more frequently reported after LESS donor nephrectomy; 1.5 versus 0%, RR= 7.51, p=0.03 (95% CI 1.25-44.94).

Mini-open versus laparoscopic donor nephrectomy

All articles comparing the mini-open technique with either one of the endoscopic techniques (*i.e.* laparo- , retroperitoneoscopic, with or without hand-assistance) with the exception of single port donor nephrectomies were included in this comparison. There was one study that compared retroperitoneoscopic procedures to mini-open procedures, and seven additional studies were identified comparing mini-open donor nephrectomies to laparoscopic ones. A total of 323 mini-open procedures were compared to 288 endoscopic procedures. This group comprised three RCTs[85, 133, 210] and five prospective studies [50, 115, 128, 195, 198]. Intraoperative complications were more frequently seen in laparoscopic procedures; 8.2 versus 3.4%, RR 2.45, 95% CI 1.13-5.35, p=0.02) (0.99-1.08), p=0.1 (Figure 3).

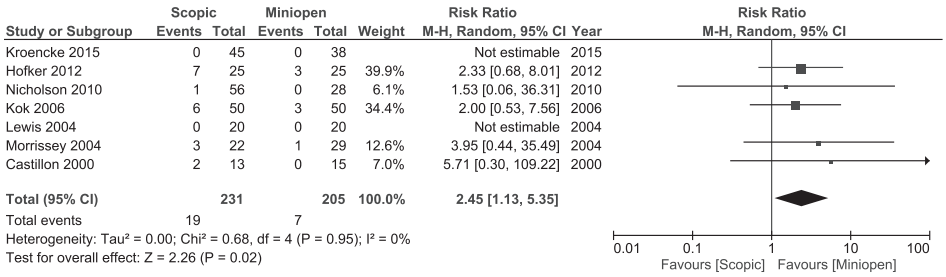

Figure 3 - Intraoperative complications compared between laparoscopic/ retroperitoneoscopic and miniopen procedures.

This difference was mostly based on intraoperative organ damage, which demonstrated a trend in favor of open procedures; 0 versus 2.8%, RR 5.18 (95% CI 0.91-29.35), p=0.06 (Supplementary figure 2). When sensitivity analysis was performed and only RCTs were included, the significant difference / trend disappeared (p=0.09 and 0.1 respectively).

Overall postoperative complication rate was comparable, but nonetheless much higher than described for the other techniques (17 versus 23%). The design of the included studies, only RCTs and prospective series, might account for this finding. The incidence of pneumonia was significantly higher after open procedures: 6.3 versus 3.3%, RR2.48 (95% CI 1.05-5.87), p=0.04 (figure 4).

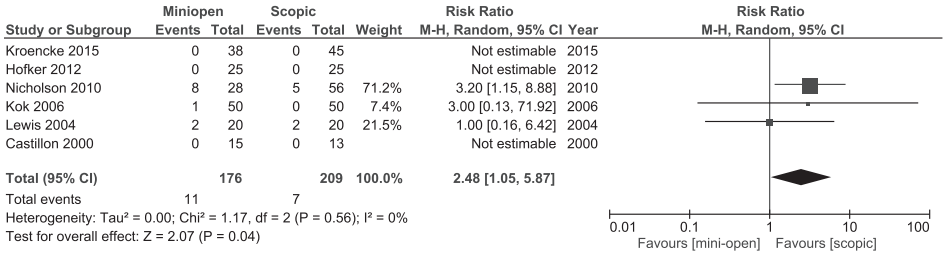

Figure 4 - Pneumonia compared between laparoscopic/ retroperitoneoscopic and miniopen procedures.

However, when performing sensitivity analysis, this difference was largely based on one study. When this group was left out of the forest plot analysis, results were quite comparable between procedures (2.0 versus 1.3%, RR1.32, p=0.73 for pneumonia). Pneumothorax was not more often seen after either procedure; 0.6% for mini-open procedures (n=1) and 1% for scopic procedures (n=2). The surgical reintervention rate was comparable 0.6% for mini-open procedures versus 1.8% for scopic ones, but this difference was not statistically significant.

All in all, none of the employed minimally-invasive techniques for live donor nephrectomy stand out from the rest.

DISCUSSION

Our study is, to the best of our knowledge, the first to extensively score all complications after minimally-invasive live donor nephrectomies and compare outcomes of all different techniques. A great number of minimally-invasive live donor nephrectomies were included from different countries all over the world. There was no significant heterogeneity encountered in the included studies. Short-term complication rates were comparable between different techniques currently employed for live donor nephrectomy, and not one of the techniques stood out from the rest. In the included studies, the pure laparoscopic approach was used in the majority of cases (57.4%). This may not be an adequate portrait of the current situation, in which the hand-assisted approach is favored in many cases[1]. It is possible that some authors did indeed use hand-assistance, but did not explicitly mention this in their article. No statistically significant differences were found in this meta-analysis comparing laparoscopic donor nephrectomies with and without hand-assistance. The overall postoperative complication rate found in the systematic review part of our study (7.0%) is lower than the complication rates found in some of the meta-analyses (12.2% for retroperitoneoscopic techniques when compared to laparoscopic techniques and 23% for laparoscopic procedures when compared to mini-open procedures, which, in turn, had 17% complications). This may imply under

reporting of complications in the systematic review part, which mainly consisted of retrospective case series. Complications were mentioned, but were not always the main outcome measure of the study. In the meta-analyses, only those studies that compared two or more techniques were included, and the focus was on complications in most studies. Conversions (316 overall) were described in a total of 160 articles. Unfortunately, complications were not specified for converted and non-converted donors in most studies, so whether the conversion itself had any negative influence on the post-operative course or convalescence period remains unknown.

If we would adhere to our national guideline, according to which only those complications with an incidence of greater than 1% or those with severe consequences have to be disclosed to patients undergoing any surgical procedure[211], we would only be obliged to mention intra- and postoperative bleeding, conversion, wound infection (and possibly overall infectious complications) and ileus. In addition, the possibility of a reintervention and mortality should be mentioned, regardless of their incidence. But is this really enough to ensure that a potential living kidney donor is optimally prepared and able to make a well-informed decision? Rare complications like damage to other organs, or cardiovascular events may or may not necessary have "severe consequences", so should these be mentioned or not? And even though many other complications are also infrequent, and may not have significant medical consequences, they may be very relevant for donors. Prolonged pain, testicular complaints, neuropathies can be quite disconcerting to a donor who has no idea these adverse events are in fact quite "normal".

Limitations

This systematic review and meta-analysis has a number of significant limitations. None of the articles provided a complete overview of all complications, events and consequences. Some focused on intra-operative complications, others on specific postoperative complications. Conversion was mentioned in most, while mortality was actually mentioned in only 31% of the articles. The overall quality of reported data was quite low, and it was interesting to see the differences in portraying complications and adverse events.

Most studies are retrospective case series, some prospective and only 16 included studies were randomized controlled trials. The definition of complications in general, and especially individual complications, is bound to vary. Not every surgeon considers every adverse event to be a complication, and results are presented in that light. Overall, major complications were more often reported than minor complications, possibly leading to an underestimation of the latter. Even the definitions of frequently encountered and considered "standard" complications like bleeding or wound infection vary among authors. Some specify bleeding as the need for transfusion, or a specific amount of blood loss, but often (especially intraoperative) bleeding is not defined. When bowel or splenic

injuries were encountered, it was often not stated whether resection was necessary. In addition, less frequently encountered complications like testicular complaints or thigh numbness were not mentioned in many articles, raising the question whether they did not occur, or weren't reported. Overall complications rates varied greatly between different studies, and it is to be expected that complications are underreported.

Second, even though we've used all available channels to obtain as much unique data as possible, we were still dependent on the quality of published studies. Many studies included donor nephrectomies using different operative techniques, but pooled their complication data. We were able to obtain split data for a small number of these. In the majority of cases, data were no longer available or no response from the authors was received. For this reason, a number of studies could not be included in the meta-analysis, resulting in a smaller population for analysis. In addition, we had to exclude a number of studies presenting pooled data for different nephrectomy indications (other than kidney donation). Reversely, even though we applied strict exclusion criteria for overlapping cohorts, a small number of donors will inevitably have been analyzed in more than one included cohort.

Mortality after live donor nephrectomy is a catastrophic complication that is rarely reported. The largest cohort addressing donor mortality is reported by Segev *et al.*[9], who found 25 donor deaths within 90 days after 80.347 live donor nephrectomies (0.03%). These were United States donors, after conventional open donor nephrectomy as well as minimally-invasive procedures, and donor death was established by checking the Social Security Death Master File. Cause of death was not reported, and even though a matched cohort of non-operated adults demonstrated lower mortality rates, this mortality rate of 0.03% cannot, with entire certainty, be attributed to live donor nephrectomy alone. In our systematic review, a reported mortality rate of 0.01% was found. Whether this is an under- or overestimate remains unclear. Based on the available literature, we do know that donor deaths still occur, and that vascular complications are often not published[212, 213]. We therefore used strict criteria during data extraction. Mortality was scored when it was literally stated, or when the authors stated that "no complications" or no "major complications" occurred. In addition, if follow-up data were presented and none of the donors were missing, it was concluded that they had not died. Using these criteria, mortality was scored as inconclusive in 48 articles. If no deaths would have occurred in these populations, overall mortality rate would be 0.01%. Thus, we state that the actual mortality rate after live donor nephrectomy will be in the range of 0.01-0.1%.

Our article presents an extensive overview of different outcome measures, with emphasis on complication rates after minimally invasive live donor nephrectomy. Even though there is a risk of publication bias, due to the number of included procedures this overview will still provide quite a representable situation of current clinical practice. Based on these results, we may state that all employed techniques for minimally invasive

live donor nephrectomy are safe and associated with low risks of complications and an even lower risk of mortality. This allows the transplant surgeon to choose this technique with which he or she is most comfortable, and which best suits the intended donor. This form of tailor-made live donor nephrectomy fits perfectly into the current trend of shared elective surgical decision making.

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APPENDIX I – SEARCH STRINGS USED IN DIFFERENT DATABASES

embase.com

('kidney donor'/de OR 'living donor'/de OR ((kidney OR renal OR nephrect* OR living OR live) NEAR/3 (donor* OR donat*)):ab,ti) AND (nephrectomy/de OR uninephrectomy/de OR (nephrectom* OR uninephrectom*):ab,ti) AND ('crossover procedure'/de OR 'double-blind procedure'/de OR 'randomized controlled trial'/de OR 'single-blind procedure'/de OR 'prospective study'/de OR review/de OR 'systematic review'/de OR 'meta analysis'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR prospectiv* OR review OR 'meta analysis' OR metaanalysis):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (OvidSP)

("living donors"/ OR ((kidney OR renal OR nephrect* OR living OR live) ADJ3 (donor* OR donat*)).ab,ti.) AND (nephrectomy/ OR (nephrectom* OR uninephrectom*).ab,ti.) AND (Randomized Controlled Trial.pt. OR Controlled Clinical Trial.pt. OR "Prospective Studies"/ OR review.pt. OR Meta-Analysis.pt. OR (randomized OR placebo OR randomly OR trial OR groups OR prospectiv* OR review OR "meta analysis" OR metaanalysis).ab,ti.) NOT (Animals/ NOT Humans/)

Cochrane

(((kidney OR renal OR nephrect* OR living OR live) NEAR/3 (donor* OR donat*)):ab,ti) AND ((nephrectom* OR uninephrectom*):ab,ti)

Web-of-science

TS=((((kidney OR renal OR nephrect* OR living OR live) NEAR/3 (donor* OR donat*))) AND ((nephrectom* OR uninephrectom*)) AND (random* OR factorial* OR crossover* OR (cross NEAR/1 over*) OR ((doubl* OR singl*) NEAR/1 blind*) OR assign* OR allocat* OR prospectiv* OR review OR "meta analysis" OR metaanalysis) NOT (animal* NOT human*))

Scopus

TITLE-ABS-KEY((((kidney OR renal OR nephrect* OR living OR live) W/3 (donor* OR donat*))) AND ((nephrectom* OR uninephrectom*)) AND (random* OR factorial* OR crossover* OR (cross W/1 over*) OR ((doubl* OR singl*) W/1 blind*) OR assign* OR allocat* OR prospectiv* OR review OR "meta analysis" OR metaanalysis) AND NOT (animal* AND NOT human*))

PubMed publisher

(((kidney[tiab] OR renal[tiab] OR nephrect*[tiab] OR living[tiab] OR live[tiab]) AND (donor*[tiab] OR donat*[tiab]))) AND ((nephrectom*[tiab] OR uninephrectom*[tiab])) AND ((randomized[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR prospectiv*[tiab] OR review[tiab] OR "meta analysis"[tiab] OR metaanalysis[tiab])) AND publisher[sb]

Google scholar

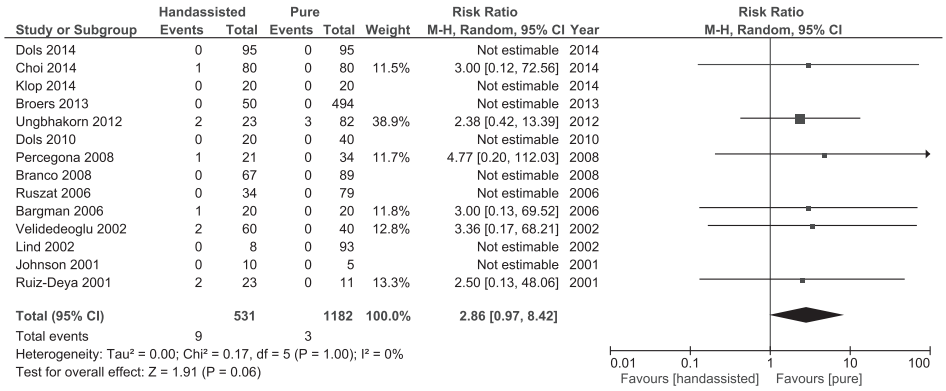
"kidney|renal donor|donors" nephrectomy randomized|randomised|randomly|trial|prospective|review|"meta analysis""surgical|operative|nephrectomy complication|complications"

1. Hand-Assisted versus Pure Laparoscopic Live Donor Nephrectomy							
Quality assessment							Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
18	3 RCTs 4 Pros cohorts 11 Retro cohorts	not serious	not serious	not serious	not serious	none	⊕⊕◯◯ LOW
2. Retroperitoneoscopic versus Laparoscopic Live Donor Nephrectomy							
Quality assessment							Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
7	2 RCTs 2 Pros cohorts 2 Retro cohorts	not serious	not serious	serious [1]	not serious	none	⊕◯◯◯ VERY LOW [1]
3. Single-Port (LESS) versus Multiport Laparoscopic Live Donor Nephrectomy							
Quality assessment							Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
9	3 RCTs 1 Pros cohort 5 Retro cohorts	not serious	not serious	serious [2]	not serious	none	⊕◯◯◯ VERY LOW [2]
4. Mini-open versus Laparoscopic Live Donor Nephrectomy							
Quality assessment							Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
6	3 RCTs 3 Pros cohorts	not serious	not serious	serious [3]	not serious	none	⊕◯◯◯ VERY LOW [3]

RCT □Randomized Controlled Trial, Pros □Prospective, Retro □Retrospective

1. Hand-assisted techniques are compared to pure techniques in all articles, however in some the pure technique is done laparoscopically while in other the pure technique is the retroperitoneoscopic procedure.
2. In one study hand-assisted laparoscopic donor nephrectomy was compared to LESS donor nephrectomy, in one study the defined technique for multiport procedure was not specified. The other seven studies compared pure laparoscopic donor nephrectomy to LESS donor nephrectomy.
3. One study compared hand-assisted laparoscopic donor nephrectomy to mini-open donor nephrectomy, where the others compared pure laparoscopic donor nephrectomy to mini-open donor nephrectomy

Supplementary figure 1 – GRADE table of quality of evidence for studies included in meta-analysis

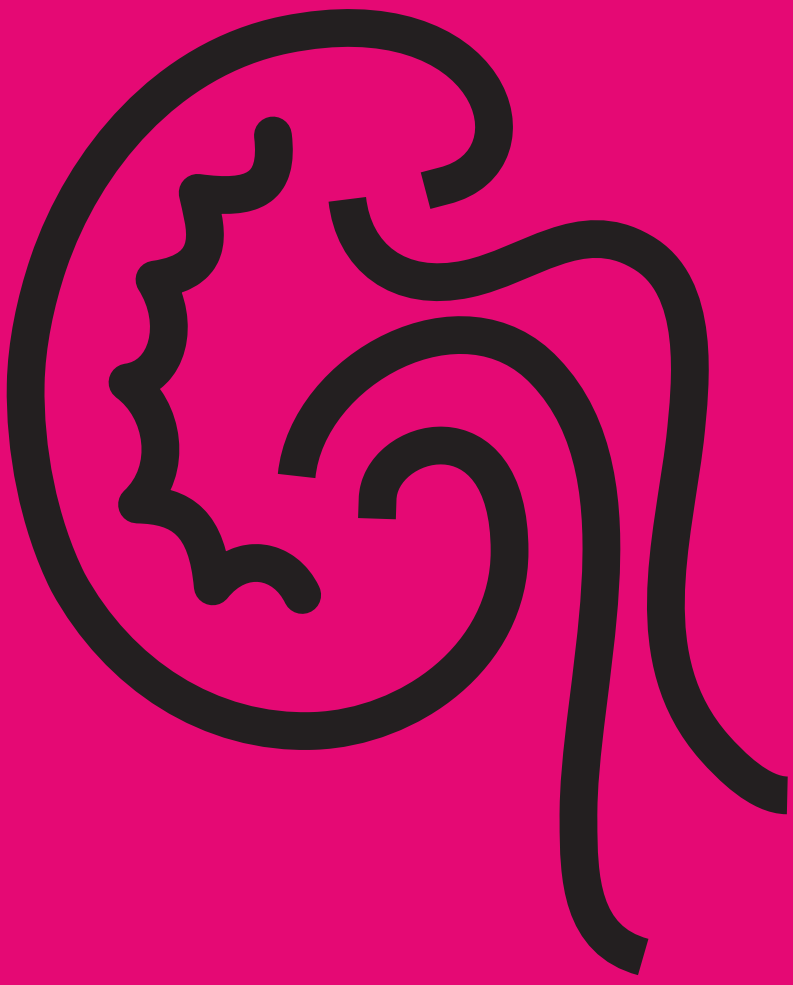


Supplementary figure 2 - Forest plot analysis for postoperative ileus after laparoscopic donor nephrectomy with or without hand-assistance.

Supplementary figure 3 - Forest plot analysis for intraoperative organ damage after mini-open and laparoscopic live donor nephrectomies.

Supplementary table 1. Country of origin of 190 included studies, percentages between brackets.

Country	Number of articles included	
Argentina	1	(0.5)
Australia	6	(3.2)
Belgium	1	(0.5)
Brazil	4	(2.1)
Canada	5	(2.6)
Chile	1	(0.5)
China	2	(1.1)
Czech Republic	1	(0.5)
France	2	(1.1)
Germany	8	(4.2)
Greece	1	(0.5)
India	10	(5.3)
Iran	1	(0.5)
Italy	5	(2.6)
Japan	7	(3.7)
Korea	11	(5.8)
Kuwait	1	(0.5)
Lebanon	1	(0.5)
Mexico	1	(0.5)
Netherlands	13	(6.8)
Norway	2	(1.1)
New Zealand	1	(0.5)
Pakistan	1	(0.5)
South Africa	1	(0.5)
Spain	3	(1.6)
Sweden	2	(1.4)
Switzerland	3	(1.6)
Taiwan	2	(1.1)
Thailand	1	(0.5)
Turkey	3	(1.6)
United Kingdom	12	(6.3)
USA	76	(40)
Vietnam	1	(0.5)



Chapter 4

Towards a Standardized Informed Consent Procedure for Live Donor Nephrectomy: What Do Surgeons Tell Their Donors?

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ABSTRACT

Introduction Living kidney donors comprise a unique group of "patients", undergoing an operation for the benefit of others. The informed consent process is therefore valued differently. Although this is a team effort, the surgeon is responsible for performing the donor nephrectomy, and often the one held accountable, should adverse events occur. Although there is some consensus on how the informed consent procedure should be arranged, practices vary. The aim of this study was to evaluate the surgical informed consent procedure for live donor nephrectomy, with special regards to disclosure of complications.

Methods A web-based survey was sent to all kidney transplant surgeons (n=50) in eight transplant centers with questions regarding the local procedure and disclosure of specific details.

Results Response rate was 98% (n=49), of which 32 (65%) were involved in living donor education; overall, transplant- (50%), vascular- (31%), and abdominal surgeons (13%), and urologists (6%) performed donor nephrectomies in the eight centers. Informed consent procedures varied, ranging from assumed to signed consent. Bleeding was the only complication every surgeon mentioned. Risk of death was always mentioned by 16 surgeons (50%), sometimes by 13 (41%), three surgeons (9%) never disclosed this disastrous complication. Reported mortality rates ranged from 0.003% to 0.1%. Mentioning frequencies for all other complications varied.

Conclusion Important complications are not always disclosed during the surgical informed consent process for live donor nephrectomy. Informed consent procedures vary. To optimally prepare living kidney donors for the procedure, a standardized informed consent procedure for live donor nephrectomy is highly recommended.

INTRODUCTION

Living kidney donors comprise a unique group of "patients", undergoing an operation for the benefit of others. Even though the surgical technique for the live donor nephrectomy is fully implemented, and associated with low complication rates, the burden of responsibility may feel different to surgeons operating on living donors instead of actual patients [1]. Every patient needs to be fully informed about the details and risks of a procedure, but because surgeons may have an increased fear of inflicting unnecessary injury and expectation of perfection with living donors [1], the informed consent procedure is valued differently. To enable donors to make a fully informed decision, it is the transplant team's responsibility to provide them with all the necessary information. This is a joint effort of the whole transplant team, but the surgeon is the one responsible for the donor nephrectomy, and is often the last in the chain of information providers. In addition, should adverse event occur, the surgeon is often the one held responsible. He should therefore ensure that the donor has been informed about all essential details and risks either by providing these himself or confirming that the rest of the team has done so. There should be no doubt about the donor's consent, and the transplant team should confirm the voluntary and informed nature hereof [2].

There are many uncertainties when it comes to information provision and informed consent, in patients in general, let alone living kidney donors. What information do they need, which details are vital in their educational process? And at what stage during this educational process should the actual informed consent be obtained? In addition, the manner in which informed consent should be documented is a much-debated subject. In the Netherlands, the law on organ donation stems from May 1996. Consent has to be obtained in writing, signed and dated. But the contents of information provision are not stated in any legal document, although some specifications can be found in the EU Directive, requiring Member States to adhere to minimum standards in live organ donation[3]. In the United States, a more detailed guideline is available [4], but compliance with this guideline varies.

A recent systematic review demonstrated that there is no consensus on how the informed consent procedure in live donor nephrectomy should be arranged[5]. There are many discrepancies in the procedure itself, provided information and the manner in which consent is obtained between different countries, transplant centers and even transplant professionals within one center. Previous surveys have demonstrated that transplant professionals vary in information and details they provide to potential donors[6, 7]. It has been suggested that donors as well as transplant professionals would greatly benefit from a standardized informed consent procedure[5, 8], and many agree that there is a need for a standardized informed consent procedure.

The Netherlands have a leading role when it comes to live kidney donation with more than half of all kidney transplants involving a living donor. In 2014, 534 live donor nephrectomies were performed out of a total of 1004 kidney transplantations (53.2%)[9]. Not every center employs the same surgical technique, which makes completely uniform information provision virtually impossible. Still, uniformity should be pursued, especially seen in light of the successful paired kidney exchange program (PKE) in the Netherlands (3.5% of all live donor nephrectomies are within the PKE program) [10]. In contrast to some other countries, where the kidney is transported from the donor's center to the recipient's center, standard national policy in the Netherlands involves donors traveling to the recipient's center for surgery, but receiving education in their own center. Most donors visit the outpatient clinic of the second center prior to surgery, and are seen by the local surgeon on the day of admission for donor nephrectomy. If information received in "their own" center differs greatly from information received in the "new" center this could be quite troubling for the donor. Hospital logistics and local practice are bound to vary. But standardization of the contents of the informed consent procedure should be possible, and is expected to further improve this process for potential living kidney donors. The first step to create this standardized format is to assess the current situation. How is the informed consent procedure arranged in the eight Dutch kidney transplant centers? And which specific details are discussed with potential donors?

The aim of this study was to provide an overview of the current situation in the Netherlands with regard to the surgical part of the informed consent procedure. Special interest is addressed to the disclosure of different complications by transplant surgeons to potential donors.

MATERIALS AND METHODS

To gain better insight in the information disclosed by kidney transplant surgeons, a web-based survey (supporting document I - appendix I) was created (SurveyMonkey, Palo Alto, CA, USA) and sent to all surgeons in the Netherlands who were, or had been in the past, involved in kidney transplantation, identified from prior surveys, registration details and by contacting the surgical kidney transplant program director in each center. Specialists included transplant, abdominal and vascular surgeons and urologists, both consultant surgeons and surgical fellows. Because the questionnaire was distributed to colleagues and included only questions regarding their own practice habits, no approval from the local ethics committee was obtained.

Questions were divided into four subgroups: personal experience, hospital logistics, contents of informed consent and the actual informed consent procedure. A list of (medical) items was created based on currently available literature [5], combined with our own

experience, that could be provided to potential donors during the informed consent procedure. These items included details regarding surgical technique (n=6, *e.g.* laparoscopy, hand-assistance, conversion), short- and long-term complications (n=22, *e.g.* bleeding, wound infection, mortality, incisional hernia, kidney failure), duration of admission and convalescence. For each possible complication, the respondents were given three options: "I always mention this complication to potential donors", "I sometimes mention this complication to potential donors", or "I never mention this complication to potential donors". Results were compared between center, type of surgeon, and personal experience.

Statistical analysis was performed using SPSS version 21. For continuous variables the student-t test or one way Anova was used. For nominal variables the Chi-square test was used, or the Fisher's Exact test for small samples. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 50 surgeons were invited to complete the survey and a response rate of 98% was reached (n=49). Of these respondents, 17 indicated they were not involved in the preoperative care for living kidney donors, 32 individual responses remained for analysis; 28 consultants and four surgical fellows. Sixteen respondents were transplant-, ten were vascular-, four abdominal surgeons, and two were urologists. Five different techniques for live donor nephrectomy are employed in the Netherlands: pure laparoscopic, hand-assisted laparoscopic (HAL), hand-assisted retroperitoneoscopic (HARP), robot assisted and mini-open. Not every center offers every technique. Two centers use only one technique, whereas the other six choose from two or more techniques. Only one center offers robotic assisted donor nephrectomy, the other techniques are available in at least two centers.

Hospital Logistics & Informed Consent

Informed consent procedures vary among centers, but even surgeons from the same center report different practices. All but two respondents evaluate the majority of potential donors at the surgical outpatient clinic (94%), the remaining two respondents, from different centers, indicated that they only evaluated living donors the day before surgery. In all but one center the surgeon or urologist is responsible for the postoperative in-hospital care for donors, the nephrologist in the remaining center. Postoperative outpatient care varies as well. With the exception of two centers all donors are invited for an outpatient clinic follow-up visit. In one center donors only receive a follow-up telephone call by the surgeon, and in the last center all follow-up appointments are arranged through the nephrology department.

When asked about the actual informed consent procedure in their hospital, answers again varied. Respondents from three centers were unanimous about the manner in which informed consent was obtained; signed in two and explicit oral consent in the third. Only one center was also unanimous about the responsible party for obtaining consent, the other responses varied between nurse practitioner, surgeon or nephrologist. Answers from the other five centers differed among their respondents. Timing of informed consent also demonstrated some differences. Respondents from four centers were unanimous; two obtained consent prior to the surgical consult and two afterwards. In the other centers, respondents disagreed on whether consent was obtained prior to or after the surgical consult, or that there was no explicit informed consent at all.

Contents of Informed Consent

The selected medical items and the frequency in which they were mentioned are demonstrated in table 1.

Table 1. Frequency of providing individual items during the surgical part of the informed consent procedure in live donor nephrectomy in percentages.

	Always	**Sometimes**	**Never**
Conversion to open procedure	84.5	6	9.5[a]
Short-term complications			
Bleeding	100	-	-
Wound infection	97	3	-
Pain	84	6	9
Fatigue	53	22	25
Damage to other organs	50	31	19
Pneumonia	44	28	28
Abscess	31	28	41
Urinary tract infection	31	34	34
Thromboembolic complications	28	34	38
Testicular pain/swelling	25	22	53
Cardiovascular complications	15.5	44	40.5
Neurapraxia	12.5	40.5	47
Neuropathy	6	47	47
Mortality	50	37.5	12.5
Long term complications			
Incisional hernia	59	28	13
Kidney failure	47	28	25
Chronic pain	28	44	28
Hypertension and other cardiovascular complications	13	34	53
Risks of living with one kidney:			
Smoking	37.5	22	40.5
Obesity	19	47	34
NSAIDs	15.5	37.5	47
Antibiotics	13	22	66

[a.] Two of three respondents from a center that only employs (mini-)open procedures

Bleeding was the only complication that every surgeon from every center always discloses to potential donors. Wound infection came in a close second with 31 surgeons always and one sometimes mentioning it. The most outstanding fact was that not all surgeons discussed the risk of death; only half (n=16) reported always telling donors about the possibility of dying, another 12 mentioned it sometimes and four never at all. In addition, surgeons provided different estimated mortality rates, ranging from 0.003 – "<1%". Long-term complications were overall less frequently reported than short-term complications. A little over half of the respondents (n=19) always mentioned the possibility of an incisional hernia, 15 mentioned the risk of kidney failure. Table 2 lists additional complications or details that surgeons indicated to discuss with potential donors.

Table 2. Additional details that surgeons indicated to discuss with potential donors, and the frequency in which these were mentioned.

Category	Details	Frequency
Short-term complications	Pain due to pneumoperitoneum	1
	Damage to graft	1
	Complications in recipient	1
	Failure to implant kidney in recipient	2
	Physical impairment	1
Long-term complications	Graft failure (recipient)	2
	Risks in case of pregnancy	1
Other	Quality of life	1
	Follow-up program	1
	Intrinsic motivation/free choice	2
	Trials	1

All surgeons discuss duration of admission and convalescence with potential donors. Timespans are comparable, ranging from one day to one week for hospital admission and two weeks to three months for convalescence.

Out of a possible 22 complications, surgeons mentioned a median of eight complications, always, to all donors (range 3-17). More short- than long-term complications were discussed (table 3).

Table 3. Distribution of mentioning frequencies for subgroups of complications (median, range).

	Always	Sometimes	Never
Overall	8 (3-17)	5 (0-13)	7 (0-17)
Short-term complications	6 (3-12)	3 (0-8)	4 (0-11)
Long-term complications	2 (0-8)	2.5 (0-7)	3.5 (0-7)

We compared these frequencies between different subgroups; center, type of surgeon, subspecialization, number of procedures performed, and gender. One significant difference was observed in the short-term never group: Surgeons who performed <20 donor nephrectomies on an annual basis never mentioned a median of six (mean 5.9) short-term complications to donors, surgeons who performed >20 procedures never mentioned three (mean 3.3) (p=0.04).

When comparing each individual complication between the different subgroups, a few statistically significant differences were observed which are demonstrated in tables 4-7. Male- and female surgeons mentioned the same number of short-term complications, but remarkably, the risk of pain was significantly more often reported by men (92 vs 63%, p=0.006). Transplant surgeons were the most likely to always mention risk of death (69%) versus 50% of vascular surgeons, and none of the abdominal surgeons or urologists.

Table 4. Differences in mentioning frequencies between type of surgeons in percentages.

	Consultant (n=28)			**Fellow (n=4)**			**p-value**
Median number of complications always disclosed (range)	8 (3-17)			7.5 (6-13)			NS
	A	S	N	A	S	N	
Complication							
Pain	89	7	4	50	-	50	0.01
Pneumonia	36	32	32	-	100	-	0.05
Abscess	32	21	46	25	75	-	0.06
Thromboembolic complications	21	36	43	75	25	-	0.07

A – Always S – Sometimes N – Never

Table 5. Differences in mentioning frequencies between surgeons' subspecialization (in rounded percentages, unless otherwise defined).

	Transplant (n=16)			**Vascular (n=10)**			**Abdominal (n=4)**			**Urologist (n=2)**			p-value
Median number of complications always disclosed (range)	9 (3-17)			7.5 (3-13)			6.5 (5-12)			9 (5-8)			NS
	A	**S**	**N**	**A**	**S**	**N**	**A**	**S**	**N**	**A**	**S**	**N**	
Complication													
Death	69	31	-	50	20	30	-	75	25	-	100	-	0.03
Neuropathy	60	50	44	-	30	70	-	100	-	50	-	50	0.03
Urinary tract infection	56	25	19	10	30	60	-	75	25	-	50	50	0.06

A – Always S – Sometimes N – Never

Table 6. Differences in information disclosure between center-volume, based on total number of nephrectomies in 2014. (in percentages, unless otherwise defined)

	Center no I (n=8)†			**Center no II (n=5)†**			**Center no III (n=4)†**			**Center no IV (n=6)†**			**Center no V (n=2)†**			**Center no V I (n=2)†**			**Center no VII (n=2)†**			**Center no VIII (n=3)†**			p-value
Median number of complications always disclosed (range)	9 (3-17)			9 (5-12)			7 (5-10)			9 (5-17)			6.5 (5-8)			10 (7-13)			5.5 (3-8)			7 (6-10)			NS
	A	**S**	**N**	**A**	**S**	**N**	**A**	**S**	**N**	**A**	**S**	**N**	**A**	**S**	**N**	**A**	**S**	**N**	**A**	**S**	**N**	**A**	**S**	**N**	
Conversion‡	87.5	-	12.5	100	-	-	100	-	-	100	-	-	100	-	-	100	-	-	50	50	-	-	33	67	0.02
Complication																									
UTI	75	-	25	20	60	20	-	25	75	33	67	-	-	100	-	50	-	50	-	-	100	-	33	67	0.02
Testicular pain	25	12.5	62.5	80	0	20	-	25	75	17	33	50	50	50	-	-	-	100	-	100	-	-	-	100	0.04
Abscess	37.5	37.5	25	20	60	20	-	-	100	67	33	-	50	-	100	50	50	-	-	-	100	-	-	100	0.05
Death	75	25	-	-	80	20	-	50	50	67	33	-	50	-	100	50	50	-	50	50	-	100	-	-	0.08

† Number of respondents per center

‡ One center only offers open technique

A – Always S – Sometimes N – Never

UTI – Urinary tract infection

Table 7. Differences in mentioning frequencies between personal number of donor nephrectomies performed on annual basis (in rounded percentages, unless otherwise defined).

	<10 (n=3)†			**10-20 (n=5)†**			**20-50 (n=20)†**			**>50 (n=2)†**			p-value
Median number of complications always disclosed (range)	7 (4-10)			7 (3-10)			8 (3-17)			12.5 (8-17)			NS
	A	**S**	**N**	**A**	**S**	**N**	**A**	**S**	**N**	**A**	**S**	**N**	
Conversion	33.5	-	66.5‡	60	40	-	-	100	-	-	100	-	<0.001
Complication													
Cardiovascular	33	33	33	20	-	80	-	65	35	50	-	50	0.03
Testicular pain	-	-	100	-	60	40	25	20	55	100	-	-	0.04
Abscess	-	-	100	20	20	60	25	40	35	100	-	-	0.09

† Two of 32 respondents indicated that although they were involved in living donor education they did not perform donor nephrectomies themselves.
‡ Both respondents who never discussed conversion came from a center that only offers open procedures.
A – Always S – Sometimes N – Never

DISCUSSION

Informed consent is important for every surgical procedure. Every surgical professional agrees that a patient, or, potential donor must make an informed decision when it comes to undergoing surgery or donating a kidney. This implies that there is a basic level of knowledge we want patients or donors to have. Nonetheless, our study demonstrates that essential items are more than once left out of surgical donor education. Short-term complications are more thoroughly discussed by surgeons with potential donors than long-term complications, which could be explained by the fact that short-term complications are more frequently dealt with in surgeons' daily practice, but information provision regarding short- and long-term complications was far from uniform. It needs to be further evaluated whether these deficits in information provision also lead to deficits in donors' knowledge. Additional studies have been initiated to assess this[11].

Sixteen of 32 surgeons reported always mentioning the risk of death to potential donors, another 12 did so sometimes but four never told donors about the risk of dying. If a mortality rate was stated, this ranged from 1 in 30.000 to "less than 1 in 100". Although rare, donor mortality has been reported in the literature[12-16], and this may still be an underestimation of the actual mortality rate. The largest cohort is reported by Segev *et al.*, who found 25 donor deaths within 90 days after 80.347 live donor nephrectomies (0.03%)[16].

Differences in information provision were encountered between the eight centers. In some cases these differences could be easily explained; one center only employs the

mini-open technique, and did thus not disclose details on laparoscopy or the possibility of conversion. But in other cases the discrepancy between centers was cause for concern. Our survey demonstrates that differences in education were also substantial between some professionals within one center.

If the information we provide is not uniform, and in some cases not even complete, we can never expect our donors to have all necessary knowledge to prepare them for donor nephrectomy. There are a few studies assessing donors' general knowledge of the donation procedure and its risks, which conclude that there are at least some deficits [17, 18]. Some donors even admit that, when looking back, they felt unprepared and not well (enough) informed by the transplant team [19].

Striking results were also encountered with regards to the informed consent procedure itself. Only three centers provided a unanimous answer to the question whether informed consent was assumed, obtained by explicitly asking, or signed. In the other centers, all options were mentioned at least once. A possible explanation is that the definition of informed consent may not be the same for everyone; in many centers, nephrologists obtain signed consent for donation, while surgeons obtain an additional, usually oral, consent for the actual nephrectomy. Still, these varied responses reflect a suboptimal situation regarding the informed consent procedure and may imply that surgeons don't exactly know how the procedure is arranged in their own hospital. It has been recommended that the informed consent procedure should be a continuous process with different evaluation moments and possibly even different consent moments along the way[20]. Implementing these separate informed consent moments for screening and donor nephrectomy in a standardized format would be a logical development.

This survey study has definite strengths. A response rate of 98% for a nationwide survey provides a reliable overview of the Dutch situation. Although there have been other studies that at least partly concur with our findings [6, 7], we cannot blindly assume that the same differences will be found in other European countries, let alone in other continents, where more detailed guidelines are available to guide the surgeon during information disclosure[4, 21]. Including international transplant surgeons would give us a better idea of how informed consent procedures are practiced abroad, but it is highly unlikely that a comparable response rate would be reached. Results may then be less reliable.

But even with this high response rate, our cohort still only comprises 32 individual surgeons involved in preoperative living kidney donor education, which is one of the main limitations of this study. In this small sample, statistical analyses are less valuable, especially for subgroup analyses. Another limitation is that as with every survey study, responses are not fully objective and subject to recall bias. Most questions are matrices or multiple choice and are naturally suggestive. We provided the answering options "always", "sometimes" and "never". The definition of "always" and "never" are clear, but

"sometimes" leaves room for interpretation. For one professional "sometimes" may mean "nearly always", whereas for the other it means "hardly ever".

We chose to only invite surgeons to complete the survey, even though the informed consent process is a joint effort of the whole transplant team, consisting of at least, but not limited to, a nephrologist, transplant coordinator and surgeon in most centers. If the surgeon hasn't told the donor all the details, one of the other team members may have done so and the donor may still be well informed. Still, the surgeon is responsible for the surgical procedure, and is the last in the chain of information provision to the donor. He should therefore ensure that the donor has been informed of all essential details and risks by either providing these himself or confirming that the rest of the team has done so.

A final point of discussion is the fact that we only looked at living donor education. This is a very specific population, and the procedure is only performed in highly specialized transplant centers. However, it is often stated that informed consent is even more important in living donors, since they do not benefit from the procedure. If relevant complications are left out of donor education, it may well be assumed that this will also be the case in the educational process of other surgical patients. A number of studies assessing the informed consent procedure in total knee- and hip arthroplasty candidates found similar results of low rates of disclosure and/or documentation of certain details and risks of the procedure [22-24]. Our results are informative for every surgical professional, and may urge them to critically assess the informed consent procedure in their own area of expertise.

Even in the Netherlands, a small country with close connections between kidney transplant surgeons, a large number of live kidney donations (31 per million of population [25]), and frequent interactions due to a successful national PKE program [26], great variations exist in surgical donor education and informed consent procedures. Important risks and complications are not always discussed with potential donors.

There are a number of possible options to further improve information provision to potential donors, some of which have already been put to use. A standardized informed consent form has already been implemented, but this form does not include specific details. Nephrologists mainly use it, not as a checklist to guide the consultation, but rather to document informed consent at the end of it. Information evenings, leaflets and DVD material, and a home-based educational team for specific donor categories [27] are some of newly implemented educational strategies. None of these methods are applied consistently, and their informational value has yet to be determined. Although donation rates ánd general knowledge regarding living donation evidently increased after home based education[27], this has not been investigated for other educational approaches. The basis for adequate donor knowledge lies in uniform information provision. Only then

can we test what donors really need, and understand, and identify aspects that need improving.

To ensure that every living kidney donor is prepared for their operation and postoperative course in the best possible way, a standardized informed consent procedure for the live donor nephrectomy is highly recommended. A nationwide inventory project has been initiated to achieve this[11].

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APPENDIX – I – ENGLISH TRANSLATION OF SURVEY QUESTIONS

Surgical Donor Education and Informed Consent in Live Kidney Donation.

Question 1.
Are you involved in the preoperative education of living kidney donors?

☐ Yes
☐ No → End of Survey

Question 2.
Do you perform live donor nephrectomies yourself?

☐ Yes
☐ No

Question 2A.
If yes, how many live donor nephrectomies do you perform on an annual basis?

☐ 0-10
☐ 10-20
☐ 20-50
☐ >50

Question 3.
How often, and where, do you see donors preoperatively? (multiple answers possible)

☐ Standard preoperative outpatient clinic appointment
☐ On admission to the ward, the day before surgery
☐ On the day of surgery
☐ Other, please specify: _____

_____

_____

Question 4.
Who is responsible for the postoperative care of living kidney donors during admission in your center?

☐ Nephrologist
☐ Surgeon
☐ Other, please specify: _____

_____

_____

Question 5.

How is the surgical follow-up arranged in your centrum, given that the procedure was uncomplicated?

☐ No surgical follow-up appointment
☐ Telephone follow-up visit
☐ One outpatient clinic visit
☐ Two outpatient clinic visits
☐ More than two outpatient clinic visits
☐ Other, please specify: _____

_____

_____

Question 6.

Which techniques for live donor nephrectomy are employed in your center? (please choose all applicable options)

☐ Pure laparoscopic donor nephrectomy
☐ Hand-assisted laparoscopic donor nephrectomy
☐ Hand-assisted retroperitoneoscopic(HARP) donor nephrectomy
☐ Robot-assisted donor nephrectomy
☐ (Mini)- open donor nephrectomy
☐ Other, please specify: _____

_____

_____

Question 7.

Which of the following aspects regarding operative techniques do you discuss with donors, and how often?

7A. Pure laparoscopic donor nephrectomy
☐ Always ☐ Sometimes ☐ Never
7B. Hand-assisted laparoscopic donor nephrectomy
☐ Always ☐ Sometimes ☐ Never
7C. Hand-assisted retroperitoneoscopic(HARP) donor nephrectomy
☐ Always ☐ Sometimes ☐ Never
7D. Robot-assisted donor nephrectomy
☐ Always ☐ Sometimes ☐ Never
7E. Mini)- open donor nephrectomy
☐ Always ☐ Sometimes ☐ Never
7F. Conversion to open procedure
☐ Always ☐ Sometimes ☐ Never

Question 8.

Which short-term complications do you discuss with donors, and how often?

8A. Bleeding

☐ Always ☐ Sometimes ☐ Never

8B. Wound infection

☐ Always ☐ Sometimes ☐ Never

8C. Abscess

☐ Always ☐ Sometimes ☐ Never

8D. Pneumonia

☐ Always ☐ Sometimes ☐ Never

8E. Urinary tract infection

☐ Always ☐ Sometimes ☐ Never

8F. Pain

☐ Always ☐ Sometimes ☐ Never

8G. Damage to other organs

☐ Always ☐ Sometimes ☐ Never

8H. Thromboembolic complications

☐ Always ☐ Sometimes ☐ Never

8I. Cardiovascular complications

☐ Always ☐ Sometimes ☐ Never

8J. Testicular pain

☐ Always ☐ Sometimes ☐ Never

8K. Fatigue

☐ Always ☐ Sometimes ☐ Never

8L. Neuropathy

☐ Always ☐ Sometimes ☐ Never

8M. Neurapraxia

☐ Always ☐ Sometimes ☐ Never

Open: Other, please specify _____

_____

_____

Question 9.

Do you discuss the risk of mortality with donors?

☐ Always

☐ Sometimes

☐ Never

Question 9A.

Open: if yes, what mortality rate do you disclose?

_____

_____

_____

Question 10.

Which long-term complications do you discuss with donors?

10A. Chronic pain

☐ Always ☐ Sometimes ☐ Never

10B. Incisional Hernia

☐ Always ☐ Sometimes ☐ Never

10C. Hypertension and other cardiovascular complications

☐ Always ☐ Sometimes ☐ Never

10D. Renal failure

☐ Always ☐ Sometimes ☐ Never

10E. Risks of living with one kidney: smoking

☐ Always ☐ Sometimes ☐ Never

10F. Risks of living with one kidney: NSAIDs

☐ Always ☐ Sometimes ☐ Never

10G. Risks of living with one kidney: antibiotics

☐ Always ☐ Sometimes ☐ Never

10H. Risks of living with one kidney: obesity

☐ Always ☐ Sometimes ☐ Never

Open: Other, please specify: _____

_____

_____

Question 11.

Do you discuss duration of admission with donors?

☐ Yes, please specify: _____ days postoperatively

☐ No

Question 12.

Do you discuss duration of convalescence with donors?

☐ Yes, please specify: … weeks/months

☐ No

Question 13.

Open QUESTION: Do you discuss anything else with donoren? If yes, please specify: _____

_____

_____

Question 14.

How is informed consent for the procedure obtained in your center?

☐ Assumed consent after consult

☐ Explicitly asked oral informed consent

☐ Signed informed consent

Open: Other, please specify: _____

_____

_____

Question 15.

Who is responsible for obtaining informed consent for donor nephrectomy in your center?

A. Surgeon

B. Nephrologist

C. Not applicable; no explicate informed consent

Open: Other, please specify: _____

_____

_____

Question 16.

When is informed consent obtained in your center?

☐ Prior to the surgical consult

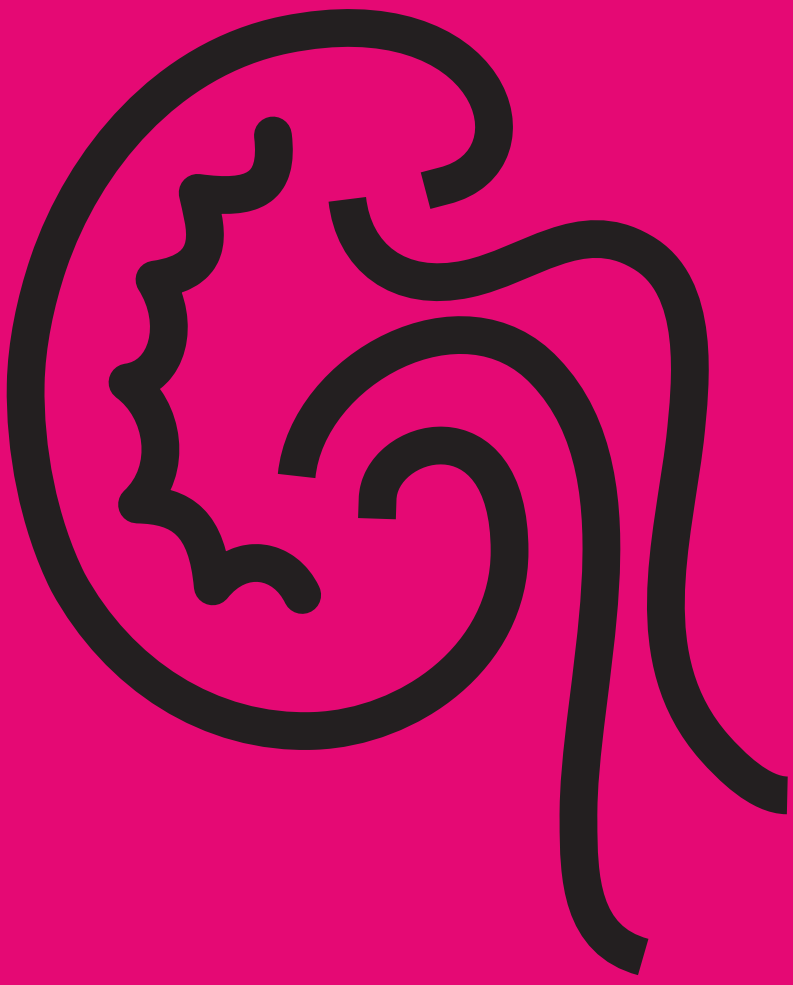
☐ After the surgical consult

☐ Not applicable; no explicate informed consent

Open: Other, please specify: _____

_____

_____



Chapter 5

Donor Knowledge of Provided Information During the Informed Consent Process in Live Donor Nephrectomy. A Pilot study.

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ABSTRACT

Introduction Donors report varying degrees of satisfaction with the information and preparation for live donor nephrectomy. Whether this stems from lack of education, or comprehension remains unclear. It is vital that donors receive all necessary details.

Research Question How well are donors informed about the live donor nephrectomy procedure and possible adverse events during the surgical part of the informed consent procedure?

Design Nine surgical transplant professionals were observed during the preoperative outpatient clinic visit of 46 potential living kidney donors. Provided information was scored using standardized checklists, team members received an "informer score". Immediately after the consult, and again on the day of admission, donors received a pop-quiz testing their knowledge. Postoperatively an evaluation and satisfaction questionnaire was sent.

Results Mean informer score was 12.5/20 (range 2-20). Mean donor score was 5.9/20 [2-11]. Donors scored best on duration of admission and convalescence, worst on long-term complications. Risk of mortality was disclosed by 91% of informers, but only reproduced by donors in 22% (clinic) and 14% (admission). Donors with younger children, a higher educational level and registered (post-mortem) donors scored significantly better. Mean donor satisfaction was 8.4/10 (4-10).

Discussion There were marked variations between information provided by informers, important complications were not always disclosed. Overall donor scores were low. Whether donors are actually well enough informed at the time of giving consent remains debatable.

INTRODUCTION

The informed consent procedure for live donor nephrectomy is ethically and legally obligatory but is not unambiguously defined in different institutes.[1-4] To safeguard donor autonomy, they must be presented with all potential risks, to be able to decide whether they are willing to accept these. In addition, donors may also need information to feel more prepared for the donation procedure.[5]

Some authors postulated that living kidney donors do not actually absorb all information provided to them, but rather focus on positive aspects to reaffirm their decision to donate.[6] The question has been raised whether they actually remember and understand everything, and it is argued that potential donors may not be fully informed at the time of giving consent.[5-9] Some donors have retrospectively reported not feeling adequately informed about certain aspects of kidney donation.[5, 8, 10, 11] Whether this is due to lack of comprehension or lack of education is unclear, but transplant professionals may vary in the information they provide,[12, 13] and potential complications and are not always disclosed.[14]

This PILOT study is one of the projects preceding in a nationwide initiative to further improve the informed consent procedure for live donor nephrectomy. The ultimate goal is to create a standardized format for this procedure, to assist transplant professionals in their daily clinical practice and to provide potential living kidney donors with all information they need. To do so requires analysis of scientific evidence, but more importantly, of daily practice from the medical professional's perspective as well as the donor's.

This PILOT study is the first step in assessing the surgical part of the informed consent procedure in live donor nephrectomy. In addition, we tried to determine the best design and set-up for a nationwide study on informed consent in live donor nephrectomy.

METHODS

Approval was obtained from the local ethics committee (Erasmus MC, MEC-2014-538, October 14th 2014). In our donor screening pathway, potential donors are first informed by a nephrologist and transplant coordinator and receive information by leaflet, DVD and website. Subsequently, they undergo a mandatory medical and psychological screening procedure and if no objections arise, they are referred for surgical screening. Potential donors, seen at the surgical outpatient clinic between September 1st 2014 and February 1st 2015, were asked to participate in this study.

After informed consent, one of two researchers observed the consultation and documented information disclosure using a standardized checklist (appendix A) using

information from our own data and data available from literature, defining items that should be included in informed consent procedures for live kidney donation.[4]

Every surgical professional ("informer") involved in preoperative living kidney donor education at our surgical outpatient clinic was included in this study. For every mentioned (informer) or recalled (donor) item one point was awarded and a maximum score of 20 could be obtained (Appendix A).

Donors received three questionnaires: the first two pop-quizzes testing knowledge of the upcoming procedure, administered immediately after the surgical outpatient clinic visit and again on the day of admission for donor nephrectomy. In addition, donors were asked to indicate how well they felt prepared for the donor nephrectomy. This was measured by means of a Visual Analogue Scale (VAS). A translated version of the pop-quiz is available as supplementary material (Appendix B). The last questionnaire was an evaluation and satisfaction questionnaire, administered 6-12 weeks after surgery.

Additional data regarding the procedure, the postoperative course and adverse events were derived from medical charts.

Donors

A total of 48 donors were seen during the inclusion period. One donor refused to participate, and one donor was not included because of a language barrier. Table 1 provides an overview of the remaining 46 donors' baseline characteristics. Ten donors have not been scheduled for the operation as renal function of four preemptive recipients remained stable, four couples preferred to postpone the donation procedure (because of family obligations, work, and holidays), and one recipient and one donor have not yet been cleared by the anesthesiologist. This left 36 donors with a complete follow-up.

Statistics

Statistical analysis was performed using SPSS version 21 and R version 3.1.2. Values are presented in means with standard deviation (SD) and, if relevant a range is provided. If absolute values were described (*e.g.* the number of complications mentioned), this was provided in a median with range.

Differences between informer scores and donor scores per type of informer were compared by One-Way ANOVA. Residuals were tested, distribution was normal. To compare differences in mentioning frequencies of individual complications between pop-quizzes completed at the outpatient clinic and those on the ward on the day of admission, McNemar tests were performed. Only those donors who completed the questionnaire on both occasions were compared. The McNemar test compares the number of those who first scored positive (*i.e.* mentioned that specific complication), and then negative (*i.e.* did not mention that specific complication) with the number who first scored negative and then positive: if these numbers differ significantly from each other an increase

or decrease can be concluded. Differences between outpatient and admission donor scores were analyzed using the pairwise comparison t-test. A two-tailed p-value of <0.05 was considered statistically significant. Multivariate analysis was performed using linear regression. All factors with a univariate p-value of <0.20 were included in the model, and were manually excluded based on their multivariate p-value. When predictors for donor scores were analyzed it was found that the residuals of linear regression were not normally distributed, thus the bootstrap method was used. Because SPSS does not allow overall p-values for categorical variables with more than two groups, which are needed for a stepwise procedure, we switched to R to find overall p-values per variable by combined Wald tests. None of the continuous variables had a non-linear effect.

RESULTS

Surgical consult

Nine medical professionals completed all consults; four attending surgeons, three surgical fellows and two specialist nurses. Disclosed information varied between informer type. Attending surgeons scored best with an average of 14.7 (±4.6) points, versus 11.1 (±2.2) for fellows and 10.8 (±1.0) for nurses (supplementary table 1). Variations were observed between individual professionals (inter-informer variability, p<0.0001). There was no significant intra-informer variability.

Table 1. Baseline characteristics of 46 living kidney donors (percentages between brackets unless otherwise defined).

	Outpatient Clinic	**Admission**
Gender (M:F)	20:26	14:22
Age (mean, SD, range)	54.6 (12.8, 27-75)	54.9 (12.3, 27-75)
Type of donation(ref.15)		
Unspecified	6 (13)	6 (17)
Specified direct	36 (78)	26 (72)
Specified indirect	4 (9)	4 (11)
Educational level[a]		
Lower	14 (30)	11 (30)
Intermediate	19 (41)	15 (42)
Higher	13 (28)	10 (28)
Current employment		
Fulltime	16 (35)	11 (31)
Part-time	13 (28)	12 (33)
Retired	11 (24)	8 (22)
Unemployed	6 (13)	5 (14)
Income		
Below average	13 (28)	11 (30)
Average	26 (57)	19 (53)
Above average	7 (9)	6 (17)

Table 1. Baseline characteristics of 46 living kidney donors (percentages between brackets unless otherwise defined).

	Outpatient Clinic	Admission
Religion		
Catholicism	11 (24)	8 (22)
Protestantism	9 (20)	7 (19)
None	20 (44)	17 (47)
Other	6 (13)[b]	4[c] (11)
Household constitution		
Alone	9 (20)	6 (17)
With partner	20 (44)	16 (44)
Alone with children <18	1 (2)	1 (3)
Alone with children >18	2 (4)	2 (6)
With partner and children <18	10 (22)	7 (19)
With partner and children >18	3 (7)	3 (8)
Other[d]		1 (3)
	1 (2)	
Registered donors[e]		
Yes	26 (57)	18 (50)
No	20 (44)	18 (50)

a. Lower: none or primary school, intermediate: high school or secondary vocational education, higher: university of applied sciences or university
b. Islam (1), Buddhism (1), Moluccan Evangelical (1), Christian (2), unspecified (1)
c. Islam (1), Buddhism (1) Christian (1), unspecified (1)
d. With brother
e. Donors who have completed their registration in the post-mortem donor registry, stating they want to be an organ donor

All professionals described the laparoscopic approach, including the pfannenstiel incision through which the kidney is removed. The possibility of conversion to open surgery was described in all but two consults (96%). A median of six short-term complications were disclosed (range 0-9). The risk of death was explicitly mentioned in 41 consults (91%). Long-term complications were only addressed in half of the cases (N=24, 52%). Table 2 provides an overview of mentioning frequencies of the individual complications by informers, and their equivalents by donors.

Duration of hospital admission was accurately described in 42 consults (91%), duration of convalescence in 31 (67%).

Pop-quiz scores

The average time between surgical outpatient clinic visits and admission for the operation was 64 days (median 56, range 21-196). Mean overall donor score was 5.9 (±2.5) and 5.7 (±2.2) at the clinic and on admission respectively. Donors scored best on duration of admission and convalescence, and worst on long-term complications (supplementary table 2). Mean outpatient scores and demographics did not differ between the 10 donors that were not included in the admission cohort, and the 36 donors that were.

Surgical technique

The majority of donors at the outpatient clinic described keyhole- or laparoscopic surgery (n=31, 67%), of which 13 (43%) added the pfannenstiel incision. Another three donors (6.5%) only mentioned the pfannenstiel incision. Only two donors (4%) recalled the possibility of conversion.

Table 2. Mentioning frequencies of individual complications by informers, outpatient donors (values whole cohort, and for the 36 donors who've completed both the outpatient as well as admission questionnaire) and admission donors, percentages between brackets.

Complication	Informer N=9	Donor Outpatient		Donor Admission N=36	p-value[ab]
		All donors N=46	Follow-up cohort N=36		
Short term					
Bleeding	44 (96)	27 (59)	21 (58)	18 (50)	0.63
Infection[c]	45 (98)	29 (63)	22 (61)	25 (69)	0.58
Wound	40 (87)	18 (39)	13 (36)	11 (31)	0.77
UTI	31 (67)	9 (20)	9 (25)	6 (17)	0.51
Pneumonia	39 (85)	12 (26)	10 (28)	6 (17)	0.22
Damage other organs	15 (33)	0	0	0	-
Pain	21 (46)	7 (15)	5 (14)	11 (31)	0.03
Thromboembolic	38 (83)	12 (26)	10 (28)	0	<0.0001
Cardiovascular	6 (13)	2 (4)	1 (3)	1 (3)	NA[d]
Death	41 (89)	10 (22)	5 (14)	5 (14)	NA[d]
Long term					
Chronic pain	10 (22)	4 (9)	3 (8)	1 (3)	0.50
Hernia	19 (41)	4 (9)	2 (6)	3 (8)	NA[d]
Hypertension	10 (22)	1 (2)	1 (3)	1 (3)	NA[d]
Renal failure	10 (22)	8 (17)	6 (17)	6 (17)	NA[d]
Risks with one kidney	13 (28)	1 (2)	1 (3)	0	0.5

NA – Not Available

a. P-values are computed for the comparison of the 36 outpatient with admission values, informer values are not included in the analysis.
b. P-values are computed using McNemar's test for the 36 donors that have completed both pop-quizzes.
c. Some donors only mentioned "infection" and did not specify which type of infection. Numerous donors mentioned more than one type of infection.
d. For the 36 donors that completed both pop-quizzes McNemar's couldn't be computed because mentioning frequencies were the same for both groups.

Short-term complications

Table 2 demonstrates how often individual complications were mentioned. Only ten (22%) donors mentioned the risk of death at the outpatient clinic versus five on admission (14%), four of whom had already mentioned it at the clinic. The remaining five donors that stated mortality at the outpatient clinic were not included in the admission group. Most complications were mentioned more often at the outpatient clinic than on

admission with the exception of pain: 31% on admission versus 15% at the outpatient clinic (p=0.03). Reversely; thromboembolic complications, being in the top five at the outpatient clinic, were not mentioned once on admission.

Long-term complications

Long-term complications were least mentioned by surgical professionals, and even less often by donors. At the outpatient clinic, 21 donors (46%) left this unanswered or answered with "unknown". Seven donors (15%) only named fatigue or deterioration of physical condition. Eighteen donors (39%) actually mentioned one or more complications at the outpatient clinic, versus nine (25%) on admission.

Hospital admission and convalescence

Three donors at the clinic (6.5%) and one on admission (2.8%) indicated that they had no idea about their length of stay. Although some (n=3, 6.5%) slightly overestimated the duration of admission at the clinic (*i.e.* one week instead of 3-5 days), none of the donors underestimated this. On admission, duration of convalescence was answered correctly by the majority of donors (n=40, 87%). Two donors said to have "no idea" regarding convalescence, two were vague ("couple of weeks") and two underestimated this (2-4 weeks). On admission, results were again comparable with three donors having no idea and three underestimations.

Preparation for surgery

The mean preoperative preparation score measured by the VAS (0-10) was 8.5 (±0.8) at the outpatient clinic and 8.6 (±1.0) on the day of admission.

When asked in retrospect postoperatively, mean preparation score was 8.4 (±1.2). The postoperative value for preparation did not vary between donors that had developed complications and those who had not, nor was it related to whether they had encountered any surprises during the peri- and postoperative course.

Donor satisfaction

Donors were quite satisfied with the donation and informed consent procedure: mean 8.4 (±1.2). No significant differences were observed between donor characteristics. A trend was observed that unspecified donors[15] were more satisfied than specified donors (9.2 versus 8.2, p=0.09), and donors living with children under 18 were less satisfied than other donors (7.4 versus 8.6 and 8.7, p=0.06).

Thirteen donors (36%) developed one or more complications; wound infection (n=5), bleeding (n=2), nausea (n=2), pain (n=2) abscess (n=1), deep vein thrombosis (DVT) (n=1), gastric bleeding (n=1), electrolyte disorder (n=1). For eight complications, donors indicated they knew this complication could develop, but the remaining seven donors

said they had no idea that their complication could happen, even though some of these had in fact been disclosed during the preoperative consult. Satisfaction scores were comparable between donors with and without complications (8.3 versus 8.5). Whether donors were aware of the possibility of a specific complication or not was not of influence on satisfaction scores.

Correlation between provided and reproduced information

While attending surgeons had the highest scores, donors informed by them had not. Donors informed by fellows scored significantly lower than the other two groups at the outpatient clinic as well as on admission (p= 0.03, 0.04 respectively, supplementary table 3). Donor scores were not significantly related to individual informer scores.

Table 3. Uni- and multivariate analysis as performed using linear regression for all factors possibly influencing donor scores.

	Univariate Beta (95%CI)	**Univariate p-value[a]**	**Multivariate Beta (95%CI)**	**Multivariate p-value[a]**
Outpatient score (N=46)				
Factor				
Female gender	1.22 (-0.17-2.60)	0.07	Removed	Removed
Age	-0.05 (-0.09- -0.01)	0.02	Removed	Removed
Relation donor – recipient (Specified)	-1.47 (-2.91-0.17)	0.08	Removed	Removed
Educational level[b]		0.13		0.02
Higher	1.78 (0-3.38)		2.11 (0.61-3.53)	
Intermediate	0.59 (-1.02-2.10)		1.05 (-0.48-2.59)	
No current employment[c]	-0.39 (-1.72-1.02)	0.58	-	-
Income[d]		0.53	-	-
Above average	-1.32 (-3.71-1)			
Average	-0.65 (-2.17-0.99)			
Religion[e]		0.82	-	-
Christian	-0.03 (-1.60-1.44)			
	-0.78 (-1.67-3.30)			
Other		0.001		0.003
Household constitution[f]	0.96 (-0.63- 2.68)		2.11 (-1.47-2.54)	
With kids	-1.4 (-3.15-0.36)		1.05 (-3.60-0.52)	
Without kids	0.81 (-0.72-2.19)	0.29	-	-
Registered Donor		0.005		0.02
Informer[g]	1.25 (-0.47-3.02)		2.11 (-0.80-3.40)	
Nurse	-1.44 (-2.86- -0.07)		1.05 (-2.63-0.06)	
Fellow	-0.36 (-1.16-0.73)	0.48	-	-
Feeling of preparation				

Table 3. Uni- and multivariate analysis as performed using linear regression for all factors possibly influencing donor scores. (continued)

	Univariate Beta (95%CI)	Univariate p-value[a]	Multivariate Beta (95%CI)	Multivariate p-value[a]
Admission Score (N=36)				
Factor				
Female gender	-0.31 (-2-1.25)	0.69	-	-
Age	-0.004 (-0.07-0.06)	0.84	-	-
Relation donor – recipient (Specified)	-0.6 (-1.68-0.75)	0.37	-	-
Educational level[b]			Removed	Removed
Higher	1.88 (0.35-3.25)	0.04		
Intermediate	0.78 (-0.83-2.3)			
No current employment[c]	-0.44 (-2-1.09)	0.53	-	-
Income[d]		0.11	Removed	Removed
Above average	1.52 (-0.86-3.61)			
Average	-0.77 (-2.37- 0.70)			
Religion[e]		0.16	Removed	Removed
Christian	-0.14 (-1.62-1.42)			
Other	-1.94 (-3.88-0.03)			
Household constitution[f]		0.07	0.60 (-0.73-2.02)	0.02
With kids	0.25 (-1.18-2.05)		-0.89 (-2.19-0.72)	
Without kids	-1.38 (-2.62- -0.13)		2.79 (1.78-3.92)	
Registered Donor	2.89 (1.68-3.96)	0		0
Informer[g]		0.16	Removed	Removed
Nurse	1.93 (-0.48-4.47)			
Fellow	-0.51 (-1.87- 0.93)			Removed
Feeling of preparation		0.12	Removed	-
Time interval outpatient – admission	-0.62 (-1.88-0.46) -0.01 (-0.03-0.01)	0.27	-	

a. Uni- and multivariate p-values were computed using linear regression with bootstrap analysis
b. Educational level was split into three levels; higher, intermediate and lower. "Lower" was taken as baseline class
c. Employment was split into yes versus no.
d. Income was divided into below average, average or above average. "Below average" was taken as baseline class
e. Religion was divided into Christian, none and other. "None" was taken as baseline class
f. Household was divided into alone, with partner but without children, and with or without partner but with children <18 years. "Alone" was taken as baseline class
g. "Consulting surgeon" was taken as baseline class

Correlation between demographics and reproduced information

Table 3 demonstrates uni- and multivariate analysis for demographic- and other factors that could possibly be influencing donor scores.

For the outpatient scores, a higher education level was independently associated with a higher score (6.9 versus 5.7/5.1, p=0.02). Donors living with children younger than 18 scored significantly higher (7.4 versus 6.4 and 5.0 respectively for the other two groups, p=0.003), but these donors were also significantly younger than the other two groups; mean age 42.9 versus 51.7 for donors living alone and 61.3 for those living with other

adults or children older than 18 ($p<0.001$). Donors informed by specialist nurses also scored better; 7.7 versus 6.4 and 5.0 ($p=0.02$). On admission, higher scores were again seen in donors living with children under 18 ($p=0.02$), and in donors who were registered as deceased donors (7.1 versus 4.2, $p<0.0001$).

DISCUSSION

Our study is the first that observed surgical consultations with living kidney donors, and correlated provided information with donors' knowledge about the different aspects of live donor nephrectomy.

Although other knowledge tests have been used[11, 16] none were as specific as ours. By observing the consult, there is no doubt about which donor has received which exact details. Our results demonstrate that, even within one transplant center, there are great variations in living kidney donor education during the surgical informed consent process. This is in accordance with the available literature:[4, 12, 13] information provided during the surgical consult differs among healthcare professionals. In our study, attending surgeons provided more detailed information than fellows and specialist nurses. However, donors informed by nurses scored better than those informed by consultants. An explanation, although hypothetical, may be that fellows and surgeons use more complex terminology while nurses may take more time to explain different items. We did not take into account the format of communication and information provision, nor the time taken for a consult. Both aspects may definitely influence donor knowledge, and this may be a topic for future research.

Most donors feel adequately prepared for surgery and report high rates of satisfaction with the informed consent procedure. Nevertheless, when tested on their knowledge of surgical technique and complications there are substantial deficits. It has been proposed that the decision-making process donors go through may differ from "regular" patients. Instead of carefully balancing risks and benefits, many donors decide to donate upon the first moment of hearing of the possibility, and they hardly ever change their mind, regardless of what information is provided to them; they only hear what they need to hear to reaffirm their decision.[6, 17, 18] This may be an explanation for the overall low donor scores that were encountered in this study.

A striking example was that although the risk of death was mentioned in all but four consults (91%), only ten donors (22%) reproduced this at the outpatient clinic, and even less at the time of admission for surgery (14%). It has been previously described that many living donors do not actively recall the risk of death. Gordon *et al* performed a study on informed consent in living liver donors: 18 of 30 living donors (60%) mentioned being told about the risk of death.[19] Although this percentage is higher than the 14 and

22% found in our pilot study, it has to be taken into account that the risk of death in living liver donors itself is greater than in kidney donors; 0.2%[20] versus 0.03%.[21] Nonetheless, living kidney donor mortality *does* occur,[21-23] and if this happens, it is disastrous not only for the donor and his loved ones, but also for the recipient (in case of specified donation). How this aspect can be improved is something that should be further investigated. We do want donors to be prepared and make an informed decision, but we do not want to scare them away by telling them repeatedly that they might die, therefore a fine balance has to be found.

Long-term complications were least recalled by donors. Similar findings have been reported; Valapour *et al*.[11] demonstrated that 48% of donors in their cohort reported a lack of understanding of long-term complications. Timmerman *et al.* [16] tested donors on their general knowledge of live kidney donation using true/false questions, and demonstrated that 32% answered the question about long-term complications incorrectly versus 12% for short-term complications. In our cohort, 35% of donors were aware of the possibility of long-term complications (versus 91% short-term complications). This finding is understandable, since long-term complications were also least mentioned by the informers in our study. It is challenging to present long-term risks, since many uncertainties and different views exist regarding this matter, and the opinions among health care professionals regarding these risks still vary.[12, 24-26]

We acknowledge that our study has a number of limitations. First, it has to be taken into account that our main outcome measure, the pop-quiz score, is not the same as actual comprehension of relevant details. It cannot be deducted with certainty if donors have actually understood all the given information, or whether they just have the ability to remember facts and words. Even if they answer a question correctly (for instance; the surgical technique with "laparoscopy"), we cannot check whether they actually comprehend the meaning of laparoscopy.

Another major limitation of this study is the use of unvalidated checklists and questionnaires. We created the pop-quiz ourselves, using information from currently available literature[4] and expertise from our own group of transplant professionals. Although validated knowledge tests are available[11, 16], these consist mainly of multiple-choice questions, and did not suit the purpose of our study. Our goal was to assess what donors pick up during the surgical consult, and we wanted them to describe this in their own words. The goal of this project was first and foremost to provide an overview of the current situation, and we believe that our pop-quiz was the best possible, and most detailed way to present this.

The scoring-system was developed alongside the checklist and the questionnaire. One point was awarded for each correctly mentioned or reproduced item. Not every item is equally important, from a medical viewpoint or from the donor's perspective. Many donors mentioned "fatigue" or "deterioration of physical condition" as a complica-

tion. We had not included these items in our checklist, and therefore, possibly wrongly, no points were awarded. The items on the checklist, and the scoring system will both be revised for the nationwide follow-up study. If the questionnaires will be used in a larger cohort, in multiple centers, they can eventually be validated, and more evidence-based conclusion can be drawn from the scores.

Our results demonstrated marked variations between information provided by transplant professionals, and important complications were not always disclosed. Overall donor knowledge scores were low, and none of the donors could recall all provided information, but overall satisfaction with the informed consent procedure was high. These findings imply that donor knowledge might not be solely dependent on the information we provide (during the surgical consult), and that more knowledge does not necessarily improve donor satisfaction.

Still, satisfaction alone should not be enough to justify the procedure. Since it is not a medical necessity for the donor, for them not to be fully informed does not seem acceptable. And even though most donors report a positive experience, the contrary is true for a minority. We believe that even one negative experience is one too many, especially if this could have been prevented by better information provision. Before we can speculate on how we can further improve the informed consent procedure, additional information is needed. A nationwide study covering all aspects of the informed consent procedure for live donor nephrectomy has been initiated.[27] This will give us more insight on donors' needs and wishes, and will assist us in creating a standardized, uniform informed consent procedure to further optimize living kidney donor education.

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Supplementary table 1. Informer score per consult, compared between types of medical professional (mean, SD), maximum score indicated between brackets

	Attending Surgeon (n=4, 18 consults)	Fellow (n=3, 22 consults)	Nurse (n=2, 6 consults)	P-value[a]
Overall score (max 20)	14.7 (4.6)	11.l1 (2.2)	10.8 (1.0)	0.003
Technique (max 4)	3.6 (0.6)	3.4 (0.6)	3.5 (0.5)	0.42
Short term complications (max 9)	6.6 (2.2)	5.7 (1.5)	6.0 (0.6)	0.29
Long term complications (max 5)	2.7 (2.1)	0.6 (1.0)	0.2 (0.4)	<0.001
Duration of admission (max 1)	0.9 (0.2)	1.0 (.02)	0.7 (0.5)	0.07
Duration of convalescence (max 1)	00.2)	0.5 (0.5)	0.5 (0.5)	0.008

SD – Standard Deviation; max – maximum score

a. P-values are calculated for mean scores, using the One-Way ANOVA

Supplementary table 2. Donor scores per group of medical professional (mean, SD), maximum scores per item indicated between brackets.

	Attending Surgeon (N=18)[a]	Fellow (N=22)[a]	Nurse (N=6)[a]	P-value[b]
Outpatient Score				
Overall score (max 20)	6.4 (2.3)	5.0 (2.5)	7.7 (1.8)	0.03
Technique (max 4)	1.4 (1.1)	1.0 (0.9)	1.7 (0.8)	0.3
Short term complications (max 9)	2.5 (1.4)	1.9 (1.6)	3.8 (1.2)	0.02
Long term complications (max 5)	0.6 (0.7)	0.3 (0.6)	0.2 (0.4)	0.35
Duration of admission (max 1)	1.0 (0.1)	0.8 (0.4)	1.0 (0.0)	0.08
Duration of convalescence (max 1)	0.9 (0.2)	0.9 (0.3)	1.0 (0.0)	0.44
Admission Score				
Overall score (max 20)	5.6 (1.7)	5.1 (2.2)	7.5 (2.7)	0.07
Technique (max 4)	1.6 (1.0)	1.3 (1.0)	2.3 (0.5)	0.1
Short term complications (max 9)	2.0 (0.7)	1.6 (1.2)	3.0 (2.1)	0.06
Long term complications (max 5)	0.1 (0.4)	0.4 (0.6)	0.9 (0.5)	0.46
Duration of admission (max 1)	0.9 (0.3)	0.9 (0.3)	1.0 (0.0)	0.82
Duration of convalescence (max 1)	0.9 (0.3)	0.9 (0.3)	0.8 (0.4)	0.82

a. Number of consults performed by this type of informer

b. P-values are calculated for mean scores, using One-Way ANOVA

Supplementary table 3. Donor scores per group of medical professional (mean, SD), maximum scores per item indicated between brackets.

	Consultant (N=18)[a]	Fellow (N=22)[a]	Nurse (N=6)[a]	P-value[b]
Outpatient Score				
Overall score (max 20)	6.4 (2.3)	5.0 (2.5)	7.7 (1.8)	0.03
Technique (max 4)	1.4 (1.1)	1.0 (0.9)	1.7 (0.8)	0.3
Short term complications (max 9)	2.5 (1.4)	1.9 (1.6)	3.8 (1.2)	0.02
Long term complications (max 5)	0.6 (0.7)	0.3 (0.6)	0.2 (0.4)	0.35
Duration of admission (max 1)	1.0 (0.1)	0.8 (0.4)	1.0 (0.0)	0.08
Duration of convalescence (max 1)	0.9 (0.2)	0.9 (0.3)	1.0 (0.0)	0.44
Admission Score				
Overall score (max 20)	5.6 (1.7)	5.1 (2.2)	7.5 (2.7)	0.07
Technique (max 4)	1.6 (1.0)	1.3 (1.0)	2.3 (0.5)	0.1
Short term complications (max 9)	2.0 (0.7)	1.6 (1.2)	3.0 (2.1)	0.06
Long term complications (max 5)	0.1 (0.4)	0.4 (0.6)	0.9 (0.5)	0.46
Duration of admission (max 1)	0.9 (0.3)	0.9 (0.3)	1.0 (0.0)	0.82
Duration of convalescence (max 1)	0.9 (0.3)	0.9 (0.3)	0.8 (0.4)	0.82

a. Number of consults performed by this type of informer

b. P-values are calculated for mean scores, using One-Way ANOVA

APPENDIX I - CHECKLIST OUTPATIENT CLINIC

Study number: _____
Initials: _____
Date: _____
Consult led by: _____
Name: _____

☐ Surgeon (consultant/attending) ☐ Surgical Fellow ☐ Resident ☐ Specialized Nurse/ Nurse Practitioner

Checklist

1. Surgical Technique

Discussed	☐ Yes	☐ No		
Side	☐ Left	☐ Right	☐ Why?	
Details	☐ Laparoscopy	☐ Robot	☐ Open	☐ Conversion

_____
_____
_____
_____
_____
_____

2. Short Term Complications

Discussed ☐ Yes ☐ No

Details
☐ Bleeding
☐ Infection ☐ UTI ☐ Pneumonia ☐ Woundinfection / abscess
☐ Damage to other organs
☐ Pain
☐ Thromboembolic complications
☐ Cardiovascular complications
☐ Death

_____
_____
_____
_____

3. Long Term Complications

Discussed ☐ Yes ☐ No

Details ☐ Chronic pain

☐ Incisional hernia

☐ Hypertension/ cardiovascular complications

☐ Kidney failure

☐ Risks of living with one kidney (smoking, NSAIDS, etc) _____

_____

_____

_____

_____

4. Duration of admission

Discussed ☐ Yes ☐ No

Details Stated duration: _____

_____

_____

_____

_____

5. Duration of convalescence

Discussed ☐ Yes ☐ No

Details Stated duration: _____

_____

_____

_____

_____

APPENDIX II - PRINCE – PILOT – POP-QUIZ – ENGLISH TRANSLATION

1. How well, on a scale of 1 – 10, do you feel to be prepared for the surgery and the convalescence period?

(1 is absolutely not prepared and 10 = couldn't have been prepared any better)

1 2 3 4 5 6 7 8 9 10

2. How would you describe, in your own words, the technical procedure of the operation?

_____

_____

_____

_____

How did you learn this information?

☐ Explained by surgeon
☐ Explained by nephrologist
☐ Explained by nurse/transplant coordinator
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

3. Which *short-term* problems and complications can occur?

Please write down all answers you can think of

_____

_____

_____

_____

How did you learn this information?

☐ Explained by surgeon
☐ Explained by nephrologist
☐ Explained by nurse/transplant coordinator
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

4. Which *long-term* problems and complications can occur?

Please write down all answers you can think of

_____

_____

_____

_____

How did you learn this information?

☐ Explained by surgeon
☐ Explained by nephrologist
☐ Explained by nurse/transplant coordinator
☐ Heard about it during information evening
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

5. How long do you expect to be admitted in the hospital?

_____

_____

_____

_____

How did you learn this information?

☐ Explained by surgeon
☐ Explained by nephrologist
☐ Explained by nurse/transplant coordinator
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

6. How long do you expect it will be before you can return to work / perform your normal daily activities?

Please strikethrough as appropriate

_____

_____

_____

_____

How did you learn this information? (Please choose all answers that apply)

☐ Explained by surgeon

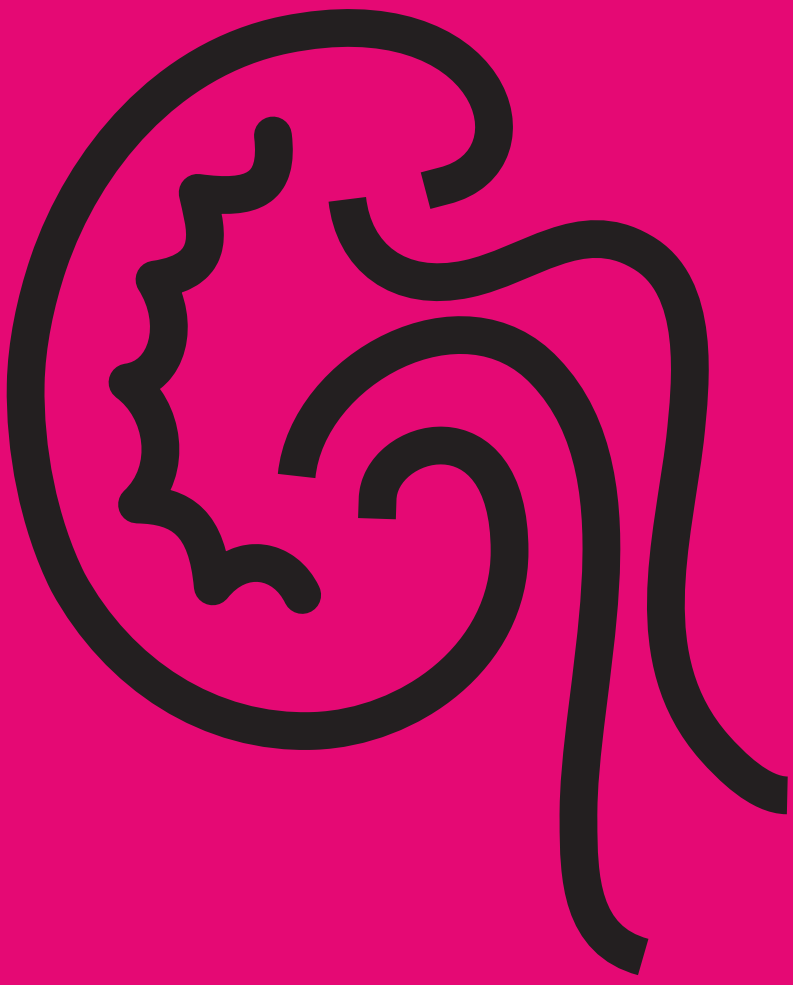
☐ Explained by nephrologist

☐ Explained by nurse/transplant coordinator

☐ Explained by family/friends

☐ Read in information provided by the hospital

☐ Read in information looked up myself



Chapter 6

Towards a Standardized Informed Consent Procedure for Live Donor Nephrectomy: the PRINCE (Process of Informed Consent Evaluation) Project: Study Protocol for a Nationwide Prospective Cohort Study.

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** On behalf of the national working group Informed Consent Live Kidney Donation*

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ABSTRACT

Introduction Informed consent is mandatory for every (surgical) procedure, but is even more important when it comes to living kidney donors, undergoing surgery for the benefit of others. Donor education, leading to informed consent, needs to be carried out according to certain standards. Informed consent procedures for live donor nephrectomy vary per center, even per individual healthcare professional. By assessing what information donors need to hear to prepare them for the operation and convalescence, the basis for a standardized, uniform surgical informed consent procedure for live donor nephrectomy can be created.

Methods and analysis The PRINCE project is a prospective, multicenter cohort study, to be carried out in all eight Dutch kidney transplant centers. Donor knowledge of the procedure and postoperative course will be evaluated by means of pop quizzes. A baseline cohort (prior to receiving any information from a member of the transplant team in one of the transplant centers) will be compared to a control group, who receive the pop quiz on the day of admission for donor nephrectomy. Donor satisfaction will be evaluated for the last group. The primary endpoint is donor knowledge. In addition, those elements that have to be included in the standardized format informed consent procedure will be identified. Secondary endpoints are donor satisfaction, current informed consent practices in the different centers (*e.g.* how many visits, which personnel, what kind of information is disclosed, in which format, etc), and correlation of donor knowledge with surgeons' estimation thereof.

Ethics and dissemination Approval for this study was obtained from the medical ethical committee of the Erasmus MC, University Medical Center, Rotterdam, February 18th 2015. Secondary approval has been obtained from the local ethics committees in six participating centers. Approval in the last center has been requested. Results will be published in a scientific journal.

INTRODUCTION

The Netherlands have a high rate of live kidney donation (31 living donors per million of population[1]), with more than half of all kidney transplants involving a living donor. In 2014, 534 live donor nephrectomies were performed out of a total of 1004 kidney transplantations (53.2%)[2]. One of the most successful paired kidney exchange (PKE) programs have been created in the Netherlands[3, 4], and many trials assessing the surgical procedure for the live donor nephrectomy have been initiated here[5-8]. With very low complication and mortality rates, live donor nephrectomy is a safe, low-risk elective surgical procedure. In contrast to patients, living donors are (generally) healthy individuals, from whom an organ is removed foremost for the benefit of others, although donors may gain psychological benefit. It is of the utmost importance that any patient is correctly informed about the specific details, risks and alternatives of a procedure, but the unique character of the live donor nephrectomy may warrant an extra vigilant approach to the informed consent process. Informed consent practices and procedures vary per center, and even per individual health care professional[9]. Standardization of this procedure, with regard to format, and contents, will greatly aid the transplant community, and improve the quality of care for living kidney donors[10, 11].

The need for a standardized format, ensuring disclosure of all important details and risks, further increases since extended criteria donors (*e.g.* overweight/obese donors, older donors, donors with hypertension and/or vascular multiplicity/anomalies) are increasingly being accepted[12]. These individuals could be more prone to complications, and potential donors must be well aware of the risks involved with their upcoming procedure, as well as future perspectives with only one kidney. These donors go through numerous steps during the informed consent procedure. In most Dutch centers, they are first seen by a nephrologist, transplant coordinator or nurse practitioner, who provide a lot of information about the donation procedure. In addition, most are evaluated by a social worker and some by a psychologist. The last person in the chain of information provision is usually the surgeon, who is responsible for performing the donor nephrectomy. In addition, the relevance of uniform information provision is underlined by paired exchange procedures, which are more frequently employed these days. It is not uncommon in the Netherlands that donors receive their education/information in one center but surgery in another. They may receive different information in these centers, which may be confusing. The Dutch situation is herein quite unique and stands in contrast to PKE programs in some other countries where the donor and recipient both remain in their own centers but the donor organ is transported[3, 4]. It is therefore mandatory that the Dutch transplant centers adopt a standardized, uniform informed consent procedure. But even if donors do not travel between centers, as is the case in

many other countries, medical professionals as well as donors will still benefit greatly from a standardized format.

The question remains what this standardized format should comprise. The living donor nephrectomy itself has become fully implemented in the general practice and much more information has become available regarding outcome and possible peri- and postoperative complications (Kortram *et al.*, submitted). Due to these developments living kidney donation has gained ground over the past decades, and numbers are increasing worldwide. This merits a revisited opinion on information disclosure and consent. Although the informed consent process has evolved alongside the surgical procedure in an attempt to incorporate the most up to date knowledge and transfer it to potential donors in an understandable fashion, it has yet to be brought to perfection[9].

Every physician, ethicist or legalist will agree that a person giving consent should be "fully informed", "free of coercion" and "competent"[13], but there is no consensus on details to be provided during the process, nor the manner in which these should be delivered. There are many different policies and guidelines outlining matters that should be disclosed to potential donors, but details are often not specified[14, 15]. These differences make it impossible for healthcare professionals to practice a uniform strategy and it is challenging to determine which patient has received which information. Recent data demonstrate that when tested on their knowledge, a large number of living kidney donors underestimate the complications and risks of living donor nephrectomy[16]. Surman *et al.* published similar findings in renal and liver transplant patients, revealing significant conceptual limitations to their knowledge about their postoperative situation, underlining the importance of adequate preoperative education[17]. Recently, a study performed by Gordon *et al.* was published regarding informed consent in living liver donors, again demonstrating that a large number of donors report a lack of understanding of the provided information (40%)[18]. Comparable results are demonstrated in other studies, where donors report varying degrees of (dis)satisfaction with and misunderstanding of provided information[10, 19, 20]. The question is raised whether the necessary information has not been provided correctly, whether donors simply not understand or remember it, or, as has been proposed by some, whether they selectively filter information and thus miss particular risks associated with donation[21-23]. Standardizing the informed consent procedure will help us better understand and address this. Two studies have been performed preceding the initiation of the PRINCE project of which the protocol is described in this article. One pilot project, to assess feasibility and design details, and a survey among Dutch kidney transplant surgeons to assess the current situation regarding live donor nephrectomy and informed consent practices in the Netherlands. These studies will be briefly highlighted in the following paragraph.

Pilot study

A pilot study was performed (Kortram *et al*, submitted), preoperative surgical outpatient clinic visits of 46 potential living kidney donors were observed and provided information was scored. Immediately after giving consent for donor nephrectomy, and again on the day of admission for the operation, donors received a questionnaire testing their knowledge of the upcoming operation. They received an evaluation questionnaire regarding their satisfaction with and understanding of the informed consent procedure 6-12 weeks postoperatively. After completion of the pilot study, pop quiz questions were rephrased where necessary, and the scoring system was adjusted.

Survey

A web-based survey was created to assess the current situation in the eight Dutch transplant centers[24]. All surgeons who were possibly involved, or had been so in the past, in live kidney donation were invited to complete the survey (n=50). The response rate was 98% (N=49, of which 32 were still active in living donor education). Respondents were asked which complications they discussed with potential donors during the informed consent process for live donor nephrectomy. Important complications were not always disclosed: bleeding was the only complication every surgeon mentioned. Risk of death was always mentioned by 16 surgeons (50%), sometimes by 12 (37.5%), and four surgeons (12.5%) never disclosed this disastrous complication. Thus, some improvements can be made regarding information provision.

METHODS AND ANALYSIS

Design

The PRINCE (Process of Informed Consent Evaluation) Inventory project is designed as a prospective, multicenter cohort study. The study is conducted in the eight Dutch kidney transplant centers, which are all University Medical Centers (to which transplantation is confined).

The study is divided into two parts: a cross-sectional study (Cohorts 1 & 3) and a longitudinal study (Cohort 2). Both parts are prospective studies. Figure 1 presents a schematic overview of the different cohorts.

The cross-sectional study comprises pop-quizzing two cohorts of donors at different stages during the pre-donation period. The cross-sectional design is chosen to include as many donors as possible. Cohort 1 will be included when the potential donors first present themselves to the hospital, at the outpatient nephrology clinic, prior to having spoken to any member of the transplant team. The second group will be included one

day preoperatively on admission for donor nephrectomy (Cohort 3). These donors will have received all information possible from different members of the transplant team.

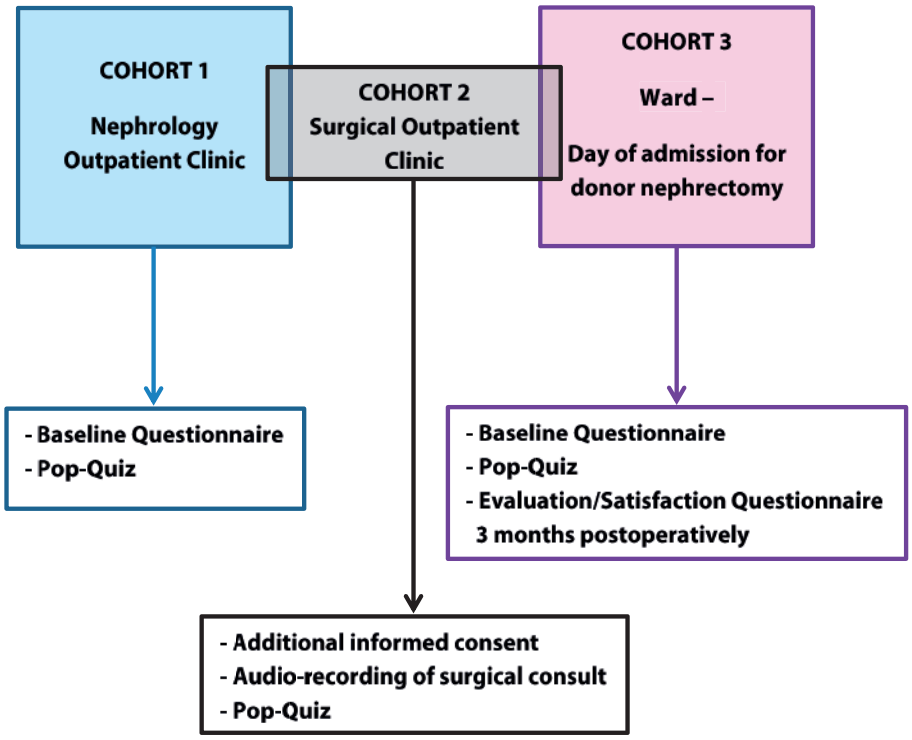

Figure 1 - Schematic overview of the three cohorts of the PRINCE study, and the questionnaires/ additional measurements they have to complete

Both groups of donors will be asked to fill out a pop quiz regarding their knowledge of the donor nephrectomy procedure, the possible short- and long-term complications and details about hospital admission and convalescence (Appendix 1 – supplementary material). The second group of donors will receive an additional questionnaire three months after surgery to assess their satisfaction with the educational- and informed consent procedure retrospectively.

The donors included in the longitudinal part of the study, *i.e.* Cohort 2, will be followed more closely to obtain a detailed conception of the informed consent process in the eight different centers. The donors that are eligible for inclusion in Cohort 2 are those donors already included in Cohort 1, that are being referred to the surgical outpatient clinic. This will mainly be influenced by their recipient's status (preemptive, comorbidity etc.), and whether the donor has been approved by the nephrologist. The surgical consult will be recorded (audio only). These recordings will be analyzed using a standardized

checklist, to assess which complications and other details are specifically disclosed by the surgeon. Donors in this cohort will be asked to fill out the same pop quiz as the first cohort, immediately after the surgical consult and again on the day of admission. They will also receive the evaluation questionnaire three months after surgery.

Objectives

The primary objectives of this inventory project are to assess the current status of the informed consent procedure for the live donor nephrectomy in all Dutch kidney transplant centers with regard to the procedure, donor knowledge and satisfaction. The ultimate objective is to eventually create a standardized format informed consent procedure.

Study population

The study population is divided into three cohorts. Cohort 1 comprises all potential living kidney donors that are seen at the outpatient nephrology clinic. Exclusion criteria for this cohort are: inability to understand the Dutch language, prior donation education in a kidney transplant center, age < 18 years and a mental illness prohibiting informed consent. Cohort 2 is obtained from a sample of referred Cohort 1 donors. The first 10 donors in each center that are referred to the surgical outpatient clinic will be included. Cohort 3 comprises all donors that are admitted to the surgical ward for live donor nephrectomy. This includes those donors that have already been included in cohort 2. Exclusion criteria for the latter two cohorts are: inability to understand the Dutch language, age < 18 years, and a mental illness prohibiting informed consent.

Sample size calculation

Since this study is an inventory project, making a comparison of informative findings rather than performing one specific measurement, a sample size calculation is not applicable.

The total number of live donor nephrectomies differs between the eight centers (figure 2), and it is therefore unrealistic to set the same goal for every center. But it is necessary that all participating centers provide a large enough number of subjects, seen by preferably all, but at least a number of different members of the transplant team to eliminate, as much as possible, inter-observer and timing-related variations in donor education. The following inclusion aims are set: 400 donors for cohort 1 (50 donors in each center), 80 for cohort 2 (10 donors in each center) and 200 for cohort 3 (Number of donors per center calculated based on procedures performed in 2014).

Primary & Secondary endpoints

The first main study parameter is donor knowledge of the donation procedure. This will be assessed by means of a pop quiz score. Scores will be compared between the

different cohorts and/or time-intervals. The elements to be included in the standardized informed consent format comprise the second main study parameter. These items will be assessed by different means. Obviously, some items will have to be included, based on the knowledge we already have from experience and the currently available literature (Kortram *et al.*, submitted). The audio recordings of the Cohort 2 donors will provide us with information about the currently disclosed items in each center. We will try to correlate this to donor knowledge of the individual items on our checklist. In addition; all Cohort 3 donors receive an evaluation questionnaire in which they are asked whether they've missed anything during the informational process.

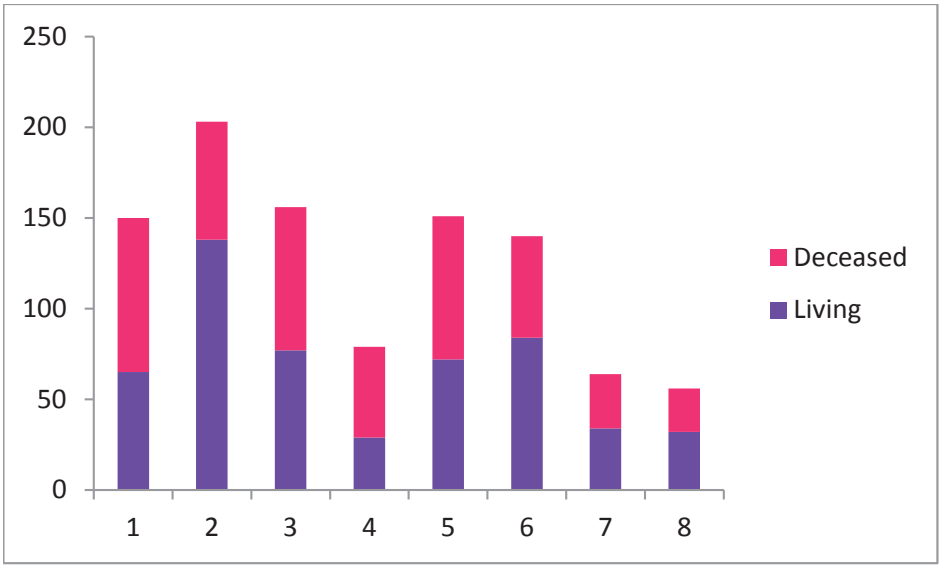

Figure 2 - Number of live donor nephrectomies per center in 2014

The first secondary study parameter is the manner of obtaining informed consent and the contents hereof in the eight Dutch transplant centers. This parameter is a descriptive parameter, which cannot be directly measured. This parameter will be assessed by interviews with the (para)medical staff in each transplant center, and by observation on site. Some aspects of the process itself will be collected and compared between centers: *e.g.* how many visits (on average) each donor has, the location where donors are seen (outpatient clinic, ward), the manner of obtaining consent (assumed, verbal, written), and who is responsible for obtaining consent (surgeon, nephrologist). These procedures will be compared to create the optimal format for all Dutch centers. In addition, provided information material (*e.g.* only orally distributed, leaflets, DVDs, websites, information evenings) will be assessed and compared between centers.

Donor satisfaction will be measured using the visual analogue scale (VAS-score, 0-10) in addition to describing questions. The last secondary parameter that will be assessed is the correlation between the donor's knowledge and the surgeon's estimate thereof. Surgeons will be asked to "predict" their donor's score after the consultation, using a 0-10 scale, 0 meaning no knowledge whatsoever and 10 meaning perfect reproduction of all details. This will be correlated to the donor's pop quiz scores.

Data collection & follow-up

Each donor will receive an anonymous study number, which will be used for the database. All subjects will be asked to fill out one or more, with a maximum of three pop quizzes. Donors included in cohort 3 will also be sent an evaluation questionnaire three months postoperatively. In addition, every donor is asked to fill out a baseline questionnaire with general questions regarding social economic status, religion and donation activities. The random sample of donors that will be followed longitudinally will be monitored more closely. The preoperative surgical consult at the outpatient clinic will be recorded (audio only), and these consults will be scored using a standardized checklist. These donors will receive one additional pop quiz immediately after the surgical consult. All other tests and procedures will be according to local protocol for the screening and treatment of living kidney donors.

Statistical Analyses

Statistical analysis will be performed using SPSS version 21 and R version 3.1.2. Dichotomous data and counts will be presented in frequencies. Continuous data will be presented in means with a standard deviation (SD) or median value with a range. In addition, some information will be presented in a literal descriptive fashion (*i.e.* specific answers to the pop-quiz questions).

Differences between scores will be compared by the independent sample t-test, the pairwise comparison t-test or One-Way ANOVA. To compare differences in mentioning frequencies of individual complications between Cohort 1 and Cohort 3, Chi^2 tests will be performed. For the donors in Cohort 2 the McNemar test will be performed to compare individual mentioning frequencies at the different time intervals. The McNemar test compares the number of those who first scored positive and then negative with the number who first scored negative and then positive: if these numbers differ significantly from each other an increase or decrease can be concluded. A p-value of <0.05 will be considered statistically significant. Multivariate analysis will be performed using linear regression. If necessary, bootstrapping will be applied. Stratification will be applied for center.

Feasibility

Approval from the medical ethical committee for the PRINCE project was obtained on February 8th 2015, and the first donor was included on March 30th 2015. At this moment approval of local ethical committees has been obtained in six of seven of the other participating centers, and donors are being included in the different cohorts in these centers. In the last center, approval from the local ethics committee has been requested.

ETHICS AND DISSEMINATION

Ethics

Approval for this study was obtained from the medical ethical committee of the Erasmus MC, University Medical Center, Rotterdam, The Netherlands, on February 18th 2015. Secondary approval has been obtained from six of seven local ethics committees in the participating centers, and has been requested in the last. Verbal informed consent will be obtained from (potential) donors prior to filling out the questionnaires.

Dissemination

Results will be published in a scientific journal, and presented on national and international (medical) conferences. Data will be used to create a standardized surgical informed consent procedure for the live donor nephrectomy.

DISCUSSION

Informed consent is mandatory for every (surgical) procedure, but is even more important when it comes to living kidney donors, undergoing surgery for the benefit of others. Donor education, leading up to informed consent, needs to be carried out according to certain standards. According to national guidelines, those complications with an incidence of >1% or those with severe consequences need to be disclosed to patients (or donors)[25]. But if we would adhere to that standard, only bleeding, ileus and wound infection would have to be mentioned, in addition to the small risk of mortality (Kortram *et al*, meta-analysis, unpublished).

A recent survey study among Dutch kidney transplant surgeons demonstrates that even these complications are not always disclosed to donors (Kortram *et al*, survey, unpublished). Moreover, it is questionable whether this information is sufficient for potential kidney donors. They are not patients, and they do not directly benefit from undergoing this procedure. Every complication is one too many, and donors need to be aware of the risks and details of the donation procedure. It is thus argued that

donors may need more and/or different information than the three most frequently encountered complications to be optimally prepared for donor nephrectomy and the postoperative course.

However, it has also been proposed that donors do not use the same decision-making strategy that patients use. Instead of carefully weighing all risks and benefits, many make their decision upon the first moment of hearing of the possibility, and many never change their mind, regardless of the information they receive during the educational and informed consent process[21, 22], although more recent studies do bring in some nuance[26].

So how does the provided information relate to donor knowledge? And how does donor knowledge relate to donor satisfaction? After all, even if donor knowledge is lacking, but satisfaction rates are high, is it even necessary to change our current policy? There have been a number of studies assessing donors' knowledge of kidney donation and transplantation[16, 19], but none of these tests were as specific as the pop quiz to be used in the PRINCE project. In addition, donors were only tested at one moment during the educational process. During the PRINCE project, donor knowledge will be measured before and after information provision in all Dutch transplant centers. The ideal design for the present study would be a longitudinal cohort study. To administer the first pop quiz at the moment a potential donor first comes to the outpatient nephrology clinic, then follow them through their educational course to the surgical outpatient clinic, the ward and postoperatively. However, in many cases, the time interval from the first donor contact to actual donor nephrectomy exceeds a year, if donor nephrectomy takes place at all. Of the 422 potential donors evaluated at our center in 2013, 227 were either rejected or decided not to proceed with the donation process themselves. In February 2015, 136 of the remaining 195 donors had already undergone surgery, and 59 were still being evaluated, on the waiting list, or postponed because their recipient's own kidney function was still good enough. Even though these numbers are from one center only, they do indicate that a longitudinal cohort, with the preferred sample size would take at least two years to complete follow-up. Comparing two different cohorts; a baseline group at the outpatient nephrology clinic and a control group on the surgical ward on the day of admission may provide us with the same information, especially since it will be a nationwide study with a large number of patients. Using a thorough baseline questionnaire for both groups will enable us to check whether the groups are indeed similar. By introducing an additional sample in the longitudinal cohort, with audio recordings of the surgical consultations, results of the two other cohorts can be compared to this group to verify reliability of the results.

Even though we believe that the current format for the PRINCE project is the best possible design to assess the informed consent procedure for the live donor nephrectomy, a number of limitations are foreseen.

First of all, there are no validated questionnaires to assess donor knowledge to the extent pursued in our study. Validation of a knowledge test with open questions instead of multiple- choice is virtually impossible, since donors may learn or forget specific information at different time points. Using multiple-choice questions is much easier to compare scores, but we believe an open question, requiring an answer in the donor's own words provides more reliable information. This way, we can be sure that they actually know this information, and not just check the boxes of words that they vaguely recall having been told about.

The open questions do again pose as a possible limitation. Donors may misinterpret the question, as we have already seen during the PILOT project, in which some answered the question about the surgical technique with "good" or "very careful". In addition, they may list one or two complications, and not everything they possibly know.

Last, a good pop-quiz score does not necessarily equal adequate donor comprehension. Donors may write down "hand-assisted laparoscopic donor nephrectomy" as the surgical technique, because they remember the surgeon talking about this, score 2 points, but have no idea what this actually means. On the other hand, a donor may write down "key hole surgery", score and score only one point, have a far better understanding of what is going to happen during the procedure.

Using the chosen approach for the PRINCE project will give us a clear overview of the actual gained knowledge during the educational process. In addition, donor satisfaction will be evaluated and related to donor knowledge. By assessing what information donors need, and want to hear to prepare them for surgery and convalescence, the basis for a standardized informed consent procedure for live donor nephrectomy can be created. It has to be taken into account that even in a small country as The Netherlands with generally harmonized protocols, details in local practice vary with regards to hospital logistics, but also with regards to the different techniques for live donor nephrectomy employed by each center. The standardized format will have to allow for (small) modifications to fit the situation in each individual kidney transplant center.

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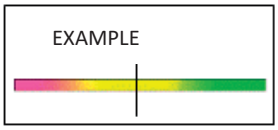
APPENDIX I - PRINCE – INVENTORY – POP-QUIZ – ENGLISH TRANSLATION

1. How well, on a scale of 1 – 10, do you feel to be prepared for the surgery and the convalescence period?

Please draw a vertical line on the rectangle below, in which 0 is absolutely not prepared and 10 = couldn't have been any better prepared.



0 10

2. What type of surgery will you undergo?

Think about surgical technique, the number of scars you will get, and where these scars will be.

_____

_____

_____

_____

How did you learn this information? (Please choose all answers that apply)

☐ Explained by Surgeon/Urologist
☐ Explained by Nephrologist
☐ Explained by nurse/transplant coordinator
☐ Heard about it during information evening
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

3. Which *short-term* problems and complications can occur?

Please write down all answers you can think of

_____

_____

_____

_____

How did you learn this information? (Please choose all answers that apply)

☐ Explained by Surgeon/Urologist
☐ Explained by Nephrologist
☐ Explained by nurse/transplant coordinator
☐ Heard about it during information evening
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

4. Which *long-term* problems and complications can occur?

Please write down all answers you can think of

_____

_____

_____

_____

How did you learn this information? (Please choose all answers that apply)

☐ Explained by Surgeon/Urologist
☐ Explained by Nephrologist
☐ Explained by nurse/transplant coordinator
☐ Heard about it during information evening
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

5. How many days do you expect to be admitted in the hospital?

Please write down the total number of days, before ánd after the surgery

_____

How did you learn this information? (Please choose all answers that apply)

☐ Explained by Surgeon/Urologist
☐ Explained by Nephrologist
☐ Explained by nurse/transplant coordinator
☐ Heard about it during information evening
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

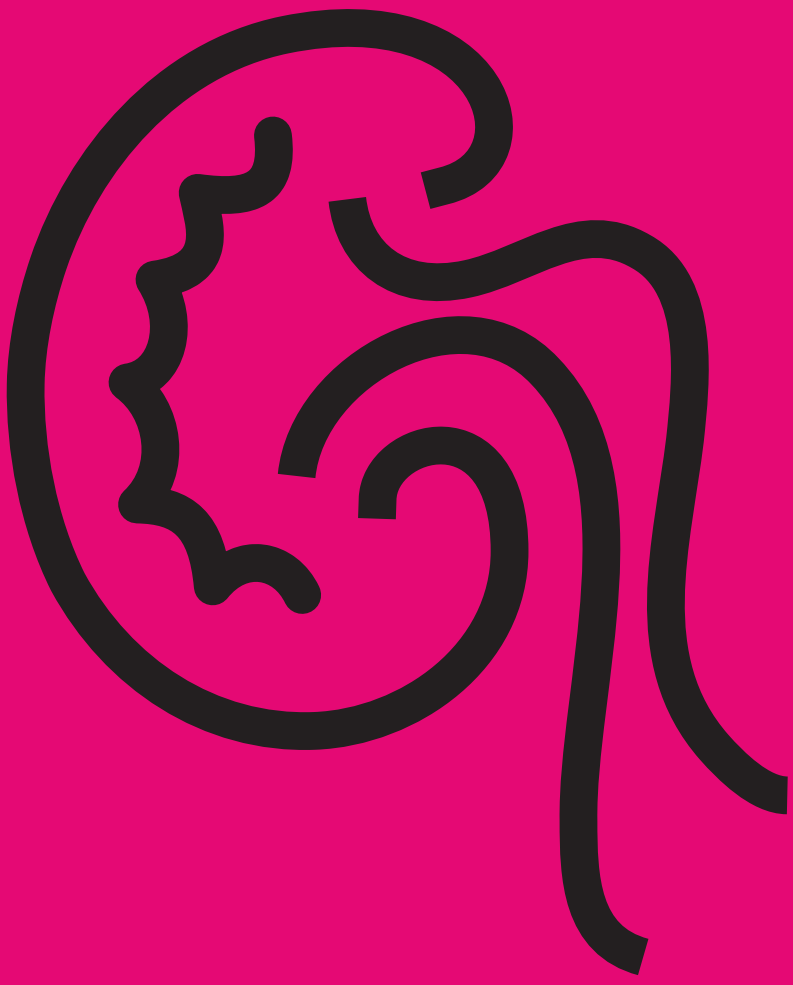
6. How long do you expect it will be before you can perform your work / your normal daily activities?

Please strikethrough as appropriate

_____ Weeks/ Months

How did you learn this information? (Please choose all answers that apply)

☐ Explained by Surgeon/Urologist
☐ Explained by Nephrologist
☐ Explained by nurse/transplant coordinator
☐ Heard about it during information evening
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself



Chapter 7

Donor Knowledge of Provided Information – A Prospective Nationwide Inventory Study

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** On behalf of the National Working Group Informed Consent for Live Donor Nephrectomy ("PRINCE")*

To be submitted

ABSTRACT

Introduction Informed consent is mandatory for every (surgical) procedure, but is even more important when it comes to living kidney donors, undergoing surgery for the benefit of others. Donor education, leading to informed consent, needs to be carried out according to certain standards. Informed consent procedures for live donor nephrectomy vary per center, even per individual healthcare professional. By assessing the information donors need to know, to prepare them for the operation and convalescence, the basis for a standardized, uniform surgical informed consent procedure for live donor nephrectomy can be created.

Methods Donor knowledge of the procedure and postoperative course was prospectively evaluated by means of pop quizzes in a multicenter national study. All potential donors who were seen for the first time at the transplant nephrology outpatient clinic (Cohort A) completed a pop-quiz about the details of the donation procedure, prior to receiving any information. A second group of donors completed the same pop-quiz on the day of admission for donor nephrectomy (Cohort B). The primary endpoint was donor knowledge. Secondary endpoints were donor satisfaction, and current informed consent practices in the different centers.

Results A total of 604 pop-quizzes were completed; 378 in Cohort A and 226 in Cohort B. Average donor score was 6.9 out of 25 (±3.9, range 0-18) in Cohort A and 10.4 (±2.8, range 0-17.5) in Cohort B. Donors generally scored best on duration of admission and convalescence, and worst on long-term complications. Younger donors, donors with a higher educational level and those who were registered as deceased donors scored higher in Cohort A, , only donors who were registered as deceased donors scored higher in Cohort B. Donors felt relatively well prepared for surgery after receiving all information: 8.3 (±1.3) out of 10, and average postoperative satisfaction with the informed consent procedure was 8.1 out of 10 (±1.6, range 0.6-10)).

Conclusion Donor knowledge of the procedure and postoperative course improves during the informed consent process but is still low. Long-term complications deserve more attention during the preoperative educational process of living kidney donors. Incentives to standardize the informed consent procedure will further improve donor knowledge and satisfaction, and will benefit consult efficiency at the outpatient clinic.

INTRODUCTION

Informed consent has been a topic of great interest in the surgical community. Although the idea of informed consent dates back many decades, it is becoming increasingly important in the current daily practice, in which shared decision-making and patient-tailored healthcare- and education are gaining in popularity[1].

It is of the utmost importance that any patient is correctly informed about the specific details, risks and alternatives of a procedure. First, to make a balanced decision whether or not to undergo this procedure, second to prepare them for the procedure itself, and the postoperative course. Living donors are (generally) healthy individuals, from whom an organ is removed foremost for the benefit of others, although they may gain psychosocial benefit. The unique character of the live donor nephrectomy may warrant an extra vigilant approach to the informed consent process. Previous research demonstrates variations in informed consent practices and procedures per country, but also per center, and even per individual health care professional[2, 3].

Every medical professional, ethicist or legalist will agree that a person giving consent should be "fully informed", "free of coercion" and "competent" [4], but there is no consensus on details to be provided during the process, nor the manner in which these should be delivered. There are many different policies and guidelines outlining matters that should be disclosed to potential donors, but details are often not specified, and vary per guideline [5-9]. In addition, any conversation with a donor will be a momentary display of the medical professional's routine, and with each consult, they will make an estimation as to how this particular donor should best be informed. These differences make it impossible for healthcare professionals to practice a uniform strategy and it is challenging to determine which donor has received which information.

Recent data demonstrate that when tested on their knowledge, a large number of living kidney donors underestimate the complications and risks of living donor nephrectomy[10]. Surman *et al.* published similar findings in renal and liver transplant recipients, revealing significant conceptual limitations to their knowledge about their postoperative situation, thereby underlining the importance of adequate preoperative education [11]. Recently, a study performed by Gordon *et al.* was published regarding informed consent in living liver donors, again demonstrating that quite a proportion of donors report a lack of understanding of the provided information (40%)[12]. Comparable results are demonstrated in other studies, where donors report varying degrees of (dis)satisfaction with and misunderstanding of provided information[13-15]. The question is raised whether the necessary information has not been provided correctly, whether donors simply not understand or remember it, or, as has been proposed by some, whether they selectively filter information and may miss particular risks associated with donation[16-18]. Standardization of the informed consent procedure, with regard to format and

contents will greatly aid the transplant community, and improve the quality of care for living kidney donors [13, 19]. Standardization however should not eliminate the possibility for donor-tailored education, thus the format should be a guideline with room for individual adjustments, rather than a strict law.

The question remains what this standardized format should encompass. The living donor nephrectomy itself has become fully implemented in transplant programs, and much more information has become available regarding possible peri- and postoperative complications[20, 21] and long-term outcome. Surgeons tend to disclose fewer long-term then short-term outcomes[3], and donor knowledge regarding long-term outcomes has been demonstrated to contain deficits [10, 14]. Recent studies have demonstrated that long-term follow-up is absolutely necessary to detect, and possibly prevent, severe consequences. For one, it is suggested that in specific populations, the risk of ESRD is indeed significantly increased after donation[22-24]. Other long term risks, like cardiovascular disease and gestational hypertension have recently received more attention, and more detailed information on these risks may have to be incorporated in the informed consent procedure for the live donor nephrectomy[25, 26].

All this merits a revisited opinion on information disclosure and consent. Although the informed consent process has evolved alongside the surgical procedure in an attempt to incorporate the most up to date knowledge and transfer it to potential donors in an understandable fashion, it has yet to be brought to perfection[2, 13]. In a single center PILOT study preceding the present study, 46 donors were tested on their knowledge of the live donor nephrectomy and postoperative course (Kortram *et al.*, unpublished). Knowledge scores were low, regardless of which, or how many details had been disclosed to them by the health care professional. This originated a fear that donors may not be informed sufficiently at the time of giving consent, a conclusion that had also been drawn by other authors in the past[13, 27-30].

The objectives of this inventory project are to assess the current status of the informed consent procedure for the live donor nephrectomy in all Dutch kidney transplant centers with regard to the procedure, donor knowledge, and satisfaction. The goal is to eventually create a standardized format informed consent procedure, which will in turn help the transplant professional to provide adequate, donor-tailored information.

METHODS

Approval for the study was obtained from the Medical Ethics Committee (MEC) of the Erasmus MC University Medical Center, Rotterdam, The Netherlands, on February 18th 2015. Secondary approval was obtained from the MECs of the other seven participating centers. Potential donors were included between March 2015 – July 2016. The study is a

prospective, multicenter, observational study, conducted in all Dutch kidney transplant centers, which are all University Medical Centers. The detailed study protocol has been previously published[31]. This article reports on the two main cohorts of the study (Cohort s1 and 3 in the protocol).

The first group consists of potential living kidney donors prior to their first visit to the nephrology outpatient clinic (Cohort A), the second entails a group of donors on the day of admission for donor nephrectomy (Cohort B). To ensure that the sample in each cohort portrays an adequate reflection of the general population, minimum sample sizes were calculated as follows: Cohort A – 50 donors per center, thus 400 donors, Cohort B – a set number of donors per center, based on each center's volume in 2014, making for a minimum total of 200 donors (details described in the protocol[31]). Due to the duration of the inclusion period, some donors from Cohort A could also be included in Cohort B.

After obtaining informed consent for participation in the study, a potential donor was asked to complete a baseline questionnaire and a pop quiz. The baseline questionnaire consisted of questions regarding gender, relationship to the recipient[32], education, employment, religion, household constitution and donation activities. The pop-quiz consisted of five open questions regarding surgical technique, complications, duration of admission and duration of convalescence (Appendix I – Supplementary material). In addition, donors were asked to indicate how well they felt to be prepared for the donation procedure by means of a visual analogue scale (VAS). A scoring system was developed to calculate the pop-quiz score. A maximum of five points were awarded for each of the five sections. All Cohort B donors received an evaluation and satisfaction questionnaire three months post-operatively. If no response was obtained, a reminder was sent after another three months.

The primary outcome of this study was donor knowledge, measured by their pop-quiz scores. The secondary outcomes were the manner of obtaining consent for donor nephrectomy in the different transplant centers and donor satisfaction with this procedure.

Statistical Analysis

Statistical analysis was performed using SPSS version 21 and R version 3.1.2. Dichotomous data and counts are presented in frequencies. Continuous data are presented in means and standard deviation (SD) or median value and range.

Differences between scores and preparation values were compared by the independent sample t-test, the pairwise comparison t-test or One-Way ANOVA. To compare differences in mentioning frequencies of individual complications between Cohort A and Cohort B, Chi^2 tests were performed. To correct for overlapping donors, linear mixed effect models were used, to account for the correlation between the donors present in both Cohorts. Missing values were imputed using single imputation.

Additional McNemar tests were performed for the overlapping donors in both Cohorts, to compare individual mentioning frequencies at the different time intervals. The

McNemar test compares the number of those who first scored positive (*i.e.* mentioned that specific complication) and then negative (*i.e.* did not mention that specific complication) with the number who first scored negative and then positive: if these numbers differ significantly from each other an increase or decrease can be concluded. A p-value of <0.05 was considered statistically significant. Multivariate analysis was performed to assess whether donor scores were influenced by specific characteristics. Linear regression was used. Every factor with a univariate p-value <0.1 was included in the multivariate model. To investigate potential differences between centers, center-specific estimates of the multivariable model were assessed.

Informed consent procedure per center

The local situation in the eight participating centers varies, with regards to the donor nephrectomy itself, but also with regards to the specific set-up of the informed consent procedure. Table 1 provides an overview of the local preferences for each center.

RESULTS

Donors

A total of 604 pop-quizzes were completed. 378 Living kidney donors were included in Cohort A, and 226 in Cohort B. 29 Donors from Cohort A were also included in Cohort B, and completed the pop-quiz at both time intervals. Table 2 provides an overview of the baseline characteristics of each Cohort.

Preparation for the donation procedure

Donors in Cohort A did not feel very well prepared yet; 5.6 (±2.5) out of 10. Donors in Cohort B, having received all possible information, reported a better feeling of preparation: 8.3 (±1.3) (p<0.001).

Pop-quiz scores

Table 3 presents an overview of scores per cohort and per sub-division.

Cohort A

Mean overall score for Cohort A donors, prior to the first visit at the nephrology outpatient clinic, was 6.9 (±3.9, range 0-18). Donors scored best on convalescence, and worst on long-term complications (table 3.)

Short-term complications: fatigue was mentioned most by donors in Cohort A (n=127, 34%), followed by pain (n=70, 18%), infections (n=69, 18%) and wound infection (n=60, 16%). The risk of death was mentioned by 19 donors (5%). Mentioning frequencies of all

Table 1. Differences in techniques, information provision and informed consent procedures per center.

	Employed techniques	Set-up preoperative visits & information	Informed consent how/when/by whom
Center 1	LD, Mini-open	Consult with TC. If approved: consult with nephrologist and surgeon on the same day (2-8 weeks prior to procedure)	Signed Prior to screening TC
Center 2	HAL	Consult with TC, nephrologist. If wish to continue: discussion in multidisciplinary meeting with surgeon. If approved, last information from surgeon at the clinic (1-2 weeks prior to surgery) or on day of admission	Signed Prior to screening TC
Center 3	LD, Mini-open	Consult with SN (If unspecified donor: also consult psychiatrist) Screening tests and consult social worker. If approved, joint clinic consult with nephrologist and surgeon.	Signed After screening and all consults TC
Center 4	LD, HARP, Robot	Consult with nephrologist, then consult TC If approved: consult with surgeon at outpatient clinic On day of admission: last information from surgeon & SN on the ward	Signed Prior to surgical consult Nephrologist
Center 5	HARP	Consult with SN, then consult with nephrologist. Two weeks prior to surgery consult with surgeon	Signed Prior to surgical consult Nephrologist (Surgeon documents informed consent in EPF)
Center 6	HAL, HARP	First consult with TC If donor wishes to continue: Two-day program, with screening tests and consult social worker, then nephrologist, SN, and surgeon in random order. One month prior to surgery consult with TC Last information from surgeon and TC on day of admission	Signed Prior to screening TC
Center 7	LD, HAL, HARP	First visit with TC, then consult with nephrologist, then with surgeon	Signed Prior to surgical consult Nephrologist
Center 8	Mini-open	Work up by SN, approved by nephrologist, 6-4 months prior to surgery consult with surgeon	Explicitly asked SN (Surgeon documents informed consent in EPF)

LD – laparoscopic donor nephrectomy; TC – Transplant coordinator; HAL – Hand-assisted laparoscopic; HARP – Hand-assisted retroperitoneoscopic; SN – Specialized nurse; EPF – Electronic Patient File

Table 2. Baseline characteristics of all (potential) living kidney donors included in this studied, specified for the two cohorts (percentages between brackets unless otherwise defined).[a]

	Cohort A n=378	**Cohort B n=226**	**p-value**
Gender (M:F)	157:219 (41.8:58.2)	102:124 (45.1:54.9)	0.45
Age (mean, SD)	53.1 (12.5)	54.1 (12.1)	0.36
Type of donation[32]			
Unspecified	55 (14.6)	45 (19.9)	
Specified	314 (83.1)	179 (79.2)	0.11
Unknown	9 (2.3)	2 (0.8)	
Educational level[b]			
Lower	257 (68)	166 (73.5)	0.23
Higher	118 (32)	60 (26.5)	
Current employment			
Yes	232 (61.4)	137 (60.6)	0.90
No	67 (17.7)	37 (16.4)	
Retired	76 (20.1)	52 (23)	
Income			
Below average	88 (23.3)	46 (20.4)	
Average	214 (56.6)	128 (56.6)	0.59
Above average	58 (15.3)	40 (17.7)	
Religion			
None	178 (47.1)	108 (47.8)	
Catholicism	88 (23.3)	60 (26.5)	
Protestantism	64 (16.9)	33 (14.6)	0.59
Islam	16 (4.2)	8 (3.5)	
Buddhism	1 (0.3)	3 (1.3)	
Hinduism	5 (1.3)	3 (1.3)	
	22 (5.8)	9 (4.0)	
Other			
Household constitution			
Alone	76 (20.1)	39 (17.3)	
With children <18	73 (19.3)	47 (20.8)	0.53
Without children <18	223 (59.0)	139 (61.5)	
Registered donors			
Yes	227 (60.1)	131 (58.0)	0.36
No	149 (39.4)	93 (24.6)	

a. Not every donor completed every question, total numbers may not add up to 378/226 for each item
b. Lower: none or primary school, high school or secondary vocational education, higher: university of applied sciences or university

Table 3. Pop-quiz scores and item scores for donors in the two cohorts (mean, SD). Maximum overall score is 25 points, 5 points for each item score.

	Cohort A n=378	Cohort B n=226	p-value
Overall Score	6.9 (3.9)	10.4 (2.8)	<0.0001
Surgical technique[a]	0.6 (1.0)	2.2 (1.2)	<0.0001
Short-term complications[a]	0.6 (0.8)	1.0 (0.9)	<0.0001
Long-term complications[a]	0.2 (0.4)	0.2 (0.4)	0.73
Admission[a]	2.5 (1.7)	3.6 (0.9)	<0.0001
Convalescence[a]	2.9 (1.6)	3.4 (1.2)	<0.0001

a. For the item scores, the 29 overlapping donors were excluded from the analysis, and p-values were calculated using the independent samples t-test. The subscores are thus calculated for 349 versus 197 donors.

complications are displayed in table 4. Aside from those complications included in the scoring system, donors mentioned additional problems that could occur. Nausea/vomiting, and constipation were stated a number of times, as were emotional/psychological problems and problems with the recipient of the kidney. All additional complications mentioned are bundled in supplementary table 1.

Long-term complications: The eventual risk on developing end-stage renal disease was described by 62 Cohort A donors (16%). Other long-term complications were only mentioned incidentally (table 4).

Cohort B

Mean overall donor score for Cohort B donors, on the day of admission for donor nephrectomy, was 10.4 (±2.8, range 0-17.5). Cohort B donors scored best on duration of admission, and again, worst on long-term complications (table 3).

Short-term complications: the order of most frequently mentioned complications remained the same, with the exception of infections overall, which was bypassed by bleeding. Each complication was mentioned more often than in Cohort A: fatigue (n=98, 43%), pain (n=70, 31%), bleeding (n=67, 30%). The risk of mortality was mentioned by 29 donors (13%) (table 4). Nausea was again often mentioned as an additional complication, as were emotional problems (supplementary table 1).

Long-term complications: the risk of renal failure was the most frequently mentioned long-term event, however, it was mentioned somewhat less often than at the clinic: n=32, 14%. The other complications were again only mentioned sporadically (table 4).

The average overall Cohort B score was significantly higher than the average Cohort A score (p<0.0001, table 3). This was also true for each of the individual item scores with the exception of long-term complications: average score was 0.2 for the outpatient as well as the admission Cohort (table 3).

Table 4. Mentioning frequencies of the individual complications, per cohort. Percentages between brackets.

	Cohort A n=378	Cohort B n=226	p-value
Short-term complications			
Bleeding	45 (11.9)	67 (29.6)	0.047
Wound infection	60 (15.9)	63 (27.9)	0.007
Infection (NOS)	69 (18.3)	50 (22.1)	0.637
Pain	70 (18.5)	70 (31)	<0.001
Fatigue	127 (33.6)	98 (43.4)	0.157
Death	19 (5.0)	29 (12.8)	0.924
Urinary tract infection	24 (6.3)	33 (14.6)	0.053
Pneumonia	30 (7.9)	32 (14.2)	0.200
Damage to other organs	3 (0.8)	1 (0.4)	0.922
Thrombosis	35 (9.3)	27 (11.9)	0.930
Cardiovascular complications	2 (0.5)	2 (0.9)	0.685
Testicular complaints	0	3 (2.9)[a]	NA[b]
Neuropathy/neurapraxia	4 (1.1)	5 (2.3)	0.207
Long-term complications			
Chronic pain	11 (2.9)	6 (2.7)	0.666
Incisional hernia	4 (1.1)	4 (1.8)	0.925
ESRD	62 (16.4)	32 (14.2)	0.281
Hypertension	8 (2.1)	12 (5.3)	0.076
Medication (NSAIDs, AB)	1 (0.3)	3 (1.3)	0.834

NOS – not otherwise specified, ESRD – End Stage Renal Disease, NSAIDs – non steroidal anti-inflammatory drugs, AB – antibiotics; NA – Not applicable

a. Since testicular complaints is a relevant complication only in male donors, the relevant percentage is 2.9% (3 out of 102 males in Cohort B) instead of 1.3% for the whole group of 226 donors

b. Because none of the Cohort A donors reported this complication, a p-value could not be computed using the generalized linear model

Overlapping donors

Donors who were included in Cohort A and Cohort B (n=29) scored, overall, significantly better the second time they completed the pop-quiz, on the day of admission for donor nephrectomy: 10.4 (±3.0) versus 8.6 (±3.3). However, six donors actually scored worse on admission than at the outpatient clinic, with a mean difference of 3.38 (±2.05, range 0.75-6). This decrease was seen in all individual item scores. The risk of eventual ESRD was the only individual item that was mentioned significantly more often on admission than prior to the first outpatient consult: 29.6% versus 7.4% of donors recalled this risk on the Cohort B pop-quiz. Supplementary table 2 provides an overview of all individual complications, and their mentioning frequencies for the longitudinal Cohort.

Score Correlation

There was some variation in the baseline scores (Cohort A) per center. Scores ranged from 6.4 (±3.1) in the lowest scoring center to 8.5 (±2.2) in the highest scoring center (overall p=0.01). Center volume (*i.e.* the number of donor nephrectomies performed per year) did not influence donor score. Younger donors scored better than older donors (p=0.02),

as did donors with a higher educational level: 8.1 (±3.3) versus 6.4 (±4.0, (p<0.0001), and donors who were currently employed: 7.3 (±3.8) versus 5.4 (±3.9) for unemployed donors and 6.0 (±4.0) for retired donors, p=0.005. However, after multivariable analysis, only younger age, a higher educational level and registration as a confirmed (deceased) donor were of associated with higher pop-quiz scores. Table 5 presents the results of the multivariate analysis for both Cohorts.

Table 5. Multivariate analysis for demographic characteristics, split fort the outpatient (Cohort A) and admission (Cohort B) cohort.

	Univariate p-value	**Multivariate Beta (95% CI)**	**Multivariate p-value**
Cohort A (N=378)			
Factor			
Gender	0.15	-	-
Age	0.02	-0.049 (-0.09 – -0.13)	0.008
Relation	0.27	-	-
Educational level	<0.0001	1.35 (0.54 – 2.17)	0.001
Employment	0.003	0.32 (-0.54 – 2.17)	0.47
Income	1.0	-	-
Religion	0.68	-	-
Household	1.0	-	-
Registered Donor	<0.0001	2.10 (1.32 – 2.87)	<0.001
Center	0.01	0.16 (-0.02 – 0.32)	0.07
Cohort B (N=226)			
Factor			
Gender	0.37	-	-
Age	0.058	-0.02 (-0.06 - 0.02)	0.30
Relation	0.18	-	-
Educational level	0.31		-
Employment	0.001	-0.31 (-0.90 – 0.83)	0.94
Income	0.91	-	-
Religion	0.38	-	-
Household	0.02	0.95 (0.00 – 1.90)	0.50
Registered Donor	0.02	1.03 (0.29 – 1.76)	0.006
Center	0.23	-	-

In Cohort B, registered organ donors (10.8 (±2.8) versus 9.9 (±2.7), p=0.02), employed donors (10.9 (±2.5) versus 9.0 (±3.4), for unemployed and 9.5 (±2.8) for retired donors, p<0.001), and donors living with children under 18 (11.3 (±2.5) versus 10.2 (±2.8), p=0.02) scored significantly higher on univariate analysis than donors without these characteristics. After multivariate analysis, only registration as a confirmed (deceased) donor was related to a higher pop-quiz score. Differences per center were not observed in this Cohort (table 5).

Descriptive results

In the pilot for this study (Kortram, unpublished), it was observed that quite a large proportion of donors had seemed to misinterpret the question regarding surgical technique. Fortunately, after reformulation, this was not the case in the nationwide PRINCE study. Only two donors stated that the technique had been explained to them, but did not elaborate on what this explanation entailed.

A large proportion of donors indicated that they did not know the answer to (some of the) question(s). In Cohort A this ranged from 28 (7.5%) for convalescence to 115 (31.2%) for long-term complications. In Cohort B, all donors gave an answer to the admission question, only two (0.9%) had no idea about convalescence, four regarding surgical technique, 14 (6.4%) for short- and 44 (20%) for long-term complications.

One donor in Cohort B answered the surgical technique question with "*this is not important to me at all*", another donor answered something similar to the risks- and complications question: "*I do not think about this, it is not important to me. I have been told about this, but risks and complications are minimal*", and yet a third said he had "*intentionally forgotten*" the details about long-term complications. In Cohort A, one donor said "*I do not really care about long term consequences; if they occur, we will see what we can do about it then*". These answers, although given by a vast minority, pose the idea that maybe some donors do not want to know all the specific details and still feel informed and prepared.

Evaluation and Satisfaction

Evaluation questionnaires were returned by 158 Cohort B donors (72%). Overall average satisfaction with the informed consent procedure was 8.1 out of 10 (SD 1.6, range 0.6-10). Although the majority of donors were positive and praised the transplant team for their services, some raised valid concerns.

One donor in a kidney pair exchange underlined the importance of standardization: "*information provision was inadequate. It would be a suggestion to create a checklist with items that have and have not been discussed, and items that should still be addressed*". Some donors, who developed complications or problems like postoperative bleeding or pain claimed that this had not been disclosed to them during the informed consent process: "*it was repeatedly stated that no complications were expected, but two out of three complications [that occurred] commonly known prior to surgery. Information was too optimistic, and not very realistic*". But also donors who had not experienced complications indicated that they had wished to hear more about potential complications prior to the donation procedure. On the other hand, some donors indicated that they had received *too much* information: "*I received so much information that a possible shortage in knowledge is due to the amount of information*".

Quite some donors addressed the fact that not enough attention had been paid to the convalescence period. Another recurring statement was that although donors remembered being told about certain risks or complications, they had assumed these would not occur: "*I was stubborn, and did not believe that the provided information would apply to me*" or "*you always know that there can be complications, but you never think it will happen to you*".

DISCUSSION

The PRINCE study is, to the best of our knowledge, the largest available prospective nationwide Cohort study testing living kidney donors on their knowledge regarding the surgical procedure, postoperative course, possible complications and long term results. It is also the first study using open questions, prompting donors to describe the answers in their own words.

Baseline knowledge scores demonstrated some variation between centers. This could be due to the fact that some donors receive information in non-acadamic hospitals, where their recipient was treated by the nephrologist. There may be regional differences in the amount of details provided to potential donors in these centers. Although donor knowledge improves during the educational and informed consent process, average knowledge scores remain low, and large deficits are present. Previous studies have also demonstrated substantial gaps in donor knowledge[10, 14, 15], but it has also been argued that their decision-making strategy differs from that in regular patients[16, 17, 33]. Donors may not even listen to provided information, but mainly focus on those statements that confirm their decision to donate. Their knowledge would not – or only slightly - improve during the preoperative work up and informed consent process. Our study demonstrates that this is not entirely true; overall scores were significantly higher on admission (the day before surgery) than at the nephrology outpatient clinic, prior to receiving any information.

Even if decision-making strategies may differ between donors and "regular" patients, knowledge deficits are also encountered in other patient categories. Lee *et al.* published quite a similar study in breast cancer patients prior to undergoing a mastectomy, who received a validated test to assess their knowledge about breast reconstruction. The overall knowledge score was 58.5% (compared to 41.6% in Cohort B of the PRINCE study), but the score for the risk of complications was only 14.3% (compared to 22% in the PRINCE study for short-term complications and 4.8% for long-term complications)[34]. Amir *et al* found that, retrospectively, only 40.5% of all interviewed patients who had undergone an elective surgical procedure actually understood the information provided to them during the informed consent process[35].

The large, multicenter Cohort and the prospective nature of the PRINCE study are definite strengths. The Netherlands is a leading country when it comes to live kidney donation (31 per million of population[36]), and the study, including all Dutch kidney transplant centers, provides a valid and reliable overview of the current national situation.

We acknowledge that our study has a number of limitations. First of all, as already discussed in the published protocol [31], un-validated questionnaires were used. Although there is a validated knowledge test available for living kidney donors[10], this is much less specific than what we wanted to pursue in the PRINCE study. Validation of a knowledge test with open questions instead of multiple choice is virtually impossible, since donors may learn or forget specific information at different time points, *and* their knowledge is, at least partly, dependent on the information they have received from their transplant team. Using multiple-choice questions would be much easier to compare scores, but we believe an open question, requiring an answer in the donor's own words provides more reliable information.

The second limitation is the fact that open questions and open answers leave room for interpretation. Some donors left questions unanswered or only stated one or two complications. It cannot be established with certainty whether this was all they knew or remembered, or that they thought this would be enough.

The risk of death for instance, was only mentioned in 48 pop-quizzes, equaling 8%. This is extraordinarily low, seeing that in the PILOT project, this was mentioned in 18% of pop-quizzes (but this was a single center study). Comparing this to the results of the nationwide survey, asking surgeons how often they disclosed the risk of mortality to donors, 50% said to always disclose it and an additional 37.5% said to do so in some of the cases[3]. An explanation for this phenomenon may be that donors may not want to know this risk, even though they might actually *be* aware of it, but writing it down makes it "real". In addition, donors may not regard death as a realistic concern: they are focused on dealing with pain and fatigue, recovering and getting back to work.

Donor satisfaction with the informed consent procedure was, with an average score of 8.1 out of 10, quite high, even though donor knowledge was lower than expected. This has been demonstrated before, in a study evaluating informed consent in elective surgical procedures: only 40.5% of patients understood the provided information, but 93.5% were satisfied with the informed consent process[35]. It may thus be argued whether there is an actual need to improve the informed consent procedure. However, in our study, some donors raised valid points of criticism on the informed consent procedure, and stated items that could be improved. Moreover, satisfaction alone cannot justify informed consent. Even if a donor indicates that he is satisfied, and does not wish to receive any further details, we still have an obligation to provide all necessary information, especially since some donors report, retrospectively, that they wish they had had more information going into the procedure[15]. Since we cannot predict which donor will

change their mind about their information wishes after they have undergone the donor nephrectomy, we have to fully inform each and every donor.

One of the main issues with a standardized format is that no donor is alike, and neither are their information needs and wishes. This has been demonstrated in other fields of preoperative surgical patient education. Beresford *et al.* interviewed 50 patients after cardiac surgery, and 25 of them indicated that they did not want to be advised of the risk of death. Forty-two percent (21 patients) did not want any risk information at all[37]. A more recent study assessing information needs in cancer patients prior to surgery demonstrated that patients were not so much interested in technical details and short-term morbidity, but more so in survival data and long-term quality of life[38]. But it can be argued that these two types of surgery (cardiac and oncological) may not be directly comparable to living kidney donors, since these patients actually need the procedure to survive, or at least to extend their lives. They may see some of these risks and details as inevitable, and not see any added value in knowing (and worrying) about them. Another study performed in 190 patients undergoing cataract surgery, showed that 93.5% of patients would want to be informed about complications with a 1 in 50 risk, and still 62.4% would want to know about a complication with a 1 in 1000 risk[39]. These patients do not necessarily *need* this procedure, and they may thus be more critical about the possible consequences when it would go wrong. Donor priorities and information needs could be a topic for future research.

Providing additional information *prior* to the surgical consult may be a possible solution. In a study in cardiac surgery patients, those patients receiving extended written information were, overall, more satisfied with the informational process, and they also felt that they could discuss alternative options with their surgeons to a significantly higher degree than those patients who did not receive the extended information[40]. Living donors already receive additional information, in the form of information leaflets, access to specific websites, and in some centers an informational DVD. In addition, some centers offer the possibility to attend multidisciplinary informational evenings. Taking this one step further, and creating an educational tool, enabling potential donors to test their own knowledge on the different aspects of the donation procedure and postoperative period, and indicate which aspect is more important to them, may be a key step in improving the informed consent process. The transplant surgeon can then focus his attention on those aspects in which the donor's knowledge is still insufficient, and skip the parts that have already been covered by other team members or sources. This way, information provision will still be standardized, but the surgical consult will be donor-tailored, leading to better informed, and likely more satisfied, donors, and will help to further improve the efficiency of the outpatient consults.

The PRINCE study provides a basis to improve living donor education and the informed consent process. One of the next steps could be to closely evaluate the available

guidelines [7-9], and update these where seen fit. For instance, although the BTS guideline provides a clear overview of the literature on perioperative mortality and morbidity, it does only specify overall percentages for a number of major complications[7]. It would be helpful to also include complications like pain, and fatigue, which appear to be important to donors. The KDIGO guidelines[9] provide ample information on long-term risks, but are less specific on perioperative complications, and state that transplant centers should "Evaluate and disclose risks to the best of currently available knowledge". Incorporating additional, more specified data on perioperative morbidity and donors' information needs and wishes into these guidelines would further aid transplant professionals in preoperative donor education.

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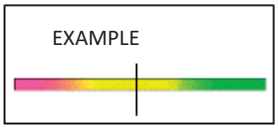
APPENDIX I - PRINCE – INVENTORY – POP-QUIZ – ENGLISH TRANSLATION

1. How well, on a scale of 1 – 10, do you feel to be prepared for the surgery and the convalescence period?

Please draw a vertical line on the rectangle below, in which 0 is absolutely not prepared and 10 = couldn't have been any better prepared.



0 10

2. What type of surgery will you undergo?

Think about surgical technique, the number of scars you will get, and where these scars will be.

_____

_____

_____

_____

How did you learn this information? (Please choose all answers that apply)

☐ Explained by Surgeon/Urologist
☐ Explained by Nephrologist
☐ Explained by nurse/transplant coordinator
☐ Heard about it during information evening
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

3. Which *short-term* problems and complications can occur?

Please write down all answers you can think of

_____

_____

_____

_____

How did you learn this information? (Please choose all answers that apply)

☐ Explained by Surgeon/Urologist
☐ Explained by Nephrologist
☐ Explained by nurse/transplant coordinator
☐ Heard about it during information evening
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

4. Which *long-term* problems and complications can occur?

Please write down all answers you can think of

_____

_____

_____

_____

How did you learn this information? (Please choose all answers that apply)

☐ Explained by Surgeon/Urologist
☐ Explained by Nephrologist
☐ Explained by nurse/transplant coordinator
☐ Heard about it during information evening
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

5. How many days do you expect to be admitted in the hospital?

Please write down the total number of days, before ánd after the surgery

_____

How did you learn this information? (Please choose all answers that apply)

☐ Explained by Surgeon/Urologist
☐ Explained by Nephrologist
☐ Explained by nurse/transplant coordinator
☐ Heard about it during information evening
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

6. How long do you expect it will be before you can perform your work / your normal daily activities?

Please strikethrough as appropriate

_____ Weeks/ Months

How did you learn this information? (Please choose all answers that apply)

☐ Explained by Surgeon/Urologist
☐ Explained by Nephrologist
☐ Explained by nurse/transplant coordinator
☐ Heard about it during information evening
☐ Explained by family/friends
☐ Read in information provided by the hospital
☐ Read in information looked up myself

Supplementary table 1. Additional complications mentioned by donors who completed the pop-quiz, and the number of times these complications were mentioned in the different cohorts.

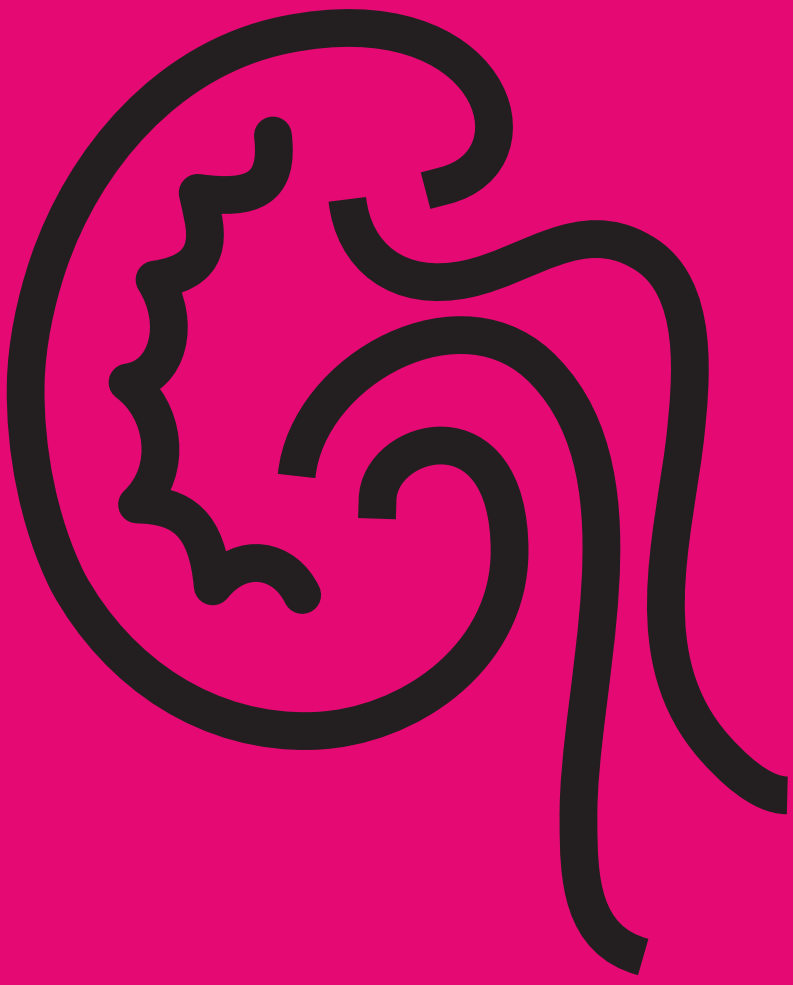
Complication	Cohort A	Cohort B
Nausea	16	39
Psyschological / Emotional problems	16	10
Inability to return to work	9	-
Not allowed to carry weight/exercise	7	6
Rejection in recipient	6	3
Increased risk of diabetes mellitus	5	4
Constipation	4	13
Allergic reaction	3	1
Lifestyle adjustments[a]	3	-
Problems with anaesthesia	2	-
Haematoma	2	7
Being involved in an accident	2	2
Increased risks during pregnancy	2	2
Diagnosing an illness during screening process	2	-
Infection with "hospital bacteria"	2	1
Need for information regarding recipient	1	-
Formation of adhesions (problem for future surgery)	1	1
Prostate problems	1	-
Proteinuria	1	3
Death of recipient	1	-
Increased risk of dehydration	1	3
Retained surgical equipment	1	-
Being rejected as a donor	1	-
Headache	-	3
Malignancy in remaining kidney	-	3
Fluid retention / edema	-	2
Urinary retention	-	2
Medication and side-effects thereof in recipient	-	2
Sexual disfunction	-	1
Dental injury during intubation	-	1
Inability to proceed with surgery due to intraoperative complication	-	1
Memory loss / disfunction	-	1

a. No alcohol consumption, no coffee consumption, staying fit, eating healthy were the specific adjustments named by (potential) donors.

Supplementary table 2. Mentioning frequencies of the individual complications, per cohort for the 29 overlapping donors. Percentages between brackets.

	Cohort A	Cohort B	p-value
Short-term complications			
Bleeding	4 (14)	9 (31)	0.13
Wound infection	4 (14)	9 (31)	0.13
Infection (NOS)	8 (28)	7 (24)	1.00
Pain	10 (35)	9 (31)	1.00
Fatigue	12 (41)	17 (59)	0.18
Death	3 (10)	3 (10)	1.00
Urinary tract infection	2 (7)	8 (28)	0.07
Pneumonia	3 (10)	5 (17)	0.50
Thrombosis	5 (17)	5 (17)	1.00
Cardiovascular	0	1 (3)	1.00
complications	0	3 (10)	0.25
Neuropathy/neurapraxia			
Long-term complications			
Chronic pain	1 (3)	1 (3)	1.00
ESRD	2 (7)	8 (28)	0.03
Hypertension	0	2	0.50

NOS – not otherwise specified, ESRD – End-Stage Renal Disease



Chapter 8

Discussion

DISCUSSION

Informed Consent for Live Donor Nephrectomy

The informed consent procedure for live donor nephrectomy is, to date, all but standardized in many transplant centers. Many differences exist between centers (who is giving the information, what is being told, who is obtaining consent, and when, etc.) and even between individual transplant professionals within one center[1-5]. This is remarkable, since every transplant professional will agree that it is of vital importance that every kidney donor is well-educated and well-prepared for the donation procedure, and that they are fully informed at the time of giving consent for donating. Moreover, it is one of the official requirements of the EU Directive for living organ donation practice[6]. How is it still possible that relevant details, like complications, or even the risk of mortality, but also the expected duration of convalescence are not always disclosed during the informed consent process? A simple and logical answer may be that surgeons try to restrain from negative information that might be related to the procedure or, less likely, are not aware of the risks to the procedure themselves. Any conversation with a donor will be a momentary display of the surgeon's routine, and not one consult will be the same as the other. No surgeon is the same as any other either: there will always be differences in their manner of donor education. What they disclose, and in which format, is largely dependent on their own experience, and their own perception of specific events. If one has never encountered a neuropathy after donation in his career, one may not find it necessary to disclose this. Another may fear that talking about mortality might scare away the potential donor, and since this is an extremely rare event, they may choose to not bring this up. On the other hand, if just last month a donor actually did die after the procedure, the surgeon would, likely, be more tempted to disclose this devastating risk to each and every donor he informs at the clinic.

Then, there are differences in donors as well. The moment a donor enters the surgeon's office, the latter will make a quick assessment of the person. All donor characteristics (*e.g.* age, gender, ethnicity, educational level) attribute to their capability and willingness to understand the complexity of the procedure they are about to consent to. This quick assessment will influence what the surgeon discloses, how many details, and in which manner.

Donor Knowledge and Satisfaction

Donor knowledge of the procedure, the possible complications and the postoperative course was found to be surprisingly low in the studies published in this thesis: 5.9 out of 20 in the pilot (±2.5) and 8.2 (±3.9) out of 25 in the national study. A handful of authors have previously demonstrated gaps in donor knowledge, either at the moment of giving consent or in retrospect, or have argued that donors may not be well enough informed

at the time of giving consent [7-12]. This is a troubling finding, even more so because donor knowledge did not seem to be influenced by the specific details that were disclosed to them during the surgical outpatient clinic visit. Surgeons (*i.e.* consultant/attending) usually provided more details compared to fellows or specialized nurses, but donors informed by surgeons did not achieve the highest scores on the knowledge tests. It was also demonstrated, that donors do not recall all information provided to them, whether this was just one item or added up to 15; they always scored lower than their informer. This finding is in itself not new[13]. Anderson *et al.* demonstrated, in 1979, that patients in a Rheumatology clinic only remembered 40% of the information provided to them, and for patients over 70 years of age, this was only 24%[14]. More recently, Godwin *et al.* tested patients undergoing reduction mammoplasty on retained information, and found that, after giving consent, an average of three out of 12 items were recalled, and the maximum score was 6 out of 12; 50% [15]. Information recollection is dependent on many factors, like the manner of information provision, age, and anxiety or distress[13]. It has been demonstrated that with an increase in information provision, a decrease occurs in the proportion of information uptake[14]. Or maybe the information was presented in too difficult a manner for the donor to comprehend[3]. Many centers already provide additional sources of information to living donors, like information leaflets, DVDs, websites and sometimes informational evenings. Still, in light of the pop-quiz scores encountered in our studies, as a transplant team, we need to look for options to further improve information disclosure, and thus donor knowledge.

It can be argued though, that donors may not necessarily need or want more information as they will not take into account this knowledge in the decision-making process. It has been previously proposed that donors do not use the same decision-making strategy as patients [16, 17], and had already made the choice to donate well before the informed consent was given, although more recent studies do bring in some nuance[18]. Some studies have been published regarding donor experience with the procedure, and the vast majority stated that it was (one of) the best experience(s) in their lives, and that they would do it again if they could[9, 16, 17, 19, 20]. But negative experiences are still encountered, an although available evidence is quite subjective, if anything, it suggests that some donors report feeling misinformed, in a single incidence to such a degree that the donor felt the transplant team had withheld the truth about possible complications, long-term results and recipient outcome[9].

In our studies, donor satisfaction was quite high: 8.4 out of 10 (±1.2) in the pilot and 8.1 (±1.6) out of 10 in the national study. Still, some donors reported, in hindsight, that they were not well informed and/or prepared, now that the procedure was behind them. Since a donor is not a patient, and does not, for medical reasons, need to undergo surgery, any complication or adverse event should be seen in a different light. Moreover, the complication itself may not cause the overall negative experience, but the lack of

knowledge about, and/or preparation for this event may very well. We are indebted to donors that they are well-informed; how the information is valued is up to the donor.

Informed Consent in Other Areas of Elective Surgery

Although it has been suggested that living (kidney) donors use different decision-making strategies than patients[7, 16-18, 21], informed consent is a topic of interest in all fields involved in elective surgical procedures. The question was posed whether patients, who directly benefit from a procedure (as compared to donors, who undergo a procedure for someone else's benefit), would have more knowledge of this procedure. To assess this, a fully elective, but highly beneficial procedure was chosen: the total knee arthroplasty (TKA). TKA candidates are, generally speaking, relatively fit, but their condition (*i.e.* gonarthrosis) has a severe impact on their daily life. The surgical procedure they consent to is not life-saving, but is intended to improve their quality of life. However, in 25% of TKAs, patients still experience pain [22-24], and other complications, some with substantial consequences, can occur. It is not inconceivable, that these patients make a more balanced risk-benefit decision, then when their loved one's life is at stake, and they may thus want to know the exact details of the procedure.

Patient satisfaction after TKA has been demonstrated to be largely based on three aspects: 1. functional outcome, 2. level of residual pain, and 3. preoperative expectations [22]. The first two cannot be completely influenced by medical practice; even after a seemingly uncomplicated TKA, up to 25% of patients still experience residual pain[22-24]. The majority mild (20%), but a small number of patients still reported moderate (3.7%) and severe (1.3%) pain after TKA[23]. Lingard *et al* tried to correlate psychological distress with functional outcome and postoperative pain. They found that distressed patients experienced significantly more postoperative pain than not-so distressed patients, but this difference could not be observed for functional outcome[24]. It could be hypothesized that adequate education could lead to less distress, and thus, better outcomes. It has been previously demonstrated that for instance perceived injustice, or catastrophic thinking may increase pain intensity[25]. The third factor influencing patient satisfaction, preoperative expectations, is within our control. We can, and must, do everything in our power to ensure that patients receive all necessary and correct information to fully prepare them for their surgery, possible complications and adverse events, and present them with adequate details regarding the expected outcome and possibility of remnant symptoms.

Stacey *et al* observed improved decision quality in TKA patients who received a standardized Patient Decision Aid (video and booklet) as compared to those receiving standard education[26]. Knowledge scores were also significantly higher in the first group: 71.2% versus 46.6% ($p<0.01$). A randomized controlled trial conducted by Johnson *et al*, however, did not demonstrate significant differences in knowledge between three

groups of patients, educated in different manners (standard form, form and video or form, video and formal educational session with specialized nurse)[27]. Patients were tested on their knowledge by means of 13 multiple-choice questions. Out of a maximum of 13 points, patients in group 1 scored an average of 10.1 points, versus 10.8 and 11.1 for groups 2 and 3 (p=0.11) after the outpatient clinic visit and 10.2 versus 10.3 and 11.0 on the day of surgery (p=0.08). The authors conclude that standardized, or additional educational tools may not be necessary because knowledge scores did not differ between their study groups. But, when evaluating patient satisfaction with the informed consent process, 77% of patients in group 1 rated this with excellent/very good versus 90% and 92% in groups 2 and 3 (postoperatively). This may imply that, even though knowledge did not significantly improve, patients may feel better prepared when they have received more, or more standardized information.

Legal Consequences

The main motivation for adequate information provision and a comprehension check is donor and patient safety and satisfaction. If donors have a negative experience, this may influence other potential donors, and living donation rates may decrease. If these experiences can be prevented by an improved informed consent procedure, every effort should be made to do so. But there is yet another reason why informed consent is so important. Litigation claims are, to date, not very common in living kidney donation. But for the TKA, this figure is quite different[28, 29]. McWilliams *et al.* studied all claims made in 1995/1996 and 2009/2010. These claims were based on a wide variety of causes, ranging from (minor) complications to alleged negligence (table 1)[28].

Some claims are justified, and substantial payments have been made. Others are clearly unjust, and have been quickly discarded by the National Health Service Litigation Authority (NHSLA). But many claims fall within a grey area, and whether or not they are just can be debated. Examples hereof, based on McWilliam's data, are infection, pain and thromboembolic complications. Obviously, a severe infection leading to amputation of the leg, even if it is not the surgeon's fault *per se*, is a good cause for a claim. Whether this was discussed as a "very rare but possible" complication does not really matter: the consequences are of such magnitude that a claim is justifiable. But what about infections leading to longer hospital admission, or longer duration of convalescence? What about deep vein thrombosis, for which additional medication has to be taken, and which may pose a risk for the development of a pulmonary embolism? Or prolonged pain after surgery, not necessarily invalidating, but at least hindering the patient? These are all quite common complications, and the consequences are manageable. But, it is not inconceivable that if a patient had no idea whatsoever that these complications could occur, even if only in a rare minority of cases, he might have reconsidered undergoing this procedure. In most TKA patients, pain is the main reason for having their knee replaced. In 20-25%

of patients pain persists after TKA[22-24]. If this possibility is not discussed preoperatively, patients may be unnecessarily worried and even a little disgruntled. However; had the surgeon explained to them that in some percentage of cases pain would still be present after surgery, they could have made a deliberate decision and taken this relatively small risk into account.

Even though we do not have insight in all claims that have been assessed by the medical sanctioning boards in the Netherlands, and we do not know how many of them were based on incomplete information provision, we hypothesize that a large number of claims can be prevented with adequate, uniform and complete information disclosure during the informed consent process. If the procedure itself is standardized, and accurately documented, there will be no doubt whether a patient – or donor – has been told of certain risks, and such claims will be futile.

There is another field in modern day medicine in which information disclosure has a high priority: pharmacology. An informed consent format for a surgical procedure could in some way be compared to a Consumer Medicine Information (CMI) leaflet, in which the specific characteristics and risk of prescription drugs are described. The Food and Drug Authority has developed guidelines that include items to be incorporated in CMI, but these are, similarly to the guidelines for informed consent procedures, not well-defined and lack details [30]. Nonetheless, in these leaflets, every possible adverse event or complication, even if it has only been reported once, is usually described. The question remains whether this is desirable for information leaflets for (potential) living kidney donors, but it would be worth wile to further investigate this comparison.

The meta-analysis, published in this thesis (chapter 3), provides an overview of the reported incidence of individual complications in the available literature. Although this is a great basis, it is impossible to disclose every potential complication, and it is inevitable that every surgeon's personal experience will influence the information he discloses. In addition, information needs vary among donors (chapter 7). Providing additional information, prior to the surgical consult, may greatly benefit donors and surgeons. All donors will have received standardized, uniform information, the surgical consult will serve to further elaborate on certain aspects, and to check whether the donor has indeed received, and understood all vital details. Incorporating this strategy will ensure standardized information provision, while still leaving room for donor-tailored preoperative education.

In conclusion, informed consent for elective surgical procedures remains a topic of great interest and much debate. This thesis focused on the informed consent procedure for live kidney donation, and has provided handles to, first and foremost, create a standardized format informed consent procedure for the donor nephrectomy. In addition, it has also paved the way for a translation to other fields of elective surgery. In the next chapter, "*Future Perspectives*", these two items will be discussed further.

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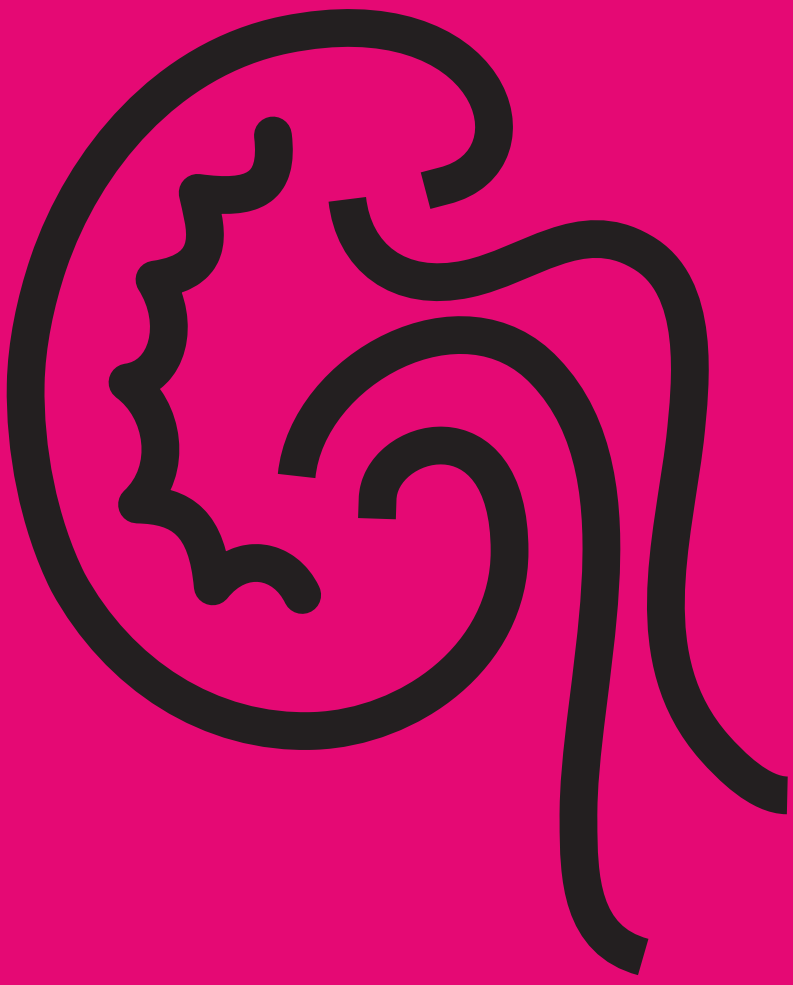

Chapter 9

Future Perspectives

FUTURE PERSPECTIVES

As of January 1st 2016, a new law has been instated in the Netherlands: "Wet kwaliteit, klachten en geschillen in de zorg (Wkkgz)", roughly translated into "Law for quality, claims and conflicts in healthcare"[1]. This law covers numerous aspects of safe and high quality care, among which the item "patient rights of choice – information" ("Recht op keuze- informatie"). This item allows patients to choose between different healthcare professionals, and hereby mandates these professionals to provide information about the type of treatment, the quality thereof and its (scientifically proven) effectiveness, its costs and other patients' experiences with this treatment.

As many other laws and available guidelines, this latest does not include specific details that have to be communicated, but it is not hard to imagine that guidelines and regulations regarding information provision and informed consent will only become more strict in the near future. It may be wise for medical professionals involved in elective surgical procedures to place themselves one step ahead of this development. Instead of waiting for a government issued standardized format, it may be profitable to develop such a format ourselves. This will, most likely, be more efficient, and easier to implement in daily clinical practice.

Informed Consent for Live Donor Nephrectomy

As we have demonstrated, the informed consent procedure for the live donor nephrectomy can be improved. The results of the studies described in this thesis can be used to do so. However, some additional data can still be helpful to achieve an even better end result. The first goal is to develop a standardized format informed consent procedure. The data acquired in the meta-analysis have provided the medical evidence, and the data from mainly the nationwide PRINCE (chapter 7) study have demonstrated 1) what donors actually know and remember, and 2) what they would have wanted to hear. Combining these two perspectives will lead to an ideal concept. Since there are logistic and procedural differences between the centers, the standardized format will have to leave room for local adjustments.

There is one aspect of donor knowledge that still needs to be further explored. As we have demonstrated in the PRINCE PILOT study (chapter 5), donor knowledge did not seem to correlate with the amount of provided information. As previously described, it may be the case that donors do not actually listen to all information provided the same way "normal" patients do [2, 3]. To further assess this, an additional cohort was included in the national PRINCE study. This cohort includes donors from the first cohort (Cohort A), at the transplant nephrology outpatient clinic. The first 10 (for high volume centers) and five (for low volume centers) donors in each center who are referred to the surgical outpatient clinic will be followed longitudinally (total sample size 60). The consult with

the surgeon at the outpatient clinic will be audio-recorded, and the donors receive the exact same pop-quiz at the end of the consult. At the time of donor nephrectomy, they will again receive the pop-quiz on the day of admission, as all Cohort B donors also have. By correlating their pop-quiz answers with the audio-recorded exact details, more information can be learned about what they remember and what not. This will provide more insight in the manner of information provision, and will possibly give some handles as to how this should be employed in the standardized format.

To date, 37 donors have been included in this longitudinal cohort (62%). Of these, 15 have completed their follow-up and three have been scheduled for surgery in the near future. Unfortunately, five donors are lost to follow-up for the admission cohort. Inclusion and follow-up for this cohort is expected to be completed by the end of 2017.

Informed Consent in Other Areas of Elective Surgery

Patients undergoing total knee replacement surgery fall within a second category of patients, undergoing an elective surgical procedure without a strict medical necessity but with an expected benefit for themselves. These patients could serve as a control group for living donors, with regard to information needs and desires and knowledge of their upcoming procedure and postoperative course.

To assess this, the PINK (Process of INformed consent in total Knee arthroplasty candidates) – study was initiated. This is a multicenter, prospective cohort study, with a design similar to that of the PRINCE-PILOT (chapter 5). Fifty total knee arthroplasty (TKA) candidates will be included in two large orthopedic surgery units; the Erasmus MC University Medical Center in Rotterdam, and the Reinier de Graaf Hospital in Delft. Patients will receive a pop-quiz immediately after the orthopedic consult at the outpatient clinic (Cohort A), and will repeat this on the day of admission for TKA (Cohort B). They will receive an evaluation and satisfaction questionnaire three months postoperatively, and knee function will be assessed according to national guidelines six months after surgery, by means of the Knee injury and osteoarthritis Outcome Score (KOOS) and Hospital for Special Surgery knee scoring system (HSS) scores, to correlate knowledge and satisfaction with functional outcome. After inclusion is completed, more detailed data will be available, and a comparison can be made with the living kidney donors from the PRINCE-PILOT study.

Clinical Implications

Patient tailored care – and thus education – is increasingly popular in modern day medicine. But to deliver patient- or donor- tailored education, a standardized format is necessary to build from. The basis for this standardized format has been provided in this thesis. It is essential that this information is implemented in the daily clinical practice.

Recent, evidence based data is available on the incidence of individual complications, and more data is acquired on donor knowledge and satisfaction.

One of the next steps could be to closely evaluate the available guidelines [4-6], and update these where seen fit. For instance, although the BTS guideline provides a clear overview of the literature on perioperative mortality and morbidity, it does only specify overall percentages for a number of major complications[5]. It would be helpful to also include complications like pain, and fatigue, which appear to be important to donors. The new KDIGO guidelines[4], published in preliminary state, provide ample information on long-term risks, but are less specific on perioperative complications, and state that transplant centers should "Evaluate and disclose risks to the best of currently available knowledge". Incorporating additional, more specified data on perioperative morbidity and donors' information needs into these guidelines would further aid transplant professionals in preoperative donor education.

Guidelines are usually lengthy and although they should be read by every medical professional involved in the field addressed in them, they are not the most convenient tool to guide the consults at a busy outpatient clinic, nor can they, in their current format, be provided to patients (or donors). Anno 2016, nearly every doctor and the majority of patients own a smartphone. It is the era of social media, and each day over 1,000 new applications are launched in the Apple store[7]. Herein lies a possibility for the surgical community. Let's, for now, focus on living kidney donors, and create its design. After being approved by the nephrologist, and referred to the surgical outpatient clinic, they get access to this particular application. It contains detailed information on the surgical procedure, short- and long-term complications, the admission-, and the convalescence period. In addition, it will provide the donor with a test-your-knowledge menu, and after taking the test, they will immediately see their result, split over the different categories. They can either look up some extra information, or, already form questions they can ask the surgeon during their clinic visit. During this visit, the surgeon can also view the test results, and will focus his information on those aspects of which this donors' knowledge is insufficient, and skip the parts that have already been covered by other team members or sources. This way, information provision will still be standardized, but the surgical consult will be donor-tailored, and it will help to further improve the efficiency of the outpatient consults.

There have already been some initiatives to create tools to guide transplant professionals in delivering donor-tailored information. An example hereof is the End Stage Renal Disease (ESRD) Risk Tool for Kidney Donor Candidates[8]. This web-based risk calculator, based on a number of important studies regarding long-term ESRD risk in living donors[9-13], allows you to enter a number of donor characteristics, and it then provides you with a 15-year risk projection of developing ESRD for this specific donor profile.

It is quite easy to imagine a translation to other areas of (elective surgery), and, we are not the only ones to think of this idea. Recently, a project was initiated in the UK: "The Surgical Consent app"[14]. Although now in beta-testing and not yet publically available, the application promises to vastly improve the information doctors give to patients. Whether it is also suitable to provide to patients remains to be determined. It will be worthwhile to see whether this app fully suits our purposes, or that modifications or a completely different set-up would be in order.

Research Implications

There is still much to learn about informing donors/patients, their knowledge, needs and wishes, the ideal format of information provision, and then there is the matter of informed consent. This thesis provided the basis of medical data, and touched on the subject of donor knowledge. Future research projects should, in our opinion, mainly focus on donors' needs and wishes, and establish ways to improve knowledge.

One Australian research group has already performed promising work, assessing which elements of information are valued most by living kidney donors. Time to recovery was ranked highest (*i.e.* donors found this the most important detail to know), followed by impact on family life, donor-recipient relationship and lifestyle restrictions. Surprisingly, the risk of eventual kidney failure and mortality were ranked 10th and 13th respectively. Possible impact on fertility and pregnancy were ranked as the least important elements (Hanson *et al.*, as presented during the 26th international congress of the transplant society, Hong Kong, 2016). Further analysis of these data, and testing these factors in larger populations, will be very helpful for transplant professionals.

Finally, if an application such as mentioned in the previous paragraph would be developed and implemented, it may be wise to test this in a (pilot) intervention study. The ideal set-up for such a study would be a randomized controlled trial (RCT). Potential donors, prior to their preoperative surgical consult, could be randomized to receive either the full content app, with detailed information and a quiz, or a dummy app, without detailed information, but with the same quiz at the end. During the outpatient clinic consult, surgeons could rate the efficiency of the consult, and donors could rate their understanding of the information, and their satisfaction. In addition, a section could be incorporated in this app where donors can make their preferences known with regard to specific information needs and wishes. This could be assessed pre- as well as postoperatively.

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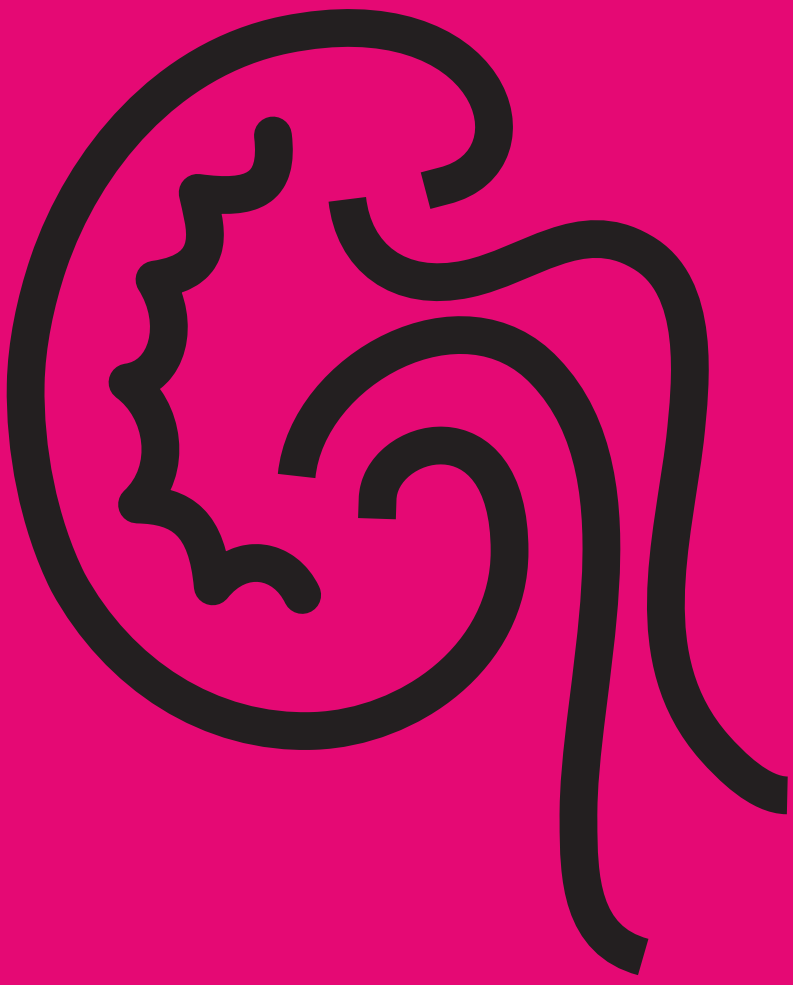

Chapter 10

English Summary

Dutch Summary / Nederlandse Samenvatting

ENGLISH SUMMARY

Part I – The Informed Consent Procedure

In the first part of this thesis, different aspects of the informed consent procedure for live donor nephrectomy are evaluated. The systematic review of the available literature (**chapter 2**) demonstrated great variations in informed consent procedures between transplant centers. Individual medical professionals also varied in the information they disclose to potential living kidney donors. Little research has been performed on donor comprehension of, and satisfaction with, the informed consent procedure. But some donors do report, retrospectively, feeling misinformed about, or unprepared for the donation procedure.

Many authors agree that there is a definite need for a standardized procedure to guide transplant professionals in their daily practice of education living kidney donors and obtaining informed consent. But the contents of this standardized procedure remain under discussion. What information do donors need, which details are vital in their educational process? There are some guidelines regarding informed consent for surgical procedures. General consensus is that every complication with an incidence of >1% should be disclosed, in addition to those complications, regardless of their frequency of occurrence, with severe consequences[1]. So, which complications would that be for the live donor nephrectomy? In **chapter 3**, the results from the meta-analysis assessing complications after minimally invasive live donor nephrectomy are described. Intraoperative complications occurred in 2.2% of live donor nephrectomies, postoperative complications in 7.0%. Infectious complications were most frequently encountered with an incidence of 2.6%, of which wound infections comprised the largest proportion (overall incidence 1.0%). Postoperative bleeding (1.0%) was the only additional complication with an incidence of >1%. The reported mortality rate was 0.02%, but an underestimation was suspected.

Does this mean that these are the only adverse events we should discuss with potential donors? Rare complications like damage to other organs, or cardiovascular events may or may not have "severe consequences", so should these be mentioned or not? And even though many other complications are infrequent, and may not have significant medical consequences, they may be very relevant for donors. Prolonged pain, testicular complaints or for instance neuropathies can be quite disconcerting to a donor who has no idea these adverse events are in fact quite "normal".

To assess which complications were actually mentioned to potential living donors by kidney transplant surgeons across the country, a web-based survey was created (**chapter 4**). All surgeons possibly involved in kidney transplantation in the Netherlands were invited to complete this survey. A response rate of 98% was reached (N=49), including 32 respondents that were actually still involved in preoperative living kidney donor education. The main finding in this project was the fact that information provision dif-

fered enormously between transplant surgeons. Bleeding was the only complications always disclosed to potential donors. Only half of the respondents indicated that they always mentioned the risk of death, another 13 did so sometimes, but three surgeons never discussed this disastrous complication with potential living kidney donors. In addition, if mortality was discussed, varying rates were reported, ranging from 0.003% to 0.1%. Mentioning frequencies for all other complications varied. In addition to variations in the contents of the informed consent procedure for live donor nephrectomy: even different respondents from the same center were not unanimous about the manner in which the procedure itself was employed in their hospital. Whether informed consent was obtained by a nephrologist or a surgeon, before or after the surgical consult, and in writing or oral after explicitly asking remained unclear.

The overall conclusion to be drawn from these results is that there is no consensus on the manner in which the informed consent procedure for live donor nephrectomy should be employed, by whom, and at which moment during the educational process consent should be obtained, and in which form this should be documented. These findings further underline the need for a uniform, standardized format informed consent procedure for live donor nephrectomy.

Part II – Donor Knowledge & Satisfaction

Part II of this thesis focuses on donor knowledge of provided information during the educational process leading up to informed consent, and their satisfaction with the informed consent procedure. The first chapter describes the results of a pilot study on donor knowledge (**chapter 5**).

The study group consisted of 46 living kidney donors, whose preoperative surgical outpatient visit was observed. They were asked to fill out a pop quiz-style questionnaire directly after the consult, and again on the day of admission for surgery. None of the donors scored the maximum of 20 points, and none had reproduced all the information discussed with them by the surgeon. Average donor score was 5.8 (±2.4, range 2-11). Donors scored best on duration of admission and convalescence, and worst on long-term complications. The risk of mortality was disclosed by 91% of informers, but only reproduced by 22% of donors at the outpatient clinic and 14% on the ward on the day of admission. Donors living with children under 18, donors with a higher educational level and registered (post-mortem) donors scored significantly better. Median donor satisfaction was 9 out of 10 (range 4-10). No significant differences were observed between donor characteristics, nor was the postoperative course of influence on donor satisfaction.

After completion of the single center pilot study, a nationwide, multicenter, prospective study was initiated to further assess donor knowledge. The protocol for this study is outlined in **chapter 6**. Donors were included in three cohorts; cohort 1 (Cohort A)

at the outpatient nephrology clinic, prior to receiving any information from transplant professionals, cohort 2 at the outpatient surgery clinic, after already being included in cohort 1, and on the ward on the day of admission for donor nephrectomy (cohort 3, Cohort B). All donors were asked to complete a similar pop-quiz as the one used in the pilot study. **Chapter 7** describes the results of cohorts A and B of this study. A total of 604 pop-quizzes were completed; 378 in Cohort A and 226 in Cohort B. There were 29 donors who were included in both cohorts. Average donor score was 6.9 out of 25 (±3.9, range 0-18) in Cohort A and 10.4 (±2.8, range 0-17.5) in Cohort B. Donors generally scored best on duration of admission and convalescence, and worst on long-term complications. Donors who were younger, had a higher educational level or were registered deceased donors scored higher in Cohort A, donors who were currently employed, living with children under 18, or were registered deceased donors scored higher in Cohort B. Donors felt relatively well prepared for surgery after receiving all information: 8.3 (±1.3) out of 10, and average postoperative satisfaction with the informed consent procedure was 8.1 out of 10 (±1.6, range 0.6-10). The postoperative evaluation led to some useful comments that could further improve the informed consent procedure for live donor nephrectomy in the future.

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NEDERLANDSE SAMENVATTING

Deel I – De Informed Consent Procedure

In het eerste deel van dit proefschrift worden verschillende aspecten van de informed consent procedure voor de levende donor nefrectomie geëvalueerd. De systematic review van de beschikbare literatuur (**hoofdstuk 2**) liet zien dat er grote variaties bestaan tussen verschillende transplantatie centra. Ook individuele medici variëren in de informatie die zij aan potentiele donoren verstrekken. Er is nog maar weinig onderzoek verricht naar het begrip van donoren, en hun tevredenheid omtrent de informed consent procedure. Maar sommige donoren geven, in retrospectie, wel aan dat zij zich niet goed geïnformeerd over, of niet goed voorbereid voelden op de donatie procedure.

Veel auteurs zijn het eens over het feit dat er een absolute noodzaak is voor een gestandaardiseerde informed consent procedure, om transplantatie chirurgen en anders medisch personeel te helpen in hun dagelijkse praktijk van het voorlichten van levende nierdonoren en het verkrijgen van informed consent. Maar de inhoud van deze gestandaardiseerde procedure blijft een onderwerp van discussie. Welke informatie hebben donoren nodig, welke details zijn essentieel gedurende hun voorlichtingstraject? Er bestaan enkele richtlijnen over informed consent voor chirurgische procedures. De algemene consensus is dat iedere complicatie met een incidentie van >1% vermeld dient te worden, net zoals die complicaties, ongeacht de frequentie van voorkomen, met ernstige consequenties[1]. Dus, welke complicaties zouden dat zijn voor de levende donor nefrectomie? In **hoofdstuk 3** worden de resultaten beschreven van de meta-analyse over complicaties na minimaal invasieve levende donor nefrectomie. Intra-operatieve complicaties traden op in 2.2% van de levende donor nefrectomieën, postoperatieve complicaties in 7.0%. Infectieuze complicaties werden het vaakst gezien met een incidentie van 2.6%. Hiervan was het grootste deel wondinfecties (1.0% van alle patiënten). Postoperatieve bloeding (1.0%) was de enige andere complicatie met een incidentie van >1%. De beschreven mortaliteit was 0.02%, maar het werd vermoed dat dit berustte op een onderrapportage.

Betekent dit dat alleen deze adverse events met potentiele donoren moeten worden besproken? Zeldzame complicaties, zoals schade aan andere organen, of cardiovasculaire complicaties kunnen al dan niet "ernstige consequenties" hebben, dus moeten dezen worden vermeld of niet? En ondanks dat veel andere complicaties niet vaak voorkomen, en ook geen substantiële medische gevolgen hebben, kunnen deze voor donoren toch als relevant worden beschouwd. Langdurige pijn, testiculaire zwelling- of pijn, of bijvoorbeeld neuropathieën kunnen zeer verontrustend zijn voor een donor die geen idee heeft dat deze gebeurtenissen kunnen optreden, en "normaal" zijn na een ingreep als deze.

Om een overzicht te krijgen van welke complicaties nu gemiddeld besproken worden met potentiele levende nierdonoren door niertransplantatie chirurgen in Nederland is een internet-survey opgesteld (**hoofdstuk 4**). Alle chirurgen die mogelijk niertransplantaties uitvoerden werden uitgenodigd de survey in te vullen. Een response rate van 98% werd bereikt (N=49), waarvan 32 respondenten nog daadwerkelijk betrokken waren bij de voorlichting van levende nierdonoren. De belangrijkste bevinding in dit onderzoek was het feit dat informatie voorziening enorm varieerde tussen verschillende transplantatie chirurgen. Bloeding was de enige complicatie die altijd werd besproken met potentiele donoren. Slechts de helft van de respondenten gaf aan dat zij het risico op overlijden altijd besproken, 13 anderen bespraken dit soms, maar drie chirurgen vermelden deze desastreuze complicatie nooit gedurende de voorlichting aan potentiele levende nierdonoren. Daarbij werd gezien dat, wanneer mortaliteit besproken werd, het geschatte risico hierop varieerde van 0.003% tot 0.1%. De frequentie van het vermelden van de overige complicaties verschilde. Ook werden variaties gezien in de inhoud van de informed consent procedure voor de levende donor nefrectomie: zelfs verschillende respondenten uit hetzelfde centrum waren niet unaniem over de manier waarop deze procedure in hun ziekenhuis werd uitgevoerd. Of informed consent werd verkregen door een nefroloog of chirurg, vóór of na het chirurgische consult, en geschreven of mondeling na expliciet vragen, blijft onduidelijk.

De conclusie die uit deze resultaten kan worden getrokken is dat er geen consensus bestaat over de manier waarop de informed consent procedure voor de levende donor nefrectomie uitgevoerd zou moeten worden, door wie, en op welk moment gedurende het voorlichtingstraject consent moet worden verkregen en ik welke vorm dit zou moeten worden gedocumenteerd. Deze bevindingen onderstrepen de noodzaak voor een uniform, gestandaardiseerd format voor de informed consent procedure voor de levende donor nefrectomie.

Deel II – Kennis en Tevredenheid van Donoren

Deel 2 van dit proefschrift focust zich op de kennis van donoren over de verstrekte informatie tijdens het voorlichtingstraject. Ook wordt hun tevredenheid over de informed consent procedure getest. Het eerste hoofdstuk beschrijft de resultaten van een pilot studie over donor kennis (**hoofdstuk 5**).

De studiegroep bestond uit 46 levende nierdonoren, van wie het preoperatieve chirurgische consult op de polikliniek werd geobserveerd. Zij werden gevraagd een kennistest in te vullen direct na het consult, en nogmaals op de dag van opname voor de donor nefrectomie. Geen van de donoren scoorde het maximum te behalen aantal van 20 punten, en geen reproduceerde alle door de chirurg gegeven informatie. De mediane donorscore was 6 (range 2-11). Donoren scoorden het best op opname- en herstelduur, en het slechtst op lange termijn complicaties. Het risico op overlijden werd door 91%

van de chirurgen vermeld, en slechts door 22% van de donoren gereproduceerd op de polikliniek en 14% op de dag van opname. Donoren die in een huishouden woonden met kinderen onder de 18 jaar, donoren met een hoger opleidingsniveau en donoren die zich hadden geregistreerd als donor (na overlijden) waren scoorden significant beter dan de rest. Mediane donor tevredenheid was 9 uit 10 (range 4-10). Er werden geen significante verschillen gevonden tussen donor karakteristieken, en ook het postoperatieve beloop leek niet van invloed op donor tevredenheid.

Na het voltooien van de pilot studie werd een landelijke, multicenter, prospectieve studie geïnitieerd om de informed consent procedure en de kennis van levende nier donoren verder in kaart te brengen. Het protocol van deze studie is beschreven in **hoofdstuk 6**. Donoren werden geïncludeerd in drie cohorten: cohort 1 (Cohort A) op de polikliniek nefrologie, voordat zij ook maar enige informatie hebben ontvangen van transplantatie professionals, cohort 2 op de polikliniek chirurgie, nadat zij reeds zijn geïncludeerd in cohort 1, en cohort 3 op de verpleegafdeling op de dag van opname voor de donornefrectomie (Cohort B). Alle donoren werden gevraagd een soortgelijke pop-quiz in te vullen als degene die gebruikt was in de pilot studie. **Hoofdstuk 7** beschrijft de resultaten van cohorten A en B van deze studie. In totaal werden 604 kennistesten ingevuld: 378 in Cohort A en 226 in Cohort B. 29 Donoren werden geïncludeerd in beide cohorten, en vulden de test op beide momenten in. . De gemiddelde donor score was 6.9 uit 25 punten (±3.9, range 0-18) in Cohort A, en 10.4 (±2.8, range 0-17.5) in Cohort B. Donoren scoorden over het algemeen het beste op opname- en herstelduur, en het slechtste op lange-termijn complicaties. Jongere donoren, en donoren met een hoger opleidingsniveau of die zich hadden geregistreerd als donor (na overlijden) scoorden beter in Cohort A, donoren met thuiswonende kinderen onder de 18, donoren die momenteel betaald werk hadden en wederom donoren die zich hadden geregistreerd als donor (na overlijden) scoorden hoger in Cohort B. Donoren voelden zich relatief goed voorbereid op de donatie procedure en de postoperatieve periode nadat zij alle informatie ontvangen hadden: 8.3 (±1.3) uit 10. De gemiddelde postoperatieve tevredenheid was 8.1 uit 10 (±1.6, range 0.6-10). De postoperatieve evaluatie leverde een aantal bruikbare commentaren op, die kunnen worden gebruikt om de informed consent procedure voor de levende donornefrectomie in de toekomst nog verder te verbeteren.

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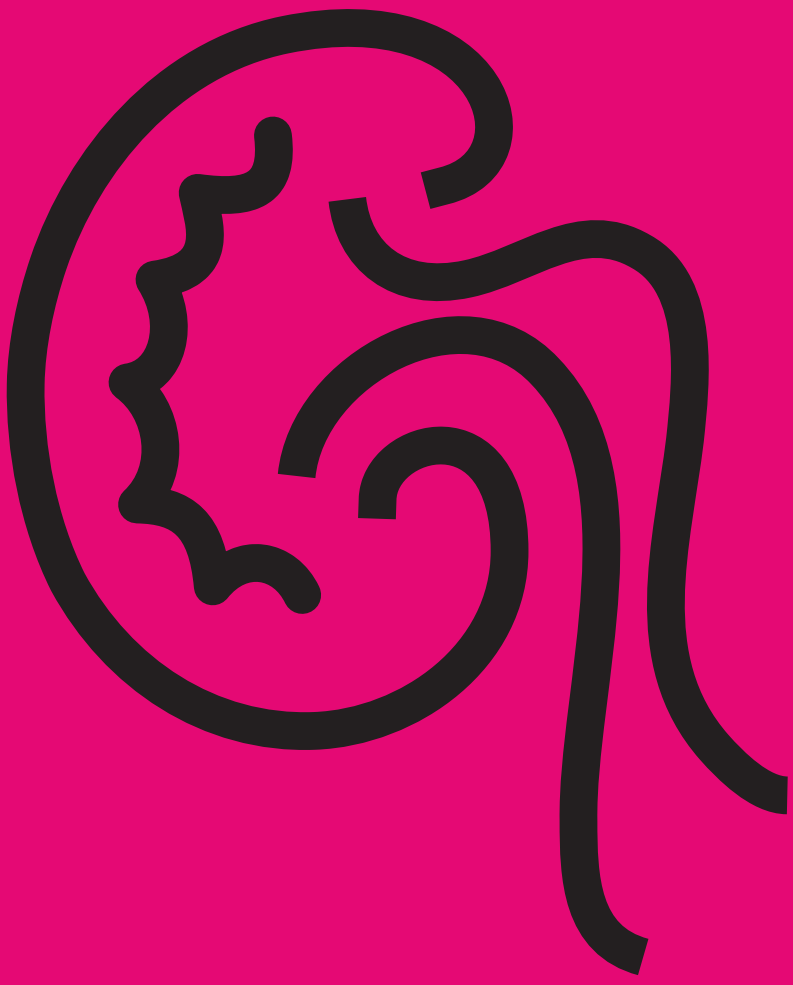

Chapter 11

Acknowledgements / Dankwoord

PhD Portfolio

List of Publications

Curriculum Vitae / About the Author

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PHD PORTFOLIO

Name PhD Student:	Kirsten Kortram	**PhD Period:**	2014-2016
Erasmus MC Department:	Surgery	**Promotor:**	Prof. Dr. J.N.M. Ijzermans
Research School:	Molecular Medicine	**Supervisor:**	Dr. F.J.M.F. Dor

1. PhD Training

General Courses	**Year**	**Workload (ECTS)**
Research Integrity	2015	0.3
Statistics – private lessons	2015	1.0
Basiscursus Regelgeving en Organisatie (BROK), Erasmus MC, Rotterdam	2015	1.5
Artikel 9 – Laboratory Animal Science Course, Erasmus MC, Rotterdam	2015	4.0
In-depth Courses	**Year**	**Workload (ECTS)**
European Society for Organ Transplantation - Evidence in Transplantation (EVIT course), Royal College of Surgeons England London	2015	1.0
The Edinburgh International Instructional Trauma Course 2016, Scottish Orthopaedic Research Trust into Trauma, Edinburgh	2016	1.0
Presentations at (inter)national conferences	**Year**	**Workload (ECTS)**
Oral presentations		
What Do Surgeons Tell Potential Donors? – TTS, Hong Kong 2016	2016	1.0
Peri-operative Events and Complications in Minimally-Invasive Live Donor Nephrectomy – TTS, Hong Kong 2016	2016	1.0
What Do Surgeons Tell Potential Donors? - ELPAT, Rome 2016	2016	1.0
Donor Comprehension of Provided Information During Informed Consent Process in Live Donor Nephrectomy – ELPAT, Rome, 2016	2016	1.0
Risk Factors for Infectious Complications after Open Fractures. A Systematic Review and Meta-Analysis – ECTES, Vienna, 2016	2016	1.0
Development of a Multivariable Risk Assessment Model for Infectious Complications after Open Fractures - 2nd Infection Advisory Board Meeting, Paris 2015	2015	1.0
What Do Surgeons Tell Potential Donors? - ESOT, Brussels 2015	2015	1.0
Donor Comprehension of Provided Information During Informed Consent Process in Live Donor Nephrectomy – ESOT, Brussels 2015	2015	1.0
Poster presentations		
Peri-operative Events and Complications in Minimally-Invasive Live Donor Nephrectomy – ATC Boston 2016/ BOOT Groningen 2016	2016	1.0
Donor Comprehension of Provided Information During Informed Consent Process in Live Donor Nephrectomy – BOOT Groningen 2016/TTS Hong Kong 2016	2016	1.0
The PRINCE Project: A Study Protocol – BOOT Groningen 2016		
What do Surgeons Tell Potential Donors? – BOOT Groningen 2016	2016	0.5
Donor Comprehension of Provided Information During Informed Consent Process in Live Donor Nephrectomy – BOOT/BTS Bournemouth 2015	2016 2015	0.5 0.5

Attendance at (inter)national Conferences	**Year**	**Workload (ECTS)**
26th International Congress of the The Transplant Society (TTS) – Hong Kong	2016	1.0
American Transplant Congress (ATC) – Boston	2016	1.0
4th Ethical, Legal & Psychological Aspects of Transplantation (ELPAT) - Rome	2016	1.0
17th European Conference for Trauma & Emergency Surgery (ECTES) - Wenen	2016	1.0
Chirurgendagen, Nederlandse Vereniging voor Heelkunde - Veldhoven	2015	1.0
European Society for Organ Transplantation (ESOT) - Brussel	2015	1.0
TOTAL – PhD Training		**26.3**

2. Teaching

	Year	**Workload (ECTS)**
Supervising Practicals and Excursions, Tutoring		
Examination Basic Life Support (EHBO) first year medical students	2014-2016	1.0
Tutor first year medical students	2015-2016	1.5
Supervisor KBP ("Kennismaking met de Beroepspraktijk") first year medical students	2016	1.0
Supervising MSc students at Erasmus MC	2015-2016	1.5
TOTAL – Teaching		**5.0**
TOTAL – Overall		**31.3**

LIST OF PUBLICATIONS

In this thesis

1. **K Kortram**, EQW Spoon, SY Ismail, D Nieboer, FCH d'Ancona, MHL Christiaans, RE Dam, HS Hofker, AWJ Hoksbergen, KAMI van der Pant, RJ Toorop, J van de Wetering, JNM Ijzermans, FJMF Dor, on behalf of the PRINCE working group, *Donor Knowledge of Provided Information – A Prospective Nationwide Inventory Study*, to be submitted
2. **K Kortram**, EQW Spoon, CWN Looman, HJAN Kimenai, JNM IJzermans, FJMF Dor, *Donor Knowledge of Provided Information During the Informed Consent Process in Live Donor Nephrectomy; Does It Matter What We Tell Donors? A Pilot Study,* submitted
3. **K Kortram,** JNM IJzermans, FJMF Dor, *Peri-operative Events and Complications in Minimally-Invasive Live Donor Nephrectomy; What Should We Tell Potential Donors? A Systematic Review and Meta-Analysis,* Transplantation 2016 Jul 15
4. **K Kortram,** JNM IJzermans, FJMF Dor, *Towards A Standardized Informed Consent Procedure for Live Donor Nephrectomy: What Do Surgeons Tell Potential Donors?,* Int J Surg. 2016 Jun 1;32:83-88
5. **K Kortram,** EQW Spoon, SY Ismail, FCH d'Ancona, MHL Christiaans, LWE van Heurn, HS Hofker, AWJ Hoksbergen, JJ Homan van der Heide, MM Idu, CWN Looman, AS Nurmohamed, J Ringers, RJ Toorop, J van de Wetering, JNM IJzermans, FJMF Dor, *Towards a Standardized Informed Consent Procedure for Live Donor Nephrectomy; the PRINCE (Process of Informed Consent Evaluation) Project: Study Protocol for a Nationwide Prospective Cohort Study*, BMJ Open. 2016 Apr 1;6(4)
6. **K Kortram,** JA Lafranca, JNM IJzermans, FJMF Dor, *The Need for a Standardized Informed Consent Procedure in Live Donor Nephrectomy: a Systematic Review*, Transplantation. 2014 Dec 15;98(11):1134-43

Other publications

1. **K Kortram,** P Oprel, WJ Metsemakers, MJ Raschke, EMM van Lieshout, MHJ Verhofstad, *Risk Factors for Infectious Complications after Open Fractures. A Systematic Review and Meta-analysis*, submitted
2. CS Loozen, **K Kortram,** VNN Kornmann, B van Ramshorst, B Vlaminckx, CAJ Knibbe, JC Kelder, SC Donkervoort, GAP Nieuwenhuijzen, J Ponten, AAW van Geloven, P van Duijvendijk, WJ Bos, MGH Besselink, HS van Santvoort, DJ Gouma, D Boerma, *Perioperative Antibiotic Prophylaxis after Laparoscopic Cholecystectomy for Acute Cholecystitis Does not Lower Infectious Complications, the PEANUTS trial*, accepted, BJS, 20-9-2016
3. SC Donkervoort, **K Kortram,** LM Dijksman, MA Boermeester, B van Ramshorst, D Boerma, *Anticipation of Complications after Laparoscopic Cholecystectomy: Prediction of Individual Outcome*, Surg Endosc. 2016 Apr 29.

4. **K Kortram,** DA Hesselink, FJMF Dor, *Fifteen Year Functional Survival of a Polycystic Kidney Transplant*, Transpl Int. 2015 Jul;28(7):870-1
5. M den Dulk, MJ Witvliet, **K Kortram**, CJH van de Velde, PA Neijenhuis, IH de Hingh, LM de Brauw, AF Engel, H Putter, MAM Brouwers, WH Steup, *The DUtch LeaKage score: actively seek for the leak*, Colorectal Dis. 2013 Sep;15(9):e528-33
6. **K Kortram**, VNN Kornmann, ThL Bollen, B van Ramshorst, D Boerma, *Hoogrisico Patiënten met Acute Cholecystitis: Opereren of Draineren?* Ned Tijdschr Geneeskd. 2012;156:A5224
7. **K Kortram,** B van Ramshorst, ThL Bollen, MGH Besselink, DJ Gouma, T Karsten, PhM Kruyt, GAP Nieuwenhuijzen, E Tromp, H Kelder, D Boerma, Acute cholecystitis in high risk surgical patients: percutaneous cholecystostomy versus laparoscopic cholecystectomy (CHOCOLATE Trial): Study protocol for a randomized controlled trial, Trials. 2012 Jan 12;13(1):7.
8. JSK Reinders, **K Kortram**, B Vlaminckx, B van Ramshorst, DJ Gouma, D Boerma, *Incidence of bactobilia increases over time after sphincterotomy*, Dig Surg. 2011;28(4):288-92.
9. **K Kortram**, TS de Vries Reilingh, D Boerma, MJ Wiezer, B van Ramshorst, *Percutaneous drainage for acute calculous cholecystitis*, Surg Endosc. 2011 Nov;25(11):3642-6.
10. **K Kortram**, JSK Reinders, B van Ramshorst, MJ Wiezer, PMN Go, D Boerma, *Laparoscopic cholecystectomy for acute cholecystitis: for laparoscopic surgeons only?*, Surg Endosc. 2010 Sep;24(9):2206-9

ABOUT THE AUTHOR

Kirsten Kortram was born on May 19th 1985 in Boxmeer. She grew up in a small Noord-Brabant village (Holthees), but was fortunate enough to travel the world with her parents. She spent a good amount of time in the United States, which had always felt like her second home. She graduated high school ("Stedelijk Gymnasium Nijmegen") in 2003, and in September of that same year she started Medical School at Utrecht University. She enjoyed the student life in Utrecht, and engaged in many extra-curricular activities, among which her position as a coxswain at the student rowing club. But America kept calling, and she dreamed of being a doctor in one of the country's leading hospitals. She thus decided to spend a semester at Stanford University Medical Center, in Palo Alto, California, and had the opportunity to observe the daily clinical practice of the surgical department. Although this was an amazing experience, she preferred the Dutch system, and in 2009 she received her Medical degree and began her career as a surgical resident. She started her PhD project in 2013, and became a fulltime PhD student in October 2014. After working in the field of general surgery for some years, she realized that her true passion was Orthopaedic Surgery. During her PhD career she engaged in a number of Trauma- and Orthopaedic related research projects. On April 1st 2016 she acquired a training position in the Orthopaedic Surgery program in ROGO Rotterdam, and she will start her training in January 2017 (program director P.K. Bos, MD PhD).