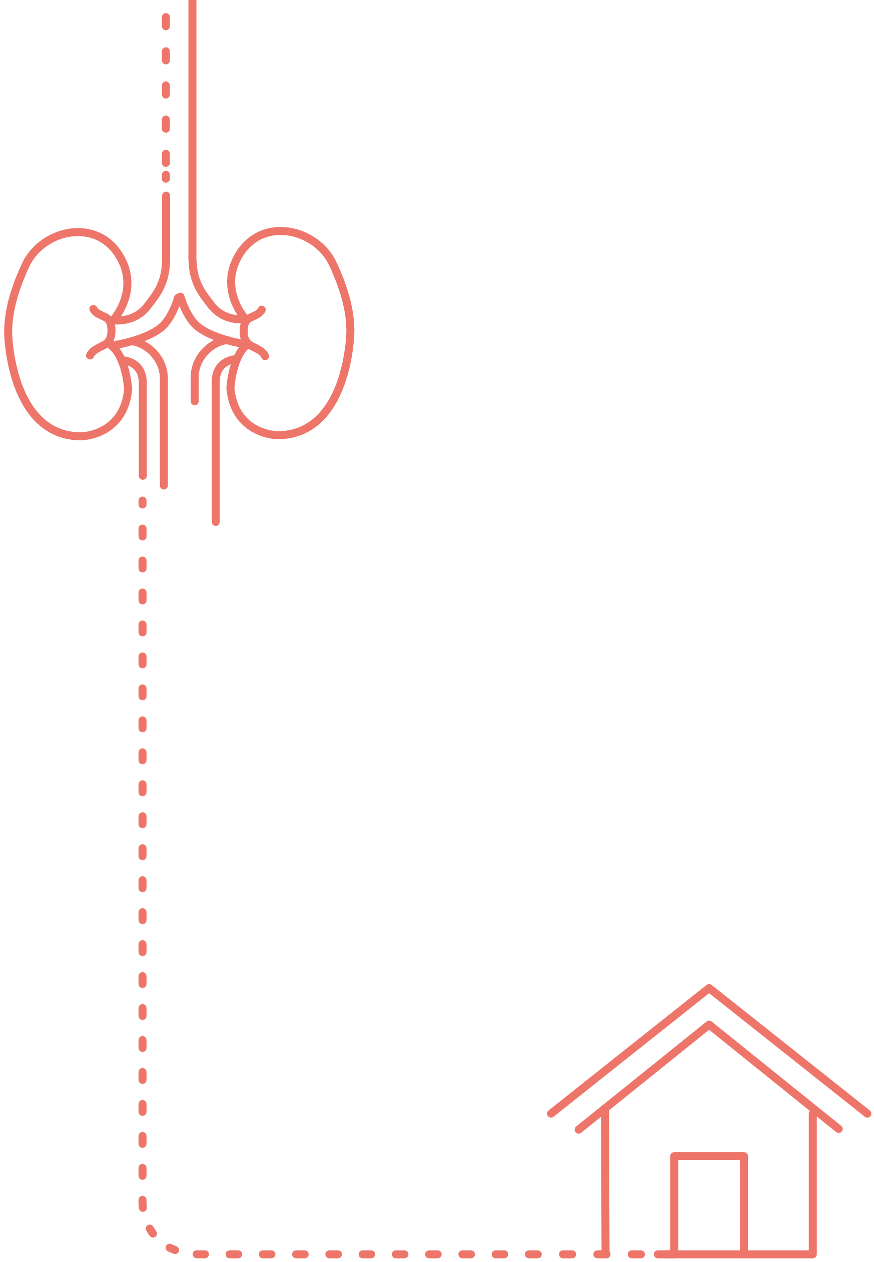

Kidneyteam at Home National Implementation and Cost-effectiveness

Steef Redeker

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Kidney Team at Home: National Implementation and Cost-effectiveness

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CHAPTER 1

General Introduction

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General Introduction

End-Stage Kidney Disease (ESKD) is a high-burden disease for patients in terms of physical and physiological well-being[1]. Patients with ESKD need Kidney Replacement Therapy (KRT) to survive. There are four major types of renal replacement therapy:

1. Hemodialysis (HD)
2. Peritoneal Dialysis (PD)
3. Deceased Donor Kidney Transplantation (DDKT)
4. Living Donor Kidney Transplantation (LDKT).

The dialysis modalities (option 1 and 2 above) are associated with low quality of life and high mortality. The median survival for patients on dialysis is 5 years[2]. Transplantation (option 3 and 4 above) is superior compared to the dialysis modalities; the 5-year patient survival for transplanted patients ranges from 86.1% to 95%[3]. Between the transplant modalities, LDKT (option 4) is preferable to DDKT (option 3) in terms of (graft) survival. In particular, clinical outcomes are optimized when a patient undergoes LDKT as the first form of KRT, so-called pre-emptive transplantations[4].

However, there is inequality in access to LDKT, let alone pre-emptive transplantations. Research has shown that socioeconomic status, age and ethnic background are factors that influence the access to LDKT[5-7]. Unfortunately, these factors are not modifiable. However, some modifiable factors are also associated with access to LDKT. Research has shown that lower knowledge of kidney replacement therapies, high risk perception on living kidney donation, and insufficient communication between the social network and the patients are all associated with reduced access[8]. To address these factors and consequently improve access to LDKT, a 'home-based educational intervention' was developed.

In 2007, a randomized controlled trial was conducted in the USA by Rodrigue and colleagues to test whether a home-based educational intervention for patients and their social network was effective in improving knowledge, risk perception and communication on kidney replacement therapies[9]. Another goal was to address the disparity in access to LDKT for black patients compared to white patients. Results of this trial showed a significant improvement of the outcomes for both the social network and the patients. In addition, the rate of LDKTs was significantly higher in the experimental group compared to the control group who received care as usual. It also showed that the effect of the intervention was greater in black patients than in white patients for living donor evaluations and LDKT, indicating that such an intervention can overcome barriers to LDKT in the black population and can help reducing inequity[10].

Like in the US, in the Netherlands certain groups of patients were less likely to receive a LDKT, including patients with a migration background[5]. Due to the positive results on home-based education in the USA in addressing this inequity, the intervention was adapted to the Dutch setting to reach patients who had less access to LDKT. Prior to adapting the intervention, an analysis on the ethical considerations of a home-based group education was conducted. The analysis showed that participation has to be a voluntary and the information has to be given in a neutral, open, that is to say, in a non-directive manner. Moreover, it is important that the aim of an intervention has to be known for every participant (i.e. education about facts of kidney failure, risk perception and communication on kidney replacement therapies) and that the aim was not to 'persuade' participants in donating a kidney[11]. Taking these ethical conditions into consideration, the intervention was tested in two randomized controlled trials in the Rotterdam transplant area; the Kidney Compass (*Nierkompas*)[12] study and the Kidney Team at Home (*Nierteam aan Huis*)[8] study. Both these interventions consisted of two home visits by healthcare professionals. In the first home visit the educators familiarized themselves with the patient and the social network. In the second home visit the education took place with the patient and social network.

The *Nierkompas* study was aimed at patients with ESKD who had not yet started KRT and was conducted at three regional hospitals and the Erasmus MC. The primary goal of the study was to educate patients and to stimulate the communication between patients and the social network about the different KRT-options in order to make a well-informed decision regarding treatment. Another goal was to monitor the choice of primary KRT-option after they received this home-based educational intervention. Both patients and the members of their social network showed a significant increase in KRT-knowledge and KRT-communication. Of the 49 patients who initiated a form of KRT during the two-year follow-up, 34 patients underwent a LDKT, 22 of them pre-emptively[12]. This suggested that the home-based group education might remove barriers to pre-emptive transplantation.

The *Nierteam aan Huis* study was aimed at patients who were either newly referred for transplant preparation at the Erasmus MC or already listed for a deceased donor kidney transplantation and unable to find a living donor. This included patients who already initiated dialysis. Following the work of Rodrigue and colleagues, the intervention was based on the principles and communication techniques drawn from multisystem therapy[13] to improve family communication and reduce fears and concerns regarding the different KRTs. Patients and their social network showed a significant increase in KRT-knowledge and KRT-communication. The intervention also resulted in a significant increase of the LDKT-rate in the experimental group that received standard care plus the educational intervention compared to the control group that received standard care only[8]. Thus, the intervention also showed effect in patients who were already undergoing dialysis. Because the results of these RCTs were favorable, the next step was nationwide implementation.

Issues to be investigated in a national implementation study include feasibility and generalizability of findings to the naturalistic setting. The two RCTs were conducted in the Rotterdam transplant area, which already had a lot of experience with novel LDKT-programs[14]. However, the extent to which these could be replicated in other settings remained to be seen. Results of RCTs are not always generalizable to a naturalistic setting, since a RCT often involves a homogenous population and is often conducted in a somewhat artificial environment, which differs from how the majority of patients react in practice[15]. Thus, nationwide implementation into standard care would not automatically result in similar results. It was therefore needed to evaluate the feasibility of implementation to other hospitals outside the Rotterdam transplant area. Moreover, in the naturalistic setting there is more variation in standard clinical practice. There is evidence that this is also the case in the kidney care pathway[16,17]. For instance, some hospitals refer none of their patients for preemptive transplantation, while other centers have a referral rate of 80%[18]. However, implementation studies are almost non-existent in renal care, which makes that evidence-based care may not reach some patients

Another important aspect of nationwide implementation are the additional healthcare costs accompanied by the intervention. The additional costs associated with the intervention should be weighed against the costs of current standard care. As it is expected that implementation of the intervention will result in more LDKTs, which gives better quality of life and survival compared to dialysis, the health benefits should also be taken into account. Evaluating costs and health benefits of new interventions is an important pillar of the Dutch healthcare system, as healthcare expenditures are gradually increasing and allocating monetary resources effectively is imperative[19]. A cost-effectiveness analysis of the intervention compared to standard care is therefore warranted to support nationwide implementation.

Successful implementation of the intervention will likely result in a shift in patients' demand for KRT-facilities, which could be troublesome if the KRT-facilities and logistics remain unchanged. For example, the intervention might not result in more LDKTs if there is insufficient capacity of transplantation facilities to conduct the extra transplantations. Another barrier for successful implementation might be an suboptimal alignment of supply and demand[20]. For instance, stakeholders might have financial incentives to choose one type of KRT over the other, which can influence the effectiveness of the Kidney Team at Home intervention. Therefore, current KRT-policy has to be evaluated to identify potential barriers for successful implementation of the educational programs.

In order to assess the generalizability and the cost-effectiveness, an implementation project was started in 2016. The protocols of the previous studies were combined into one, and the name *Nierteam aan Huis* was adopted. This thesis presents and discusses the findings of the *Nierteam aan Huis* implementation project.

The aims of this thesis are:

1) To assess the generalizability of the intervention
2) To assess the cost-effectiveness of the intervention compared to standard care
3) To assess current KRT-policy

To achieve the aforementioned aims, the following research question are answered in the three chapters that form this thesis: implementation, cost effectiveness and policy.

Implementation

1. Is nationwide implementation of the *Nierteam aan Huis* intervention viable in terms of feasibility, fidelity and intervention costs? (Chapter 3)
2. Are the results of the previous randomized controlled trials conducted in the Netherlands replicable to other Dutch regions (Chapter 3)

Cost-effectiveness

3. What are the total costs and effects of the *Nierteam aan Huis* intervention when nationwide implemented? (Chapter 4)
4. What is the cost-effectiveness ratio of the *Nierteam aan Huis* intervention compared to standard care? (Chapter 4)

Policy

5. How will the demand for dialysis and transplantation facilities change when the *Nierteam aan Huis* intervention is implemented, and how can policy of the kidney replacement program improve? (Chapter 5)

The final chapter (chapter 6) provides a general discussion.

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CHAPTER 2

Cost-effectiveness of a home-based group educational programme on renal replacement therapies: a Study Protocol

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Abstract

Introduction

Living donor kidney transplantation (LDKT) is the optimal treatment for most patients with end-stage renal disease (ESRD). However, there are numerous patients who cannot find a living kidney donor. Randomized controlled trials have shown that home-based education for patients with ESRD and their family/friends leads to four times more LDKTs. This educational intervention is currently being implemented in eight hospitals in the Netherlands. Supervision and quality assessment are being employed to maintain the quality of the intervention. In this study we aim to: (1) conduct a cost-effectiveness analysis of the educational programme and its quality assurance system; (2) investigate the relationship between the quality of the implementation of the intervention and the outcomes knowledge, communication, and LDKT activities; and (3) investigate policy implications.

Methods and design

Patients with ESRD who do not have a living kidney donor are eligible to receive the home-based educational intervention. This is carried out by allied-health transplantation professionals and psychologists across 8 hospitals in The Netherlands. The cost-effectiveness analysis will be conducted with a Markov model. Cost data will be obtained from the literature. We will obtain the quality of life data from the patients who participate in the educational programme. Questionnaires on knowledge and communication will be used to measure the outcomes of the programme. Data on LDKT activities will be obtained from medical records up to 24 months after the education. A protocol adherence measure will be assessed by a third party by means of a telephone interview with the patients and the invitees.

Ethics and dissemination

Ethical approval was obtained through all participating hospitals. Results will be dissemnitated through peer-reviewed publications and scientific presentations. Results of the cost-effectiveness of the educational programme will also be disseminated to the Dutch National Health Care Institute.

Introduction

Living donor kidney transplantation (LDKT) is the optimal treatment for most patients with end-stage renal disease (ESRD) in terms of Quality Adjusted Life Years (QALYs), survival and cost-effectiveness [1]. However, there is a significant number of patients who cannot find a living kidney donor and many patients first undergo dialysis before transplantation with a living donor kidney. Interventions are needed to improve access to LDKT.

Research has shown that knowledge of renal replacement therapies (RRT) and communication between patients and their social circle play an important role in the access to LDKT [2]. Studies have shown that a home-based interventional programme had positive effects for patients with ESRD [3-5]. In our transplant center in Rotterdam, the Netherlands, we have conducted two studies on this home-based educational approach: one randomized controlled trial (RCT) and one cross-over study. The RCT among 163 patients on dialysis showed significant increases in knowledge and communication about LDKT among the patients in the experimental arm who received the home-based education compared to the standard care control arm. Furthermore, there were significantly more actual LDKTs in the experimental group compared to the control group (17 vs 4, $p=0.003$) [3].

The cross-over trial was aimed at patients who had not previously undergone RRT and who were eligible for transplantation. In the first phase, the experimental arm received the home-based education while the control group waited. In the second phase, the control group also received the education. This study also showed that there was a statistically significant increase in knowledge and communication regarding RRT among patients and invitees after receiving the home-based education. Of the 80 participants, 49 underwent RRT during the two year follow-up. Of these, 34 underwent a living donor kidney transplantation, of which 22 were pre-emptive [4].

Given these positive results, a home-based educational programme for ESRD patients and their social network is currently being implemented in four regions in The Netherlands. Per region, a regional hospital and a university transplant hospital are implementing the programme. The regional hospitals will target patients who are yet to start renal replacement therapy, while the university hospitals will target both these patients and dialysis patients. The educators organize the intervention in such a way that they will do 'whatever it takes', in line with one of the basic principles of multisystem therapy (MST), to make this event as patient-tailored as possible [6]. Supervision and quality assessment are being employed to mantain the quality of the intervention. The first aim of this study is to evaluate the cost-effectiveness of the education to support continued implementation. In this article, we present the study protocol of a cost-effectiveness analysis of the educational programme and its quality assurance system. The patient population, the standard care, the quality of the educations and the setting differ per hospital. Therefore, our second objective is to investigate the relationship between the quality of the implementation of the programme, as measured by protocol adherence, and outcome. Outcome is defined in terms of knowledge, communication, and LDKT activities.

Hypotheses

Previous research has provided convincing evidence that transplantation cost less, gives a better survival and a higher quality of life compared to dialysis [7-9]. We therefore hypothesize that the relatively small incremental costs of the home-based educational programme, should be cost-effective. Since it is desirable that in the future all waiting list patients can benefit from the effects of the home-based intervention, this programme should be part of standard care. Hence, a solid basis of the cost-effectiveness of that educational programme is warranted.

The second hypothesis is that higher protocol adherence among healthcare providers will be associated with more positive effects of the educational interventions. These effects include an increase in knowledge of renal disease and the treatment options, an increase in communication with family/friends about renal replacement therapies, an increase in living kidney donation activities, and an increase in QALYs. If a relationship between protocol adherence and effects is shown, a quality assurance system should be an inseparable part of the educational programme.

The third hypothesis is that a full implementation of the educational programme leads to policy implications regarding care for patients with ESRD. Full implementation may affect the need for dialysis centers and transplantation facilities. By modelling the prevalence we can estimate the need for allocating the health care budget. We aim to present the outcomes of the model in a budget impact analysis (BIA).

Thus, the main aim of this article is to discuss the protocol of the cost-effectiveness study of the home-based educational programme and of the quality assurance programme which currently being implemented in The Netherlands. Additionally, potential policy implications of our hypotheses are discussed in this article.

Methods and Design

Participants and procedure

The implementation study is being conducted in the following regions of the Netherlands: Rotterdam, Amsterdam, Nijmegen and Groningen.

The home-based educational programme is currently being implemented in eight hospitals in the Netherlands; four university transplant hospitals and four regional hospitals. Regional hospitals were included to reach those patients who are yet to start renal replacement therapy and in this setting, this is the target population. In these hospitals there is a large dialysis unit but no transplants are conducted. For these hospitals, the inclusion criteria are: ≥18 years of age, are eligible for transplantation, and primary RRT required within the coming 12 months. In the regional hospitals allied health professionals carry out the intervention. The four university hospitals incorporate both a dialysis unit and a transplant center, therefore in this setting both patients who are yet to start renal replacement therapy and dialysis patients are the target population. Eligible patients for these hospitals are required to be ≥18 years, currently undergoing RRT or required within the coming 12 months and eligible for transplantation. In the university hospitals, allied health professionals are accompanied by psychologists to carry out the intervention. The distinction between the university hospitals and the regional hospitals is in line with the protocols of the aforementioned Cross-over study and the RCT.An estimate of the potential candidates for this implementation is about 50 patients per year per university center and 20 patients per regional hospital. The implementation study will take two years.

If patients have not been able to find living donor candidates in their social network, they will be asked whether they and their social network wish to receive home-based education from health-care educators. The nephrologist explains to the patients that the educators will provide information about renal diseases, the different types of RRT and their impact on quality of life. Furthermore, the educators can help to discuss the possibilities of living donation within the social network of the patient. If the patient consents to the intervention in consultation with his/her nephrologist, the health-care educators contact the patient to make an appointment for the first home session. Patients are supported in inviting their family/friends to the second educational session. After completion of the programme an evaluation consultation is planned with the nephrologist. The number of patients who do not consent to participate in the study is recorded, as well as the reason for nonparticipation.

Patient and Public Involvement statement

Patients were involved in the design of the educational programme. When designing the intervention we anchored the patient pariticipation in the project approach by relying on the results of focus groups among fifty patients from the intended target group. Their opinion was sought regarding two methods described in the literature of additional information/coaching: 1) an additional telephone consultation by the transplant doctor [10] and 2) home education where family and friends are invited to receive knowledge about RRT. Eighty-eight percent of the participants favoured the home-based education over the telephone consultations [11]. Additionally, a patient panel and organizations were involved in the development of the educational programme protocol and materials. Patients were not involved in the design of the cost-effectiveness study.

The intervention: home-based education

The intervention consists of two sessions at the patient's home. The intervention is carried out by allied-health transplantation professionals and psychologists. In the first session the goals of the educational programme are discussed and the home-based educational meeting will be prepared. The educators will make an inventory of individuals in the patient's social network using a socio-gram. This helps open the discussion on who to invite for the second session, the home-based educational meeting. The need for an independent translator is also dicussed.
In the second session the education takes place. The educators organize this session in such a way that they will do 'whatever it takes', in line with one of the basic principles of multisystem therapy (MST), to make this event as patient-tailored as possible [6]. The primary goal of this intervention is educational, therefore, it is not necessary that all the invitees are or become potential donors. The intervention is based on the previous RCT and Cross-Over studies [3,4]. A more detailed description can be found in a published protocol manuscript [12].

Measures

Knowledge and communication are evaluated through questionnaires among all patients and for at least one relative/friend in attendance at the home-based educational session. The knowledge about renal disease and renal replacement therapies is measured through a validated knowledge questionnaire R3K-T. This 21-item knowledge questionnaire has been developed specifically for kidney disease, and has good psychometric properties [13]. Answer categories are multiple choice and the number of correct answers are summed. The 3-item communication questionnaire can be answered on a scale from 1 (completely disagree) to 5 (completely agree). An example item is 'I can talk about renal replacement therapies with my loved ones'. Finally we assess patients' and invitees' attitude towards RRT through a 9-item questionnaire. This questionnaire can also be answered on a scale from 1 (completely disagree) to 5 (completely agree). An item example is 'I am afraid donation will harm the health of the donor'. The administration of questionnaires will take place at two occasions 1) prior to the education either during an outpatient visit after signing the 'informed consent form' or during the first session; and 2) shortly after the second session.

Protocol adherence measures: After every completed home intervention an independent telephone evaluation is conducted with the patient and a relative/ friend who attended the education programme, to measure the degree of protocol adherence of the educators. The independence is guaranteed through an independent party, specialized in treatment adherence measurement (www.Praktikon.nl). Protocol adherence in this implementation is defined as the extent to which the different teams carry out the educational programme as described in the protocol. Measurement is done with an adaptation of the 'Treatment Adherence Measures' (TAM) questionnaire [14]. TAM is scored on a 0-1 scale, where 1 stands for complete protocol adherence. The results of the TAM can not only be used for research purposes, but also to give the educators feedback on the quality of their interventions during the implementation phase.

Cost-Effectiveness

Costs: The latest published research on costs of dialysis and transplantation in The Netherlands dates back from the late 1990s [7]. Currently, research on costs of dialysis and transplantation is in its final phase. We will use this forthcoming data (De Wit, personal communication). This cost data is of high quality, as it is based on the national database of insurance companies from 2014, which consists of records from 99% of all Dutch citizens. Costs calculations will include costs of dialysis modality, dialysis access, transplant procedure, other hospital costs, primary care costs, mental health care, medication outside the hospital, medical devices, health care abroad, transport, and other costs. Health care costs for transplantation, include preparatory research, transplant operation, guidance, after care, donor expenses, dialysis procedure, other hospital costs, primary care, mental health care, medication outside hospital, medical devices, health care abroad, transportation and other costs. These include all the health care costs associated with RRT. Since it is recommended that cost-effectiveness analysis are conducted from a societal perspective, we also aim to calculate the productivity costs[15]. Productivity costs will be estimated with the friction-cost method, as recommended in the Dutch guidelines for economic evaluation [16]. Besides that the work situation of patients participating in the study is recorded, some research has been done regarding labor participation of patients with ESRD [17,18]. The costs of the home-based intervention and the quality assurance will be estimated on the basis of the current practice in the implementation. Informal care costs will be estimated from the literature [19]. The costs of the intervention are recorded per center.

Effects: In health economics the effects of interventions under evaluation are preferably expressed in QALYs [15]. Research on QALYs of different dialysis modalities are widespread [8,20,21], but instruments and patient background variables vary. Therefore, we are currently in the process of collecting quality of life data from both patients who are yet to start renal replacement therapy and dialysis patients prior to the intervention, through the EQ-5D-5L, the quality of life instrument recommended in the Dutch guidelines for health economics [16]. We also collect quality of life data from patients after the intervention. The educators administer the EQ-5D-5L questionnaire to patients at baseline, 6, 12 and 24 months after the intervention by telephone.

Markov Model: To assess the cost-effectiveness of the implementation of the home-based educational programme, we will build a 'Markov simulation model'. This model will assess the costs and effects of ESRD treatments as it simulates the course of treatment and disease of the patients. The model will have a similar structure as a previously published model on this population [7], with some important updates and improvements. Unlike that Markov model, which used multivariate and univariate sensitivity analyses [7], our model will include probabilistic sensitivity analysis using Monte Carlo simulation. Consequently, uncertainty of all values are considered simultaneously, and the uncertainty in each parameter is assumed to possess a probability distribution [22]. The model will run 10,000 simulations in Microsoft Excel, version 2010. By using probabilistic sensitivity analyses we follow current guidelines in health economics [16,23,24]. A Markov modelling technique is applicable because the decision problem involves risk that is continuous over time, the timing of events is important, and events may happen more than once [25]. Within a Markov simulation, the time horizon of the study is divided into a number of discrete time-periods, the so-called Markov cycles. A Markov process is based on the idea that patients are always in a certain disease state and that they can change between disease states once during each cycle. By assigning effects to each disease state and keeping track of the time patients remained in each disease state, long-term effects can be calculated. For this cost-effectiveness analysis the effects and cost per health state do not change because of the intervention. We expect that there will be more LDKTs because of the intervention. Therefore, besides the costs of the programme, only the transition probabilities will change because of the intervention and will be the only difference between the baseline and the post-implementation situation. Table 1 shows an overview of the parameters used and the source.

Parameter	Sources
Costs 1. Medical Costs 2. Intervention Costs 3. Costs of Productivity Losses 4. Informal Care Costs	1. Costs study of RRT in the Netherlands by de Wit et al. (Forthcoming) 2. Are recorded in the current implementation study 3. Work situation of patients is recorded in the implementation study and use of (Dutch) literature [16,17] 4. Will be estimated from existing literature[18]
Effects (QALYs)	EQ-5D-5L are conducted prior at the intervention and 6, 12 and 24 months after the intervention.
Transition probabilities 1. Between treatment modalities 2. Mortality rate	Estimated from the database of Nefrovisie
Incidence rates	Estimated from the database of Nefrovisie
Effect size of the intervention	Used from previous studies [3,4]

Table 1 overview of parameters and sources in the Markov Model

Model description: A simplified graphical representation of the Markov model showing only the treatment categories, rather than all the individual Markov states is represented in figure 1. Patients continuously enter the model (inflow) at the start of the cycle and can start on Hemodialysis, Peritoneal dialysis, or Transplantation. From there they can move between these treatment modalities. Diabetics and non-diabetics are modeled separately since the transition probabilities between the treatment modalities differ between these groups. Since the incidence of kidney failure is increasing, we will also model this in the cost-effectiveness analysis. This will be calculated using data from the database of *Nefrovisie*, a large national database with records of ESRD patients. As stated before, the model will include probabilistic sensitivity analysis using Monte Carlo simulation. This means that not only mean numbers of patients per year per treatment modality will be modeled, but also the uncertainty surrounding those mean number of patients, (i.e. 95% confidence intervals). Transition probabilities and incidence rates will be based on primary data and will include uncertainty. Costs and utilities will be included in the model as distributions rather than point estimates.

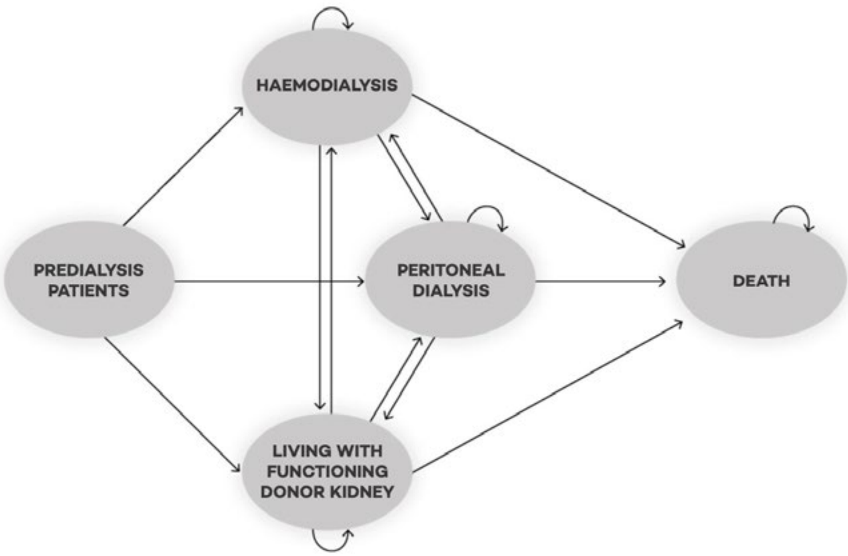

Figure 1 A simplified graphic representation of the Markov model with the different health states and the transition possibilities between the health states.

Markov States: The Markov states are based on the treatments currently available in The Netherlands. These are: full care centre hemodialysis, limited care centre hemodialysis, home hemodialysis, continuous ambulatory peritoneal dialysis, continuous cyclic peritoneal dialysis, deceased donor kidney transplantation, and living donor kidney transplantation. Since transition probabilities and costs may differ over time, i.e. a patient who is in his second year of hemodialysis has a different mortality chance than a patient who just started with hemodialysis, we will define separate Markov states for the 1st year of treatment and subsequent years of treatment for each specific modality. Incident patients that enter the model and prevalent patients that switch between treatment modalities are assigned to the 1st year Markov states, whereas patients that spend more than one year in any health state are transferred to the subsequent years of that same treatment modality.

Outcomes: The outcome of the implementation will be compared with the baseline situation; the situation before this programme was implemented. The effect size, in terms of an increase in LDKT, will be used from the RCT conducted earlier. Through sensitivity analyses an estimation can be made of the cost-effectiveness of the intervention whether this assumption is either an under- or overestimation. A critical assumption will be the extrapolation of the effects after the 2 years.

Quality Assurance

This study has also implemented a central quality assurance system. We hypothesize that the effectiveness is moderated by the protocol adherence of the team of healthcare professionals. In the implementation study, it might be possible that there are differences in the way teams and centers adhere to the protocol. Protocol adherence measures will be assessed by a third party by means of a telephone interview with the patients and the invitees. Patients and invitees are asked for their opinion and level of satisfaction regarding the way in which the intervention was delivered. Patients and invitees are asked to answer the 15-item TAM-scoring list. Items are rated on a Likert-scale (1 not at all – 5 very much). Only items that are rated with a 5, will be regarded as fully adherent. Items scored with a 1-4 will be regarded as non-adherent. The outcome of the protocol adherence will be associated with the gain in knowledge and communication skills. We will also look if there is a correlation between the protocol adherence and the amount of LDKTs. A part of the quality assurance is a training that all professionals who conduct the home interventions must take part in. During this training, issues are discussed such as: how to convey uniform and complete information to the patient, how to behave during the home visits, how to create an alignment of the goals of the home visit with the patients, how to assist the patient in inviting friends and relatives, how to deal with emotional moments, how to discuss delicate topics with respect to individual feelings and opinions and finally, how to ensure no detrimental psychosocial effects of the education occur for the patients and his/her family/friends. All these aspects can be executed in different ways by the educators. A supervisor evaluates the home visits with each team separately every six weeks and discuss difficult cases. After these meetings the supervisor is graded by the educators through a 10-item questionnaire regarding the content of the teaching and the interpersonal delivery of the supervisor. Furthermore, the supervisor will bring together all educators for a so-called intervision meeting every three months. These intervision sessions are meant to discuss the home visits with each other in order to learn from each other and to keep the procedures similar.

Discussion

We presented a protocol for assessing the cost-effectiveness of our home-based educational programme and its generalizability. The implementation of the educational programme might both benefit patients and society.

Cost-effectiveness: If indeed our hypotheses are confirmed, and the home-based educational programme is cost-effective, then there are convincing arguments to make the programme standard care in The Netherlands. Health insurers already expressed their interest in the programme; this implementation study is supported by *Zorgverzekeraars Nederland* (Health insurers The Netherlands), which is the 'umbrella organization' of all health insurers in The Netherlands. Additionally, the Dutch Kidney Foundation supports the programme and contributed through three grants in the developmental phases of the home-based educational programme. The Dutch Kidney Foundation is a non-profit organization which subsidizes research and innovation in nephrology and renal transplantation care. Indeed, the health insurance companies have good reason to be interested, as dialysis is costly. In The Netherlands, 1% of the total healthcare budget is spent on ESRD patients, who only constitute 0.0006% of the population [26,27]. Furthermore, transplantation is associated with higher quality of life for ESRD patients compared to dialysis treatment. It is therefore valuable, from both patient and societal perspective, to conduct a complete and extensive cost-effective analysis and consequently to follow up those results in terms of policy.

Quality Assurance System: Protocol adherence may be of importance to guarantee the effects of the home-based education. First, we expect a positive relation of adherence with outcome in terms of communication, knowledge and the number of transplantations. Second, any problems or regrets of donors and/or patients can only be justified if the evidence based protocol was followed. The protocol has also been developed after thorough ethical consideration (23), which justified all characteristics of the programme. It can therefore be argued that health insurance make reimbursement indispensable of the degree of protocol adherence of healthcare suppliers. Moreover, they should facilitate the quality assurance system as an integral part of the programme and ensure that the quality of the interventions is independent of the healthcare suppliers.

Limitations: Investigating the (cost-)effectiveness of the home-based educational programme has its limitations. In health economic modelling, there is always a trade-off between the feasibility and transparency of the cost-effectiveness model and the level of details of real life conditions as represented in the model. The more details, the more the model resembles real life, but the down side is that data should be available at that same level of detail and that the model becomes too complex in its feasibility. An example is that we assume that the mortality on dialysis is the same in the second and following years on dialysis. Hence, we know from literature that the mortality chance changes, but the data in later years is scarce and again the model would become more complex, as more 'tunnels states' have to be introduced. We expect that this trade-off will be most prominent in the transition changes between health states. We expect less obvious trade-offs for costs and utility assessment, as we have sufficient data for those variables.

Cooperation: This investigation is a cooperation between many parties, who all have expressed their support. Obviously, it is possible that this support can be withdrawn for several reasons. For instance, we depend on data from a large national database with records of patient with ESRD (*Nefrovisie*). Hence, much efforts are and will be put in preserving relationships and communication in order to maximize fair successful implementation chances for the programme.

Ethical considerations: Another challenge that we face, is the ethical consideration of promoting living kidney donation through a home-based intervention. Previous studies on the ethics of this argued that such promotion is justified, only when the conditions are met, such as 1) participation must be completely voluntary throughout the intervention, 2) no undue pressure should be put on the participants, 3) the education is neutral and non-directive and 4) the purpose and the procedure should be clear to all participants [28,29]. That does not mean there are no negative consequence whatsoever, but it does mean that the positive outcomes outweigh the negative. It could well be that a patient and/or a donor may regret the decision to have undertaken a transplantation with a kidney of a living donor, and that the donor and/or patient, in hindsight, may have felt undue pressure to donate a kidney. Adherence to the protocol will minimize these potential negative effects. However, it is possible that regret or pressure could lead to negative publicity for the programme. That is a risk since such negative publicity could impede the chances of implementing the programme as standard care [30]. Especially considering that deceased organ donation is currently subject to controversy in The Netherlands since the government and parliament have accepted a donor law. This law is an opt-out system entailing a positive 'no-objection' deceased donor organ donor registration as a default for all Dutch citizens [31]. Given this potential harm due to negative publicity it is crucial to have 1) a protocol which is justifiable from a medical ethical perspective, 2) widespread support from the various organizations involved and 3) a high quality in terms of protocol adherence and trained adequate educators. If these conditions are met, the quality of the process then justify its outcome, which is a subtle trade-off between positive and negative outcomes.

Implementation: Another challenge is the generalizability of the results of the previous effect study on home-based interventions done in Rotterdam. The randomized controlled trial in the Rotterdam transplant area has shown that the home-based educational programme leads up to four times more LDKTs. The trial took place at the academic transplant center (Erasmus Medical Center in Rotterdam) where extensive efforts were already undertaken as part of the standard care to promote LDKTs [3,32]. It is possible that in other transplant areas in The Netherlands, with less experience regarding promoting LDKT, effectiveness in terms of amount of LDKTs may differ. On one hand this more cautious attitude may lead to lower results than in the Rotterdam transplant area. Hence, organizational conditions within those transplant centers may not optimally facilitate the favorable results of the interventions. On the other hand, if the number of LDKT was lower than in the Rotterdam area, and the uptake of the intervention is high, the effect could even be higher than in the Rotterdam area. This is due to a higher effect potential in those centers where living donation was not promoted as actively.

Learning curve: As with all new programmes, educators will inherently experience a learning curve during the first part of the implementation, which could influence the effectiveness of the programme. For instance, the goal of 50 patients per year per academic transplant center and the goal of 20 patients per regional hospital may not be reached. Regular supervision, (on the job) training and peer-to-peer coaching may help to overcome this, but a learning curve is unavoidable.

Policy implications*:* One of the main pillars of an efficient health care system is the ability to provide effective care to patients when needed. It is therefore necessary to have information on the effectiveness of the interventions and their cost to convince policy makers to reimburse the treatment. If the analysis confirms the effectiveness as well as the cost-effectiveness of the home-based educational programme, we recommend that this intervention should be part of standard-care. If the home-based educational interventions would become standard-care, this could have several implications. First, it can be expected that patients who are unable to find a living donor will nevertheless profit from an increase number of living kidney donations, as the demand for deceased donor kidneys drops. In other words, the increase in living donation will further lower the waiting list for deceased donor donation as well and thereby increase the chance of a deceased donor donation for those patients without a living donor increases.

Second, the composition of the population of patients with ESRD may change. For instance, it can be expected that the proportion of patients on dialysis will drop and patients with a life sustaining transplanted kidney will increase. This might have an influence on the demand for dialysis centers and the need for transplantation facilities. We, therefore, aim to incorporate this in a so-called dynamic model to estimate the prevalence over time. When modelling the prevalence, we could make estimates of the need for dialysis centers and transplantations facilities. However, modelling the facility is surrounded by uncertainty. For instance, dialysis centers may have financial incentives to fulfill dialysis capacity. If this would be the case, there will be no monetary benefits for society by increasing the transplants facilities if the proportion of dialysis capacity remains the same. This would mean that there will only be an increase in the average quality of life of ESRD-patients.

Finally, a cost-effectiveness analysis only might not be sufficient to set policy change in motion. Therefore, we anticipate that a policy recommendation accompanied with a BIA will also be required. A BIA addresses the expected changes in the expenditure of a health care system after the adoption of a new intervention. It can also be used for budget and resource planning [33,34].

Conclusion: If our hypotheses are confirmed, we hope by presenting an extensive cost-effectiveness analysis, a BIA, and a policy recommendation that policy change will be set in motion, which again would benefit both ESRD-patients and society.

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CHAPTER 3

Implementation of the Kidney Team at Home Intervention: Evaluating Generalizability, Implementation Process, and Effects

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Abstract

Research has shown that a home-based educational intervention for patients with chronic kidney disease results in better knowledge and communication, and more living donor kidney transplantations (LDKT). Implementation research in the field of renal care is almost non-existent. The aims of this study were (1) to demonstrate generalizability, (2) evaluate the implementation process, and (3) to assess the relationship of intervention effects on LDKT-activity.

Eight hospitals participated in the project. Patients eligible for all kidney replacement therapies (KRT) were invited to participate. Effect outcomes were KRT-knowledge and KRT-communication, and treatment choice. Feasibility, fidelity and intervention costs were assessed as part of the process evaluation. 332 patients completed the intervention. There was a significant increase in KRT-knowledge and KRT-communication among participants. 129 out of 332 patients (39%) had LDKT-activity, which was in line with the results of the clinical trials. Protocol adherence, knowledge and age were correlated with LDKT-activity.

This unique implementation study shows that the results in practice are comparable to the previous trials, and show that the intervention can be implemented, while maintaining quality. Results from the project resulted in the uptake of the intervention in standard care. We urge other countries to investigate the uptake of the intervention.

Introduction

While living donor kidney transplantation (LDKT) is the best treatment option with chronic kidney disease (CKD) in terms of survival and quality of life [1,2], research has shown that there is inequality in access to LDKT [3,4]. A number of modifiable factors, such as patients' knowledge on kidney replacement therapy (KRT), communication with family and friends about KRT and cultural sensitivity of health care professionals are independently related to the access to LDKT [5,6]. A home-based educational intervention has been developed to address these factors. This intervention was tested in the United States in a randomized controlled trial (RCT) by Rodrigue et al. [7,8]. The intervention took place in the home of the patient and was highly interactive. The patients invited members of their social network to attend a group educational session on KRT at the patient's home, delivered by health educators. This home-based educational intervention resulted in better knowledge about LDKT, increased the willingness to talk with the social network about LDKT, and reduced fears and concerns about LDKT compared to patients who received education in the hospital [7]. Based on these findings, two RCTs testing effectiveness of a home-based educational intervention were conducted in the Netherlands [9,10].

The first study was aimed at patients who were either newly referred for transplant preparation or already listed for a deceased donor kidney transplantation (DDKT) and unable to find a living donor. The control group received standard care, including standard education by the nephrologist. The experimental group received a home-based educational intervention in addition to standard care. The patient invited his or her social network for the intervention and two health educators provided information about dialysis and transplantation. Following the work of Rodrigue and colleagues, the intervention was based on the principles and communication techniques drawn from multisystem therapy (MST) [11] to improve family communication and reduce fears and concerns regarding the different KRT. Patients and their social network showed a significant increase in KRT-knowledge and KRT-communication. The intervention also resulted in a significant increase of the LDKT-rate in the experimental group compared to the control group [9].

The second RCT was aimed at patients with CKD who had not yet started KRT and was conducted at three regional hospitals and at the pre-dialysis department of a university hospital. The primary goal of the study was to educate patients and to stimulate the communication between patients and the social network about the different KRT options in order to make a well-informed decision. Another goal was to monitor the choice of primary KRT-option after they received this home-based educational intervention. Both patients and the members of their social network showed a significant increase in KRT-knowledge and KRT-communication. Of the 49 patients who initiated with a form of KRT during the two-year follow-up, 34 patients underwent a LDKT, 22 of them pre-emptively [10].

The positive results of these studies led to an implementation project, involving 8 hospitals in the Netherlands [12]. The 1st goal of the project was to assess the generalizability of the results of the previous studies to other regions in the Netherlands. If the project is deemed to be successful, the results could support nationwide deployment of the program as standard care. This study is unique as implementation studies are almost non-existent in renal care. This is remarkable as large variation exists in how centers treat patients with CKD. For instance, some hospitals refer none of their patients for preemptive transplantation, while other centers have a referral rate of 80% [13]. In the US, similar variation in referral rates among centers exists [14]. To prevent such variation, and due to the growing interest in research to understand barriers and facilitators of successful implementation [15], the 2nd goal was to evaluate the implementation process of the protocolled intervention in terms of feasibility, fidelity and intervention costs. Additionally, we were interested in the influence of intervention effects on LDKT-activity.

To summarize, three research questions emerge. First, are the results of the previous RCTs conducted in the Netherlands replicable to other Dutch regions, thus demonstrating generalizability? Second, is a nationwide implementation viable in terms of feasibility, fidelity and intervention costs? Third, do patients with higher knowledge and communication skills on KRT have a higher probability of LDKT-activity?

Materials and Methods

Participants & Procedure

The home-based educational intervention was implemented in eight hospitals in the Netherlands; four university hospitals and four regional hospitals. In the Netherlands, kidney transplantations are carried out by university hospitals. Regional hospitals screen their patients for transplantation and refer them to the university hospital for approval for kidney transplantation. Regional hospitals were included to reach those patients who were unable to find a living donor and who have yet to start KRT. For these hospitals, the inclusion criteria for patients were: ≥18 years of age and eligible for all KRT options. In the regional hospitals, medical social workers and dialysis nurses carried out the intervention. The four university hospitals targeted both patients who had yet to start KRT and patients who were already on dialysis, and who were unable to find a living donor. For these hospitals the inclusion criteria were: ≥18 years of age, currently undergoing dialysis or expected to start KRT within the coming 12 months and eligible for all KRT options. The patient's nephrologist determined whether the inclusion criteria were met. In the university hospitals, transplant coordinators were accompanied by psychologists or medical social workers to conduct the intervention. The university hospitals were selected on the following criteria: hospital capacity, to reach as many patients as possible as it would result in a sufficient sample size to evaluate the intervention outcomes, sufficient geographical spread to assess the generalizability to other parts of the Netherlands, and willingness to participate in the implementation project. The four regional hospitals were chosen by the university hospitals as their partner in the transplantation region. The study was approved by the institutional review board of the participating hospitals (Erasmus MC: MEC-2016-496).

The educators first approached patients in-person or by telephone to offer the intervention/recruit them into the study, followed by two home visits. The aim of the first home visit for the educators is to get familiarize themselves with the social network of the patient and to prepare the group educational session. In the second session, the group educational intervention took place. After the second session, patients and invitees were asked by an independent party to evaluate the protocol adherence of the educators. All participants were required to sign an informed consent form, either during recruitment or the 1st home visit.

Prior to the start of the implementation project, educators received a one-day training from supervisors educated in family communication and social network resilience. After the training, regular supervision meetings were conducted (one hour, every six weeks) per participating hospital by one clinical psychologist (SI). Furthermore, 4 consortium meetings were organized per year, with the educators (see Consortium), the project group (SR, SI, JB, WW & EM), supervisors (SI & CB), and with the supervising nephrologists (see Consortium). Goals of these meetings were to discuss protocol implementation, inclusion of patients and motivating them to participate and complete the intervention, data entry, protocol adherence and case studies. A quality assurance system, namely the consortium meetings, supervision, and the independent evaluation with patients and invitees, was put in place to measure and maintain a high degree of protocol adherence.

Questionnaires were completed at two time points: prior to the home-based educational intervention and after the intervention. Both the patient and at least one invitee completed these questionnaires. A website was used to coordinate

data entry over the various study sites. A researcher (SR) monitored every hospital three times during the study period to check accuracy of data entry (comparing the hard-copy of the questionnaires with the data entered on the website).
This implementation study was conducted between September 2016 and December 2018. All patients approached within this time period were included in the analyses, although some patients received the intervention after this period. Since regional hospitals and university hospitals approached different patient populations, results were reported either per hospital group (university and regional hospital group) or, when of interest, per hospital separately. More details on participants and procedures are described elsewhere [12].

Effect Evaluation Measures

We measured three effects: KRT-knowledge, KRT-communication with individuals from the social network, and the KRT during the 24 months follow-up after the intervention. KRT-knowledge was measured using a validated questionnaire: the R3KT-questionnaire [16]. Answer categories are multiple choice and the number of correct answers is summed to get to a KRT knowledge score (1 to 21). Communication was measured using three items which could be answered on a Likert scale from 1 (completely disagree) to 5 (completely agree). The questions addressed the attitudes towards communication of patients and invitees with their social network on all forms of KRT. The total communication score is the mean of the three questions. The patients' pre-measurement of these questionnaire were administered at the intake. All invitees were asked to fill in the pre-measurement before the start of the group education on a voluntary basis. The post-measurement was administered on paper directly after the education ended.
The KRT of patients was recorded 6, 12 and 24 months after the intervention date. Treatment modalities were: no KRT necessary yet, peritoneal dialysis, hemodialysis, DDKT, and LDKT. Any LDKT-activity (either LDKT-inquiry, work-up, or actual LDKT) at these time points was also recorded.

Process Evaluation Measures

To evaluate the implementation, a framework for implementation research (IR) was used. IR examines processes of installation of interventions in standard care to evaluate successful implementation. Proctor et al. [17] introduced a conceptual framework of eight outcomes to evaluate an implementation; acceptability, adoption, appropriateness, feasibility, fidelity, intervention costs, penetration, and sustainability. In this study we assessed the three outcomes that were most relevant to the project goals: feasibility, fidelity, and intervention costs. Other outcomes, such as acceptability, adoption and appropriateness were either already researched [18] or were deemed less relevant. Penetration and sustainability should be investigated after the adoption of the intervention in care-as-usual.

FEASIBILITY

Feasibility is the extent to which a new treatment can be successfully carried out in a new setting [17]. The concept of feasibility is often operationalized in recruitment and/or participation rates [19,20]. In this study, the participation rate is defined as the percentage of those who completed an intervention out of those approached. In the implementation project, educators registered every patient who had been approached; whether the patient wanted to receive the home-based educational intervention or not.

FIDELITY

Fidelity is defined as the degree to which an intervention was implemented as it was prescribed in the original protocol [21]. In this implementation project, protocol adherence measure was conducted by a third party by means of a telephone interview with every patient and one invitee who attended the group educational session. The patient and one invitee were asked for their opinion about the extent to which certain topics were discussed during the intervention. Patients and invitees were asked to answer 15 questions. Items were rated on a Likert scale (1-not at all to 5-very much). The protocol adherence score was the average score of these 15 items. The questionnaire was based on the protocol adherence measure questionnaire used in MST [22].

INTERVENTION COSTS

Intervention costs were assessed using the micro-costing approach. The eight teams were asked to register how many hours they spent per patient per home-based intervention including travel, how many patients they have approached, how many patients received the intake session, how many patients received the group educational session (considered a completed intervention), and how many hours the educators spent per year attending training, supervision and consortium meetings. Furthermore, we registered costs of training, traveling and consortium meetings. All these cost components were converted into a cost price per completed intervention. For the salary of the personnel, the 2020 collective labor agreement for Dutch personnel of university hospitals was used [23].

Statistical analysis

Analyses were conducted using IBM-SPSS Statistics version 25 (SPSS Inc., Chicago). Paired T-tests were used to explore differences between the pre- and post-measurement of the effect outcomes. Cohen's definition was used for the interpretations of the effect sizes: an effect size of 0.20 is considered a small effect, 0.50 medium and 0.80 a large effect [24].

To determine the relationship between effect and process evaluation outcomes on LKDT, a Cox-regression model was used to determine the hazard ratio for patients who received an intervention and had LDKT-activity as a result of the intervention. Patients who dropped-out before the second session due to a transplantation were not included in the model, as they did not complete the intervention trajectory. Covariates used in the model were post-interventional knowledge and communication, protocol adherence, and socio-demographic characteristics that have been shown to influence the access to LDKT: age, gender, ethnicity and religion [25,26]. An organization level was also introduced to take into account dependence between patients from the same hospital. Patients who were approached between September 2016 and December 2018 were included in the analysis. The follow-up period was up to 1st July 2020.

Results

Between 2016 and 2018, 812 patients were approached for the home-based educational intervention. Of these patients, 332 completed the intervention. Figure 1 shows the flow of these patients and Table 1 shows the characteristics.

Intervention effects

KNOWLEDGE & COMMUNICATION

In total, 272 patients and 630 invitees completed the questionnaires both before and after the intervention. There was a significant increase in KRT-knowledge for both the patients and the invitees in both hospital groups. Patients' and invitees' KRT-communication increased significantly in the university hospitals. In the regional hospitals the KRT-communication was high but did not change significantly. Table 2 shows these scores of the patients and invitees per hospital group.

3

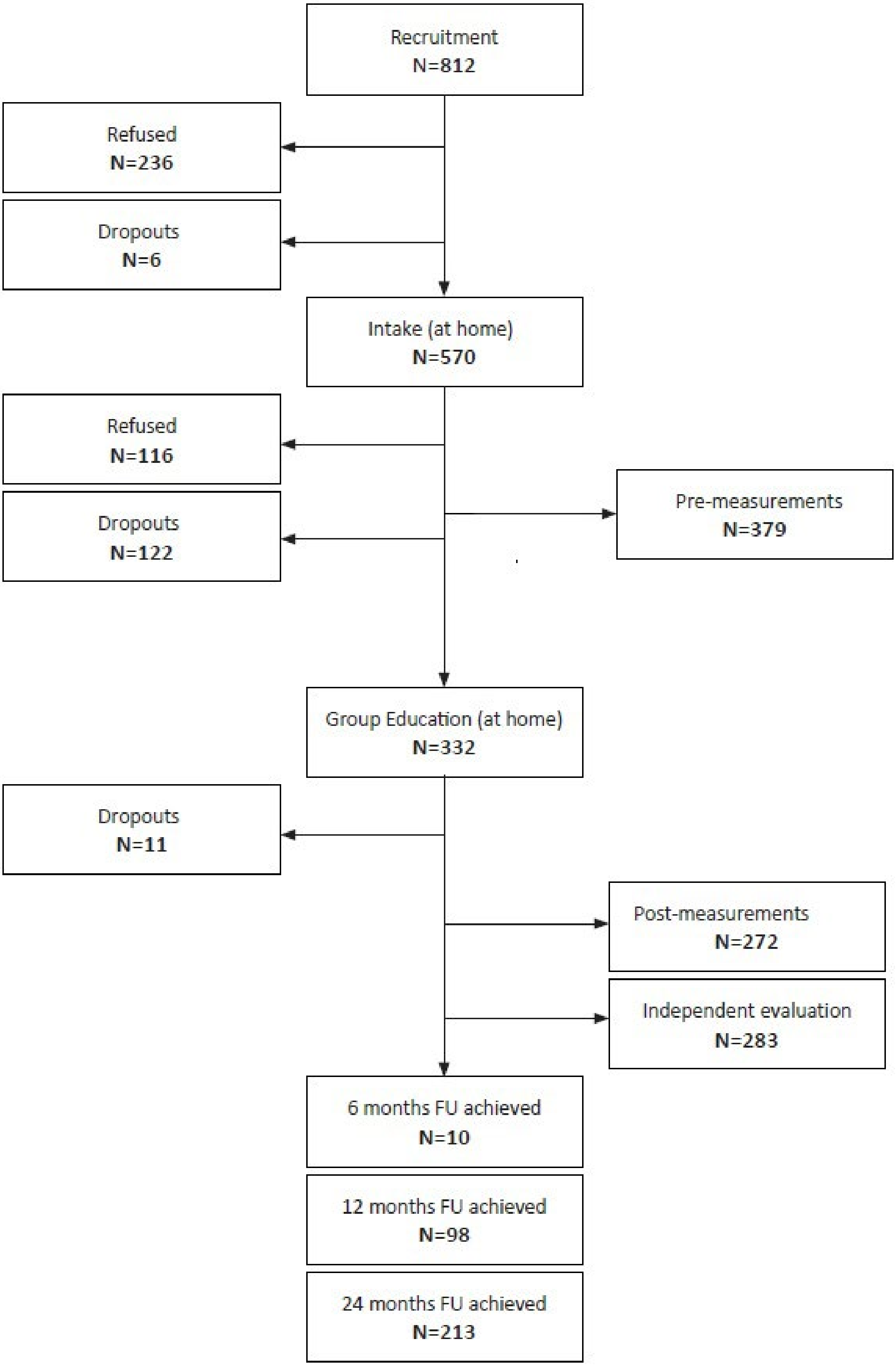

Figure 1 Flow-chart of the Kidney Team at Home implementation project.

Characteristics	Total N=332	University hospitals N=210	Regional hospitals N=122
Gender (M/F)	205/127	120/90	85/37
Mean age (SD)	55.2 (13.5)	52.90 (13.7)	59.05 (12.2)
Married or living together %	66.9%	61.4%	76.2%
Religious (Yes/No) %	40.1% / 59.9%	42.4% / 57.6%	36.1% / 63.9%
Ethnicity (Western / Non-Western) %	69.6% / 30.4%	70.5% / 29.5%	68.0% / 32.0%
Education level %*			
Low	12.6%	9.7%	17.1%
Average	68.9%	70.9%	65.8%
High	18.5%	19.4%	17.1%
Employment (full or part-time %)	125 (37.7%)	83 (39.5%)	42 (34.4%)
Treatment modality at baseline (%)			
No KRT	228 (68.4%)	113(53.8%)	115 (94.3%)
Hemodialysis	65 (19.7%)	61 (29.0%)	4 (3.3%)
Peritoneal dialysis	32 (9.9%)	32 (15.2%)	0 (0.0%)
Living with transplant	7 (2.1%)	4 (1.9%)	3 (2.4%)
History of transplantation N (%)	36 (10.8%)	30 (5.0%)	6 (4.9%)

* Education level was valued at three levels; Low = elementary school, Average = high school (+some college) and high = at least college degree

Table 1 Patient Characteristics

TREATMENT MODALITY

The follow-up time was a maximum of 24 months after the intervention date. 213 patients (64.2%) completed the follow-up time. 98 (29.5%) had their last follow-up moment at 12 months and 10 (3.0%) patients at 6 months, 11 (3.4%) patients dropped-out after the group education and before the first follow-up. Table 3 shows an overview of the treatment modality after the intervention.

Another 46 patients, who were either undergoing HD, PD or no treatment yet, were in preparation for a living donor transplantation at their final follow-up moment. In total, 129 (39%) of the 332 patients that completed the intervention had LDKT-activity (either in preparation or actual LDKT) at some point during their follow-up.

Measure (scale range)	N=	Pre-interventional score (Mean ± SD)	Post-interventional score (Mean ± SD)	Effect size	p
Patients – Knowledge (1-21)					
University Hospitals	180	14.45±4.50	18.62±2.18	1.18	<0.001
Regional Hospitals	92	11.94±5.43	17.08±3.81	1.09	<0.001
Patients – Communication (1-5)					
University Hospitals	179	4.07±0.92	4.22±0.86	0.17	0.028
Regional Hospitals	91	4.21±0.92	4.27±0.96	0.06	0.527
Invitees – Knowledge (1-21)					
University Hospitals	517	11.55±4.30	18.42±2.20	2.01	<0.001
Regional Hospitals	113	11.08±5.15	17.84±3.16	1.58	<0.001
Invitees – Communication (1-5)					
University Hospitals	509	3.64±0.90	3.95±0.87	0.35	<0.001
Regional Hospitals	112	4.10±0.82	4.18±0.84	0.10	0.373

Table 2 KRT-knowledge and KRT-communication – Patients & Invitees

Treatment Modality	University hospitals (N=210)	Regional hospitals (N=122)	Total (N=332)
No KRT	39 (18.6%)	59 (48.4%)	98 (29.5%)
Hemodialysis	38 (18.1%)	19 (15.6%)	57 (17.2%)
Peritoneal dialysis	27 (12.9%)	13 (10.7%)	40 (12.0%)
Living Donor Kidney T ransplantation after dialysis	23 (11.0%)	4 (3.3%)	27 (8.1%)
Pre-emptive Living Donor Kidney Transplantation	34 (16.2%)	15 (12.3%)	49 (14.8%)
Deceased donor transplantation	40 (19.0%)	4 (3.3%)	44 (13.3%)
Conservative treatment	0 (0.0%)	1 (0.8%)	1 (0.3%)
Died	4 (1.9%)	1 (0.8%)	5 (1.5%)
Drop-out	5 (2.4%)	6 (4.9%)	11 (3.3%)

Table 3 Follow-up (up to 24 months after the intervention)

Process Evaluation

FEASIBILITY

The participation rate was 40.9%: 332 of the 812 patients approached completed the intervention. Participation rates between the university hospitals and the regional hospitals differed substantially. The average participation rate of the university hospitals was 34.9% (210 out of 602), while in the regional hospitals the participation rate was 58.1% (122 out of 210). Sociodemographic variables such as employment, age, and ethnic background could not explain the differences in participation rate. Table 4 shows the participation rate per hospital.

Initially, 460 (57%) patients indicated that they wanted to receive an intervention. Six patients dropped out after the first contact moment, and 105 patients dropped-out after the first home visit. Most frequently reported reasons for drop out were "Do not want to receive an education" (23%), "received an DDKT in the meantime (11%)", and "not necessary anymore (8.6%)". For non-participators, the most reported reasons were: "do not want to receive education" (30%), and "do not find it necessary" (20%).

FIDELITY

In total 118 supervision meetings and 8 consortium meetings took place. The independent third party conducted 283 protocol adherence evaluations with patients and 250 with invitees. The overall average protocol adherence scores given by patients and invitees were 4.71 and 4.65, respectively (on a scale of 1-5).

INTERVENTION COSTS

On average educators spent 22.1 hours on each completed intervention. Incorporated in the total adjusted hours are the number of patients (1.43) that have to be approached in order to include one patient, and the proportion of completed interventions per patient included (0.59). In the Dutch context the cost per intervention amounts to €2500 - €3000. Table 5 shows a breakdown of the estimated number of hours per intervention. Sessions 1 and 2 are home visits and include travelling hours.

	Patients approached	Completed interventions	Participation rate
University hospital A	140	30	21.4%
University hospital B	143	60	42.0%
University hospital C	156	64	41.0%
University hospital D	163	56	34.3%
Total university hospitals	**602**	**210**	**34.9%**
Regional hospital A	52	28	53.8%
Regional hospital B	82	30	36.6%
Regional hospital C	33	23	70.0%
Regional hospital D	43	41	95.3%
Total regional hospitals	**210**	**122**	**58.1%**

Table 4 Participation rate per hospital.

Activity	Hours
Approaching patients	1.3
Home visit 1	4.4
Home visit 2 (both educators)	15.6
Training (both educators)	0.8
Total hours per intervention	**22.1**
Supervision (supervisor, consultant and both educators)	2.9
Multidisciplanary consultation	0.3
Total hours	**25.3**

Table 5 Breakdown of hours spent per intervention

Intervention effects & LDKT-activity

Figure 2 shows the cumulative hazard ratio of LDKT-activity. Post-interventional knowledge (HR = 1.267; CI = 1.134 - 1.416; $p<0.001$) and protocol adherence (HR = 2.328; CI = 1.102 - 4.917; p=.027) were positively related to the rate of LDKT, indicating that a higher protocol adherence increases the probability of LDKT-activity. A younger age (HR: 0.976; CI = 0.951 - 0.983; $p<0.001$) was also significantly related to the rate of LDKT-activity. Post-interventional communication was not related to the rate of LDKT-activity. Eventually, 222 patients completed both the post-measurement questionnaires and the independent evaluation.

Discussion

Conclusions

The favorable findings of this implementation project resulted in national uptake of the intervention in the Netherlands as of 2021. To our knowledge, this is the first time a psychosocial intervention has gone from bench to bedside and been implemented as part of standard care and reimbursement at a national level in a kidney replacement therapy program worldwide. Results demonstrate that the results of the previous studies are generalizable and replicable. Protocol adherence was high throughout the implementation project and the intervention comes with relatively low costs. The relationship between intervention effects and LDKT-activity shows support for the importance of the protocol and quality assessment.

Intervention Effect Evaluation

Results of the previous RCTs [9,10] were replicated in terms of increase in KRT-knowledge for all participating hospitals and KRT-communication in the university hospitals. Communication skills did not significantly improve for patients and invitees in the regional hospitals. This might be due to a ceiling effect, as both patients and invitees scored relatively high on the pre-measurement of the questionnaires. Patient's treatment choice after the intervention are also in line with the results of the previous studies. Among participants with follow-up data, 39% had LDKT-activity, which is comparable to the previous RCT in which 29 of 71 (40%) had LDKT-activity [9]. It is reassuring that the implementation project yields comparable results to those from the previous conducted studies. Results of a RCT are not always generalizable to a naturalistic setting, since a RCT often involves a homogenous population and is often conducted in a somewhat artificial environment, which differs from how the majority of patients react in practice [27].

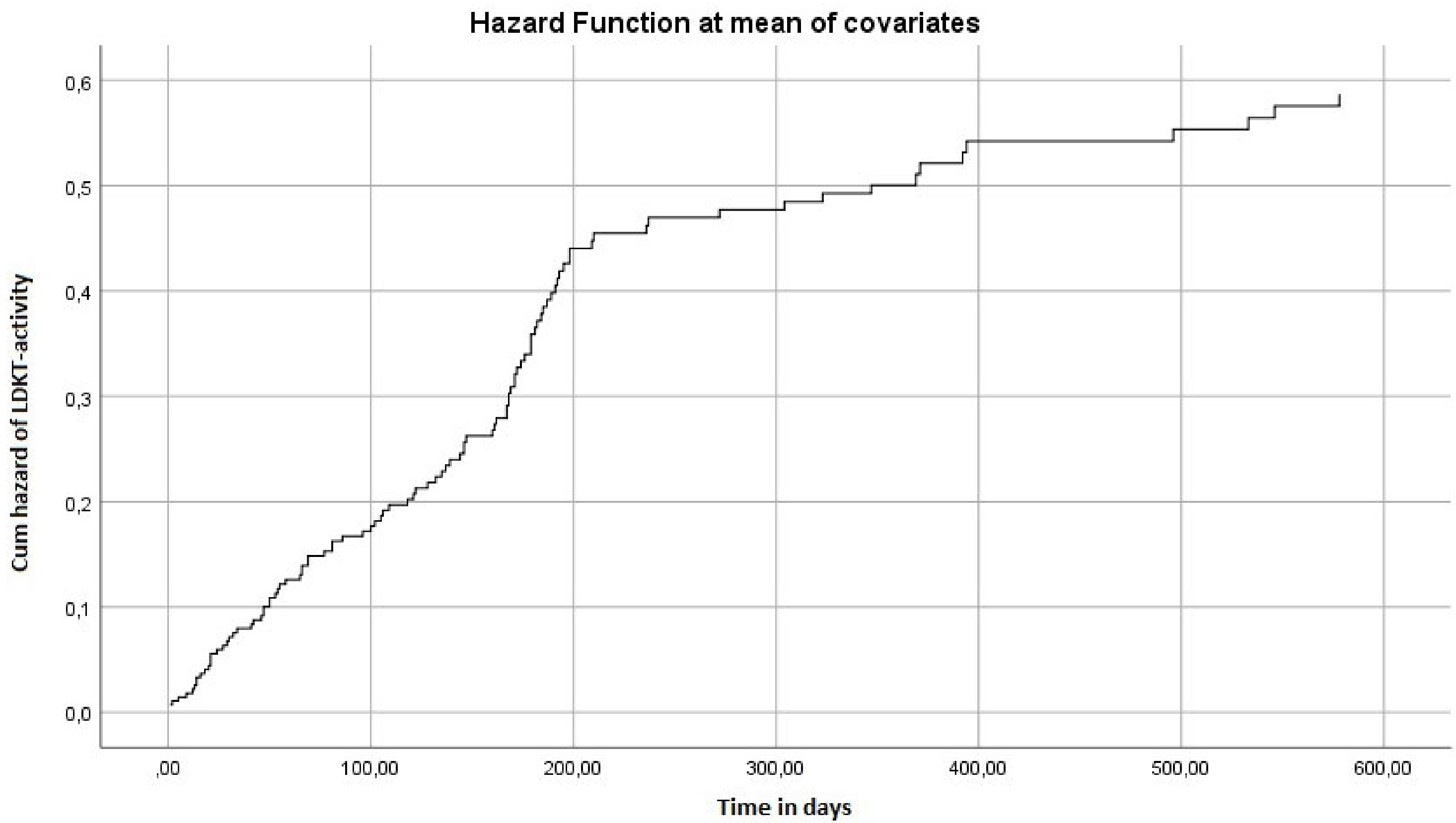

Figure 2 This graph depicts the cumulative hazard time-to-event data for the rate of LDKT-activity. Covariates used were: age, post-interventional knowledge, post-interventional communication, gender, religion and ethnicity (Western / non-Western).

However, in this study we found evidence supporting generalizability of findings that home-based education can successfully be implemented throughout the Netherlands.

Process Evaluation

The overall participation rate was relatively low (40.9%), which had several reasons. First, the project involved questionnaires and written informed consent, which is often a barrier to participate in a study [28]. Second, 122 patients dropped-out after the first home-visit, because some patients underwent a transplantation, were not eligible for transplantation or found a living donor candidate in the meantime. Initially, 57% of the patients had signed the informed consent form. Thus, the participation rate might be significantly higher when the intervention is implemented in standard care without research components.

There was variability among the hospitals in terms of the participation rate of patients. Among the university hospitals, participation rates ranged between 21.4% and 42.0%. In the regional hospital group this rate ranged from 36.6% to 95.3%. The difference between the hospital groups could be explained by the different target population. Contrary to university hospitals, regional hospitals only targeted pre-KRT patients who were more recently been diagnosed with CKD and are less familiar with the information on treatments and are probably more interested in an educational intervention. This is also reflected by the pre-interventional knowledge, which was lower in the pre-KRT group.

Another contributing factor for the variability of the participation rate might be a form of selection bias. The hospitals with the highest participation rate had the lowest number of patients approached. It is possible that the educators of these hospitals offered the intervention to patients who were most likely to participate. Unfortunately, data on the case load of each hospital were not available. Other important factors may be the timing, the method and the team member who approached the patients for participation.

With the micro-costing approach, it was estimated that in the Netherlands the cost for an intervention lies between €2500 and €3000. These costs include costs of the consortium meetings, supervision, training, interpreter and protocol adherence measure. The total costs were adjusted for the number of prematurely terminated interventions and first sessions, i.e. the cost estimation accounts for the number of patients that have to be approached to achieve a complete intervention. A cost-effectiveness analysis should reveal whether the intervention is cost-effective compared to standard care.

Protocol adherence was high throughout the project and the intervention costs were relatively low. Most attention must be paid to the recruitment of patients when implementing the intervention. Offering the intervention in an early disease stage might reduce the number of drop-outs.

Intervention effects & LDKT-activity

Multivariable analysis showed a significant relationship between the rate of LDKT-activity and age of the patients, post-interventional knowledge, and protocol adherence scores. This result indicates the importance of implementing the home-based educational intervention according to a standardized protocol and the clinical relevance of the quality assurance system. A higher age and lower knowledge are often associated with a reduced likelihood of LDKT [25,29].

Limitations

There are a few limitations to this study. First, the evaluation of the effect of the intervention on KRT-communication may have been suboptimal. The questionnaire consisted of three questions regarding communication and the post-intervention measurement was performed directly after the intervention. The main reason to administer the questionnaire on the same day as the intervention was to ensure a high response rate. However, it failed to capture the effects of the intervention on communication in the days and weeks after the intervention.

Second, cultural differences, differences in organization of the nephrology department, and difference in standard educational materials and current education practices might all have an influence on the intervention effects. Hence, one needs to be cautious drawing conclusions while comparing the different hospitals with one another.

Third, it is difficult to draw conclusions on the differences in uptake across the hospitals. The variability in the participation rate is interesting from an implementation point of view. However, there is very little data on non-participants, nor are data on active hospital files and data on comorbidities of patients available. Moreover, it is difficult to determine the role of individual healthcare professionals during the initial approach, the hospitals and the timing and placement in the care pathway.

Practical implications

Addressing disparities in LDKT has been highlighted as a research priority [30]. Here, we showed that the intervention can also be implemented in multiple regions and different types of hospitals while maintaining impact and quality. This approach should be assessed in other countries to further support generalizability. In the United States several RCTs have been performed regarding home-based education for CKD-patients [8,31]. Also in the UK, initiatives to address disparities have been undertaken with home-based education [32-34]. The results of these single-center studies were favorable.

A set of recommendations emerged from this study. We recommend that the quality assurance structure of regular supervision and the independent evaluation should remain an integral part of the intervention. It safeguards the quality of the intervention at small incremental costs, justified by the fact that protocol adherence is associated with a higher probability of LDKT-activity. In addition, we recommend that the home-based educational intervention should be integrated in the nephrology guidelines, offering the intervention before patients start with any form of KRT, if possible [35]. In this way, patients receive complete information on all types of KRT, so they are fully informed prior to decision-making regarding their treatment. Importantly, a timely educational intervention can also facilitate preemptive transplantation, which avoids the harmful effects of dialysis in terms of morbidity, mortality and deterioration of the quality of life, and is associated with better patient and graft survival than transplantation after a period of dialysis [36-39].

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CHAPTER 4

A dynamic Markov model to assess the cost-effectiveness of the Kidney Team at Home intervention in the Netherlands

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Abstract

Objectives

The Kidney Team at Home program is an educational intervention aimed at patients with chronic kidney disease to assist them in their choice for kidney replacement therapy. Previous studies have shown that the intervention results in an increase in knowledge and communication on kidney replacement therapy, and eventually in an increase in the number of living donor kidney transplantations. The study assesses the cost-effectiveness of the intervention compared to standard care.

Methods

A dynamic probabilistic Markov model was used to estimate the monetary and health benefits of the intervention in the Netherlands over 10 years. Data on costs and health-related quality of life were derived from the literature. Transition probabilities, prevalence and incidence rates were calculated using a large national database. An optimistic and a pessimistic implementation scenario were compared to a base case scenario with standard care.

Results

In both the optimistic and pessimistic scenario, the intervention is cost-effective and dominant compared to standard-care: savings were €108,681,985 and €51,770,060 and the benefits were 1382 and 695 QALYs respectively.

Conclusions

The superior cost-effectiveness of the intervention is caused by the superior health effects and the reduction of costs associated with transplantation, and the relatively small incremental costs of the intervention. The favorable findings of this implementation project resulted in national uptake of the intervention in the Netherlands as of 2021. This is the first time a psychosocial intervention has been implemented as part of standard care in a kidney replacement therapy program worldwide.

Introduction

Patients with chronic kidney disease (CKD) need kidney replacement therapy (KRT) to survive. There are four major types of KRT: Hemodialysis (HD); Peritoneal dialysis (PD); Deceased donor kidney transplantation (DDKT); Living donor kidney transplantation (LDKT).

Hemodialysis and peritoneal dialysis are associated with impaired quality of life and a high mortality. The median survival for patients on dialysis is 5 years [1], while the 5-year patient-survival after transplantation ranges from 86.1% to 95% [2]. Transplantation is the optimal treatment for most patients in terms of survival and quality of life. Because of a continuous scarcity of deceased donor kidneys, patients need to be on a wait list to be considered for deceased donor kidney transplantation. The average wait time for a kidney of a deceased donor in The Netherlands is 3.5 years, from the first day of dialysis [3]. For a living kidney donor transplantation, patients have to find a living kidney donor themselves.

A LDKT is the best treatment option in terms of quality of life and survival [4,5]. However, there is inequality in access to LDKT for patients with CKD [6-8]. In particular, non-Western patients were less likely to undergo a LDKT [6,9,10]. To address this inequality, a home-based educational intervention has been developed in the United States, resulting in better knowledge on LDKT, an increase in the willingness to discuss LDKT with others, and an increase in LDKT-rates [11]. As a result of these findings, two randomized controlled trials (RCTs) testing the effectiveness of home-based educational interventions were conducted in The Netherlands [12,13].

Despite differences in the patient population, these studies showed comparable results as the RCT in the USA: an increase in knowledge on all KRTs, better communication on LDKT, and an increase in LDKT-rates. These positive results led to an implementation project in which the Kidney Team at Home program was implemented on a larger scale at 8 hospitals in 4 regions of the Netherlands [14]. The goal of this program was to assess whether the results of the previous studies could be replicated when the intervention was widely implemented in daily practice. This implementation project was conducted between 2016 and 2020. Replication of the RCT results would support nationwide deployment of the program as standard care. Demonstrating cost-effectiveness of the program could support further adoption of the program in standard care.

Augmenting standard care with the Kidney Team at Home program will increase costs and should be weighed against the health benefits of the program. Even more, because CKD is a costly disease. Per patient, the costs of dialysis in the Netherlands per year are between €80,000 and €120,000 and the cost of a single transplantation is around €80,000 [15]. As healthcare costs in the Netherlands are rising [16], there is a need to assess whether these additional costs are well spent. The present study therefore assesses the cost-effectiveness of the effects of the Kidney Team at Home intervention on the KRT-program compared to standard care.

Methods

Markov model

The Markov model used for the cost-effectiveness analysis has a similar structure as the model from De Wit et al. (1998) [17]. A Markov modelling technique is applicable because the decision problem involves risk that is continuous over time, the timing of events is important, and events may happen more than once [18]. Within a Markov simulation, the time horizon of the study is divided into a number of discrete time periods, the so-called Markov cycles. A Markov process is based on the principle that patients are always in a certain disease state and that they can change between disease states once during each cycle. By assigning cost and effects to each disease state and keeping track of the time patients remained in each disease state, long-term cost and effects can be estimated.

A simplified graphic representation of the Markov model showing only the treatment categories rather than all the individual Markov states is presented in Figure 1. It is a so-called dynamic Markov model, as incident patients are added to the cohort and enter the model each cycle (inflow). The size of the inflow per month is based on epidemiological predictions as described in the paragraph "Incidence rates and prevalence". After entering the model, patients can start on various treatment options. From there they can move between different treatment modalities until they die (outflow).

Markov States

The Markov states were based on the treatments currently available in the Netherlands. These were: Center Hemodialysis (CHD), Home Hemodialysis (HHD), Continuous Ambulatory Peritoneal Dialysis (CAPD), Continuous Cyclic Peritoneal dialysis (CCPD), Deceased Donor Kidney Transplantation (DDKT) and Living Donor Kidney Transplantation (LDKT). Dialysis treatment was divided into these four treatment modalities and transplantation into two since the expected transition probabilities may differ for each of them. Palliative care or conservative treatment were not included in the model, as it is not expected that the intervention will lead to a shift in the number of patients on these treatment options. Note that Figure 1 is a simplified version of the model and does not show these refined differences in treatment modalities.

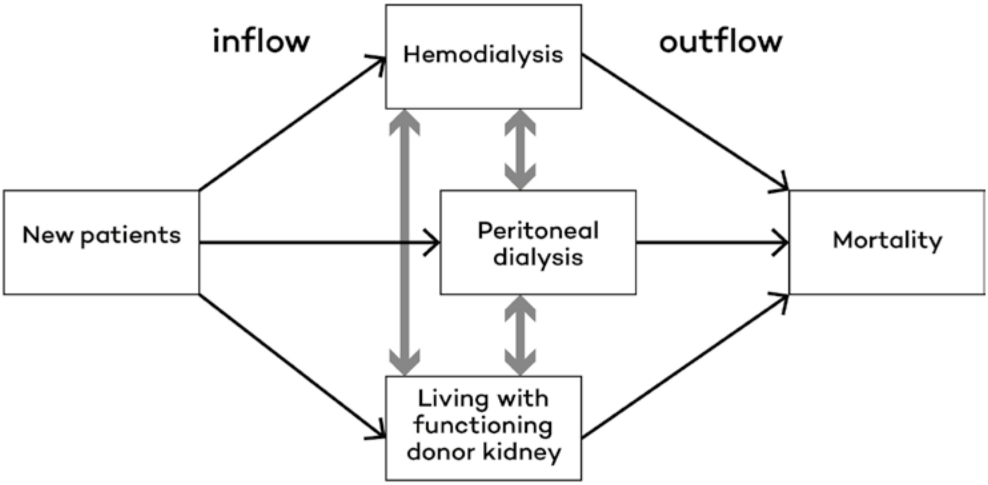

Figure 1 Simplified graphic representation of the Markov model.

The transition probabilities between states in the model are not constant over time. The largest differences are between the first year and subsequent years. Therefore, we defined separate Markov states for the 1st year of treatment and for subsequent years of treatment within a specific modality. Incident patients that enter the model and prevalent patients that switch between treatment modalities are assigned to the 1st year Markov states, whereas patients that spend more than one year in any one Markov state are transferred to the subsequent year's state of the same treatment modality. The cycle time of the model is one month, and the model was run for 120 cycles, i.e. 10 years.

Patient cohort

New patients flow into the model at the start of each cycle. These new patients are added to the number of patients that were already present in the model. These prevalent patients in the model represent the total Dutch CKD-population, as of January 1st 2018. Table 1 shows the demographic characteristics of that starting population, which is based on data of the Dutch Renal Registry 'Renine' [19]. Patients were divided into 6 different groups: age 0-44 / 45-64 / 65+ combined with being diabetic/non-diabetic.

Baseline Characteristics	Mean (SD)
Age	61.3 (15.7)
Male / Female (%)	61 / 39
Diabetes / Non-diabetes (%)	15 / 85
Treatment Modality	N = 16,917
Center Hemodialysis	5,516
Home Hemodialysis	238
CAPD	402
CCPD	517
DDKT	4,817
LDKT	5,427

Table 1 Baseline characteristics of prevalent patients on 1-1-2018.

Parameters and data sources

COSTS

Costs for the various KRT-treatments were retrieved from a Dutch study on the average annual healthcare costs for Dutch patients with a claim for dialysis or a kidney transplantation [15]. These costs include costs made by patients unrelated to KRT, such as costs related to complications or comorbidities. This cost study was based on the national database of all Dutch health insurance companies of the years 2012 to 2014 [20]. This detailed database holds the records of 99% of all Dutch citizens. The costs per KRT treatment are distinguished according to the following healthcare components: hospital care (in- and outpatient), primary care, mental health care, medication, medical devices, transportation, health care incurred abroad and claims of other types of health care. Hospital costs are subdivided in costs related to KRT, including costs of the dialysis procedure (including surgery for dialysis access), the kidney transplant (including donor expenses) as well as the preliminary and post-transplantation care. In the model, the costs per KRT treatment, and thus per Markov state in the model, were discounted at a rate of 4% per year which is in line with the Dutch guidelines for economic evaluations [21]. Intervention costs were estimated to be €2811 [22]. This estimation was made based on the implementation project with a micro-costing approach [14]. All baseline costs were expressed in 2018 Euros.

OUTCOMES (EFFECTS)

The effects were expressed as Quality Adjusted Life Years (QALYs). These 'utilities' used for this economic evaluation, were obtained from a systematic review and meta-analysis by Liem et al [23]. This systematic review extracted utilities from English studies that reported the EQ-5D, time-trade off and standard gamble values of CKD-patients. Mean utilities were calculated using random-effects models. Because of the preference of the Dutch health care institute for utilities estimated using the EQ-5D [21], the reported mean EQ-5D values and confidence intervals of the systematic review were used in the analysis. Since effects of cost-utility analyses are preferably expressed in Quality Adjusted Life Years (QALYs), QALYs were derived from these utility scores. In line with the Dutch guidelines QALYs were discounted at a rate of 1.5% per year [21].

TRANSITION PROBABILITIES

The rate patients transition from one state to another, the transition probabilities, were calculated using empirical data from the Dutch Renal Registry 'Renine' [19]. The 'Renine' database contains information concerning all Dutch patients who undergo a non-experimental form of KRT. This database contains complete patient histories regarding treatment modalities, primary diagnosis and background variables such as age for every CKD patient in the Netherlands. The first-year probabilities were based on data regarding the first 12 months of registration of the patients. The annual transition probabilities for subsequent years were based on the pooled annual event rates for the 2nd, 3rd and 4th years of the data.

TREATMENT INCIDENCE AND PREVALENCE

In order to estimate the incidence rates for the following ten years, parametric functions were estimated for each of the six patient groups (age 0-44 / 45-64 / 65+ and diabetic/non-diabetic) and the six treatment modalities. These 36 functions (6 mutually exclusive groups x 6 treatment options) were fitted using linear and non-linear regression analysis on the annual number of incident patients in the 'Renine' database from January 1st 2008 to December 31st 2017. The resulting predicted annual incidence rates were then transformed to monthly incidence rates to match the cycle time of the model. These monthly incidence rates represents the monthly inflow of new patients into the model. In some cases, there was insufficient data available to model incidence using regression techniques: i.e. in some cases almost none of the patients start KRT with a specific treatment, such as 65+ diabetic patients starting KRT with DDKT. In these cases the last observed value was carried forward. The baseline prevalence was the observed prevalence on January 1st 2018. In other words, the model uses the data on prevalence from

January 1 2018 as the initial distribution of patients over the health states and age groups. An overview of all parameters is presented in Table 2.

Dimension	Base case value	SE	Distr. For PSA
Health state utilities [23]			
CHD	0.56	0.033	Beta
HHD	0.56	0.033	Beta
CAPD	0.58	0.043	Beta
CCPD	0.58	0.043	Beta
DDKT	0.81	0.046	Beta
LDKT	0.81	0.046	Beta
Costs of intervention	€2811	281	Gamma
Therapy costs per year [15]			
Costs of CHD (1y-2y+)	€98,914	367	Gamma
Costs of HHD (1y-2y+)	€92,967	958	Gamma
Costs of CAPD (1y-2y+)	€82,824	1935	Gamma
Costs of CCPD (1y-2y+)	€96,043	1124	Gamma
Costs of DDKT 1y	€106,210	1009	Gamma
Costs of DDKT 2y+	€23,212	162	Gamma
Costs of LDKT 1y	€78,297	980	Gamma
Costs of LDKT 2y+	€22,716	149	Gamma

Table 2 Parameter values and distributions.

Base case scenario

In the 'base case scenario', patients receive standard care: patients visiting the outpatient clinic receive standard education about the various modalities of KRT from a (transplant) nephrologist. Note that in this scenario, living donation is encouraged, as it is common that nephrologists ask if the patient has a living donor candidate in their social network and they will encourage the patient to discuss this with their loved ones. In 2017, 552 LDKTs were conducted in The Netherlands, and a parametric function based on the years 2008 to 2017 was used to estimate number of the LDKTs in 2018 and subsequent years.

Kidney Team at Home scenario

Patients receiving the Kidney Team at Home intervention, receive two home visits: an intake and group education. The aim of the first home visit for the educators is to familiarize themselves with the social network of the patient and prepare for the second session. In the second session, the group educational intervention took place. The content and process of the intervention has been described elsewhere in more detail [24]. Patients who are eligible for the intervention are >18 years of age and eligible for all KRT-options. Based on figures of the implementation study [25] we estimated that 35% of all incident patients would be eligible for the intervention. Results from the implementation project show that 42.5% of the eligible patients completed the group education. Of the patients who completed the intervention, approximately 18% underwent a LDKT within the two-year follow-up and another 17% was in preparation for a LDKT. Approximately 2/3 of these patients underwent a LDKT as the first form of KRT, a pre-emptive transplantation. These parameters were used in the model to estimate the number of incident patients receiving the intervention and the effect size of the intervention.

In the Kidney Team at Home scenario, the effect of the intervention was evaluated in the model. Quality of life in terms of 'utilities values' and costs associated with the different treatment modalities (the Markov states) were not expected to differ between patients receiving the intervention and those who do not. Thus, for example, costs of dialysis remain the same, irrespective of receiving the Kidney Team at Home intervention. The cost of the intervention is added separately. In the model, the effects of the intervention are only expressed as an increase in LDKT, both pre-emptive LDKT (incident patients that come into the model in the LDKT health state) and LDKT after a period of dialysis. The impact of the intervention is therefore solely reflected in the incidence rates and transition probabilities. Transition probabilities and incidence rates to the other health states are proportionally lowered as the LDKT-rates increases. The effect of the intervention is built into the model after the first 6 cycles (six months), which coincides with the moment the first effect was observed in the first RCT [12].

Analysis

In addition to a deterministic analysis, the model includes probabilistic sensitivity analysis using Monte Carlo simulation. This means that not only the mean number of patients per year per treatment modality were estimated, but also the uncertainty surrounding those mean numbers of patients. Consequently, all model parameters (e.g. the transition probabilities) were used in the model as distributions rather than

point estimates. In the Monte Carlo simulation, the model was evaluated a large number of times (5,000 times). For each evaluation, the model parameters were drawn from their distributions. This way all uncertainty from the model parameters was taken into account and reported in the results. The study was approved by the institutional review board of the Erasmus MC (MEC-2016-496).
Health utilities were assigned a beta distribution, costs were assigned a gamma distribution. Dirichlet distributions were estimated for all transition probabilities based on annual count data. For the effect size (number of extra transplantations as a result of the intervention) a standard error of 20% was assumed to account for uncertainty. For the intervention costs a standard error of 10% was used.
Compared to the base case scenario, two scenario analysis were conducted concerning the effect size. First, an optimistic scenario where we assume that 35% of the patients that received an intervention will end up undergoing a LDKT (scenario 1). Second, a pessimistic scenario where we assume that 18% of the patients undergoing a LDKT (scenario 2). These numbers were estimated based on the results of the implementation project [14].
Results of the cost-effectiveness analysis (optimistic scenario vs base case scenario, and pessimistic scenario vs base case scenario) were represented as incremental cost-effectiveness ratios (ICER).

Data analysis

The model was implemented in Excel 2016 (Microsoft Corp., Redmond). IBM-SPSS Statistics version 25 (SPSS Inc., Chicago) was used to estimate the functions of the incidence rates.

Results

Results of the deterministic and probabilistic sensitivity analysis scenarios after ten years are shown in Table 3. It shows that the Kidney Team at Home 'dominates' the base case (i.e., it results in more QALYs at lower costs) over a time horizon of 10 years. Table 4 shows the predicted costs and QALYs of the base case scenario per year, which means that the second year is not a cumulative result of the first and second year, but only represents the costs and QALYs of all patients in the model in the second year. Table 5 and 6 represent the results of the optimistic and pessimistic scenario, respectively. The results show that the costs of the base case scenario are lower than the optimistic and pessimistic scenario in the first year, but is higher in subsequent years compared to both scenarios. The QALYs are higher for the Kidney Team at Home scenarios from the first year onwards.

	Deterministic			Probabilistic		
Outcome	**Costs**	**QALYs**	**ICER[a]**	**Costs (CI)**	**QALYs (CI)**	**ICER[a]**
Basecase	€7,836,028,014	136,927		€7,881,810,446 (€7,503,847,711 - €8,273,443,343)	135,960 (130,384 - 141,328)	
Scenario 1 (Optimistic)	€7,728,204,065	138,335	-76,559	€7,773,128,461 (€7,404,698,547 - €8,158,246,557)	137,341 (131,661 - 142,934)	-78,666
Scenario 2 (Pessimistic)	€7,773,028,092	137,779	-73,954	€7,830,803,911 (€7,456,069,881 - €8,218,423,115)	136,630 (130,996 - 142,162)	-74,498

[a] Compared to basecase

Table 3 Deterministic and probabilistic results of the cost-effectiveness analyses.

Base case	Costs					QALYs				
	Mean	[95% CI]				Mean	[95% CI]			
12mo	€ 889,847,159	[	€ 883,046,634	;	€ 896,790,066]	12,169	[	11,741	;	12,553]
24mo	€ 878,195,028	[	€ 861,623,929	;	€ 895,772,638]	12,526	[	12,083	;	12,929]
36mo	€ 855,140,830	[	€ 830,153,319	;	€ 881,424,105]	12,865	[	12,396	;	13,301]
48mo	€ 828,799,465	[	€ 796,411,726	;	€ 862,720,881]	13,188	[	12,686	;	13,670]
60mo	€ 801,884,676	[	€ 763,279,030	;	€ 842,124,977]	13,497	[	12,951	;	14,019]
72mo	€ 775,347,290	[	€ 731,413,386	;	€ 821,316,907]	13,793	[	13,207	;	14,356]
84mo	€ 749,548,362	[	€ 700,947,659	;	€ 799,743,021]	14,078	[	13,445	;	14,689]
96mo	€ 724,639,297	[	€ 672,367,167	;	€ 778,997,109]	14,353	[	13,672	;	15,007]
108mo	€ 700,687,584	[	€ 645,302,303	;	€ 758,520,920]	14,618	[	13,891	;	15,319]
120mo	€ 677,720,755	[	€ 619,649,947	;	€ 738,505,236]	14,874	[	14,101	;	15,624]

Table 4 Discounted costs and QALYs Basecase.

Optimistic	Costs			QALYs		
	Mean	[95% CI	]	Mean	[95% CI	]
12mo	€ 890,275,006	[€ 883,513,448 ;	€ 897,238,767]	12,172	[11,743 ;	12,557]
24mo	€ 875,710,486	[€ 859,323,557 ;	€ 892,900,803]	12,553	[12,107 ;	12,959]
36mo	€ 848,860,963	[€ 824,311,730 ;	€ 874,646,089]	12,919	[12,447 ;	13,364]
48mo	€ 819,139,714	[€ 787,581,230 ;	€ 852,575,480]	13,272	[12,755 ;	13,762]
60mo	€ 789,566,213	[€ 751,704,041 ;	€ 829,212,434]	13,613	[13,061 ;	14,152]
72mo	€ 761,109,269	[€ 718,245,901 ;	€ 805,813,440]	13,943	[13,345 ;	14,529]
84mo	€ 734,060,475	[€ 686,816,062 ;	€ 783,645,314]	14,262	[13,613 ;	14,892]
96mo	€ 708,479,670	[€ 657,445,420 ;	€ 761,379,425]	14,572	[13,868 ;	15,244]
108mo	€ 684,341,404	[€ 629,900,823 ;	€ 740,523,221]	14,872	[14,119 ;	15,595]
120mo	€ 661,585,261	[€ 604,605,948 ;	€ 720,289,001]	15,163	[14,363 ;	15,939]

Table 5 Discounted Costs and QALYs for Scenario 1 (optimistic).

Pessimistic	Costs		QALYs	
	Mean	[95% CI]	Mean	[95% CI]
12mo	€ 890,448,971	[€ 883,617,657 ; € 897,315,478]	12,170	[11,757 ; 12,565]
24mo	€ 877,319,806	[€ 860,732,312 ; € 894,275,424]	12,539	[12,104 ; 12,954]
36mo	€ 852,355,786	[€ 827,257,505 ; € 878,168,895]	12,891	[12,421 ; 13,343]
48mo	€ 824,317,626	[€ 792,049,124 ; € 857,697,413]	13,229	[12,725 ; 13,717]
60mo	€ 796,068,004	[€ 757,487,125 ; € 835,880,126]	13,553	[13,008 ; 14,089]
72mo	€ 768,563,807	[€ 724,792,614 ; € 813,911,486]	13,866	[13,277 ; 14,450]
84mo	€ 742,129,718	[€ 694,013,699 ; € 791,708,245]	14,168	[13,531 ; 14,797]
96mo	€ 716,870,513	[€ 664,759,902 ; € 770,435,770]	14,459	[13,772 ; 15,132]
108mo	€ 692,806,806	[€ 637,797,873 ; € 749,999,247]	14,741	[14,005 ; 15,462]
120mo	€ 669,922,874	[€ 612,277,467 ; € 730,267,126]	15,014	[14,225 ; 15,788]

Table 6 Discounted Costs and QALYs for Scenario 2 (pessimistic).

Incremental cost-effectiveness ratios: The deterministic ICERs are € -76.559 and € -73.954 for the base case compared to the optimistic and pessimistic scenario, respectively. The following Tables (7-8) present the probabilistic ICERs per year while comparing the base case to the Kidney Team at Home scenarios. In line with the costs and effects of Table 4-6, Table 7 shows that, in both the optimistic scenario and the pessimistic scenario, the first year yields additional costs and approximately the same number of QALYs. In the subsequent years, not only does the intervention results in more QALYs, but also produces monetary benefits, resulting in negative values for the ICERs. Figure 2 shows the cost-effectiveness plane of the base case compared to the optimistic scenario for the different years, which all appear at the bottom-right quadrant of the figure indicating dominance. The crosses represent point estimates of the ICERs and expand as time increases due to increasing uncertainty. The triangles represent the mean ICERs of the particular year.

Base case vs Optimistic				
		Δ Cost	Δ QALY	ICER
12mo	€	427,847	3	122,649
24mo	€	-2,484,542	26	- 94,584
36mo	€	-6,279,867	54	-115,633
48mo	€	-9,659,752	85	-114,179
60mo	€	-12,318,463	117	-105,617
72mo	€	-14,238,020	150	-94,942
84mo	€	-15,487,887	184	-84,077
96mo	€	-16,159,627	219	-73,783
108mo	€	-16,346,180	254	-64,341
120mo	€	-16,135,495	289	-55,829
Totaal	€	-108,681,985	1,382	-78,666

Table 7 Incremental cost-effectiveness ratio. Base Case versus scenario 1 (optimistic).

Base case vs Pessimistic				
		Δ Cost	Δ QALY	ICER
12mo	€	601,628	2	344,565
24mo	€	-882,334	13	-66,787
36mo	€	-2,811,232	27	-102,873
48mo	€	-4,531,139	43	-106,425
60mo	€	-5,889,038	59	-100,334
72mo	€	-6,876,749	75	-91,132
84mo	€	-7,529,722	93	-81,249
96mo	€	-7,894,182	110	-71,660
108mo	€	-8,016,672	128	-62,749
120mo	€	-7,940,620	145	-54,645
Totaal	**€**	**-51,770,060**	**695**	**-74,498**

Table 8 Incremental cost-effectiveness ratio. Base Case versus Scenario 2 (pessimistic).

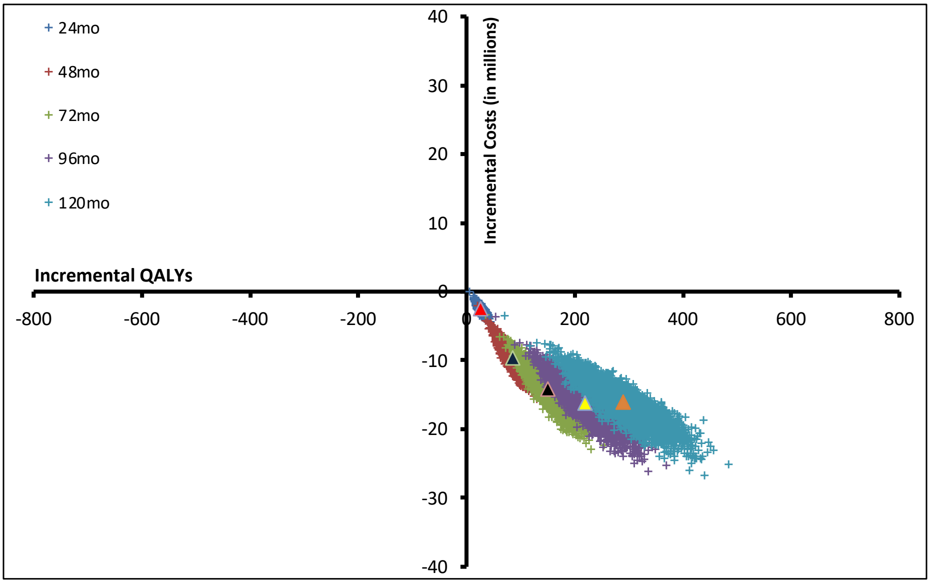

Figure 2 Graphic representation of the mean difference in incremental costs and incremental effects when comparing base case scenario to the optimistic KTAH scenario using 5000 simulations. The crosses represent point estimates of the ICERs. The triangles represent the mean ICERs of the particular year.

Conclusions

The Kidney Team at Home has been shown to be highly cost-effective compared to standard care. This is caused by the superior effects and the reduction of costs associated with transplantation, which is propelled by the intervention at small incremental costs. This is caused by the superior health effects and the reduction of costs associated with transplantation, and the relatively small incremental costs of the intervention. The favorable results of this analysis resulted in national uptake of the intervention in standard care. To our knowledge, this is the first time a psychosocial intervention has been implemented as part of standard care in a kidney replacement therapy program worldwide.

Discussion

The present study shows that the Kidney Team at Home intervention is cost-effective compared to standard-care. The results show that both Kidney Team at Home scenarios are superior to standard-care: the intervention 'dominates' standard-care with a higher number of QALYs and lower costs. From the first year onwards, the intervention saves costs while gaining health in terms of quality of life. In the Netherlands, with approximately 17.4 million inhabitants, the optimistic scenario and pessimistic scenario predict a cost saving of €107,823,949 and €62,999,923 respectively and a gain of 1,408 QALYs and 852 QALYs over the next 10 years for the total KRT-program, compared to standard care.

Our findings are consistent with other studies concerning the cost-effectiveness of KRT-programs [17,26,27]. These studies found a large increase in health effects while saving costs when the number of LDKTs increased. We showed that our home-based educational program is a cost-effective strategy to educate patients and reduce the inequality in access to LDKTs. The incremental costs of the intervention are small compared to the costs of the treatment modalities. For instance, the cost per intervention is about 3% of the cost of one-year dialysis.

The effectiveness of the intervention (i.e. the number of additional LDKTs due to the Kidney Team at Home intervention) impacts the ICER, as is seen in the difference in QALYs between the optimistic and pessimistic scenario in Tables 5 and 6. It is therefore important to safeguard the quality and hence the effects of the intervention. Indeed, a lot attention was given to maintaining the quality of the intervention during the implementation project, by having regular supervision, peer-to-peer meetings and training sessions. The costs of this quality assurance were also included in the costs of the intervention. Given that the influence of the costs on the ICER is less than the effect of the quality of the intervention, it seems justified to support this quality assurance system.

IMPLICATIONS

Our findings suggest that the demand for the various treatment options for CKD may change. More LDKTs may lead to a drop of the number of patients needing dialysis. This might influence the demand for dialysis centers and transplantation facilities. Furthermore, it can be expected that patients who are unable to find a living donor in the program, will nevertheless profit from an increase in the number of LDKTs, as the total demand for deceased donor kidney reduces. The increase in living donation may lower the time spent on the waiting list for a DDKT. Future research should investigate whether it is indeed possible to reduce the number of dialysis centers and their associated costs.

Our cost effectiveness results support the request for national funding of the Kidney Team at Home. The favorable results of this analysis resulted in national uptake of the intervention in standard care in the Netherlands. There is little reason to think that the conclusions from this study will be much different for other countries with a developed health care system, as the effectiveness of home-based education has been demonstrated elsewhere and previously conducted cost-effectiveness analyses of KRT-programs. Some countries are already investigating the implementation of home-based education, most notably in the UK were several initiatives have been undertaken to address disparities in access to LDKT. The results of these single-center studies were favorable. We therefore recommend that other countries should also investigate implementation of the Kidney Team at Home intervention.

STRENGTHS AND LIMITATIONS

There are certain strengths of our study. First, the parameters were derived from large datasets. The transition probabilities and incidence rates were calculated using the database of the Dutch Renal Registry 'Renine', containing virtually all patients receiving KRT between 2000-2018. The costs of the different health states were based on a study that used claims data of adult patients with at least one health insurance claim related to KRT in the period 2012-2014. The authors of this cost study stated that the number of incident and prevalent patients on KRT identified by the claims data were comparable to those identified by 'Renine', indicating that there is an overlap in patient population used for calculating the costs and transition probabilities. Because these parameters were based on large datasets, the uncertainty surrounding the ICERs is relatively small, as seen in the cost-effectiveness plane. This relative small degree of uncertainty is also the reason why we did not present one-way sensitivity analyses. The standard errors of the point estimates were relatively low (see: Table 2), which resulted in a minimal range of the ICERs. We therefore decided not to include the results of these analyses in this study.

There are also limitations of our study. First, the utility values were derived from the literature published in 2008 [23]. Another systematic review and meta-analysis was also available [28], however, this study only incorporated one study that used the EQ-5D among patients living with a kidney transplant. Most of the utility values reported in the study were derived from the SF-36, and they had to impute standard deviations, which may have affected their results [28]. Therefore, the systematic review of Liem et al. seemed the better choice for this economic evaluation [23].

Second, some parameters were derived from the implementation project, such as the percentage of patients who are willing to receive the home-based intervention (42.5%). If implemented in standard-care, this percentage will likely be higher as the participation rate in studies are often lower than in the real-life setting, partly because of questionnaires and informed consent forms which were part of the implementation project [29]. In other words, the used participation rate may be an underestimation, which suggests that the ICER is even more favorable.

Finally, one needs to keep in mind that the accuracy of the model predictions depends on the accuracy of the transition probabilities and the model structure. Therefore, unexpected shifts in the trends of transition probabilities can have a profound impact on the accuracy of the forecasts by the model. For example, a change to the donor registration or allocation system (such as from opt-out to opt-in), could increase the number of deceased donor kidneys substantially [30]. This could have an effect on the willingness to donate a living donor kidney, as the urgency to 'save' a patient from dialysis may reduce. Consequently, the transition probabilities would change for and to every health state. In addition, the consequences of the Covid-19 pandemic has a large influence on the care of CKD-patients. Hence, the transplantation program had been temporarily put on hold, and at the time of writing, the number of transplantation is still significant lower than before the pandemic [31,32].

NEXT STEPS

The model was designed in such a way that it can easily be extended to allow for different endpoints. For example, updating the number of available deceased donor kidneys due to the new Dutch opt-out donor law, will allow the assessment of predicted prevalence of this policy change.

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CHAPTER 5

Induced Demand in Kidney Replacement Therapy

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Abstract

There are three notable aspects of the current kidney replacement therapy program. First, the number of patients on home dialysis have dropped substantially over the last decades. Second, the rate of transplantation has stabilized in recent years. Third, there is variation in referral rate for transplantation among hospitals. These trends are the result of overutilization of in-center dialysis and that demand for kidney replacement therapy is moderated by suppliers.

Current healthcare policy leads to overutilization of in-center dialysis and underutilization of home dialysis and transplantation. This overutilization is the result of supplier-induced demand and leads to suboptimal care for patients and excessive healthcare expenditures. The main drivers of this overutilization are the overcapacity of in-center dialysis beds and the high financial disincentives on empty dialysis beds. Policymakers should address this by reducing dialysis capacity and increasing the capacity of transplantation facilities.

This is the first attempt to address the overutilization and the nonalignment of supply and demand by looking at the capacity of in-center dialysis and the financial disincentives for physicians on empty in-center dialysis beds. In our analysis, we conclude that limiting the capacity of in-center dialysis beds is the most effective strategy to better align supply and demand, which will result in better patient outcomes and lower societal costs.

Introduction

Patients with end-stage kidney disease (ESKD) need kidney replacement therapy (KRT) to survive. There are four major types of KRT: hemodialysis (HD), peritoneal dialysis (PD), deceased donor kidney transplantation (DDKT), and living donor kidney transplantation (LDKT). Transplantation is a better treatment option for patients compared to the dialysis modalities in terms of quality of life and survival [1-3]. On top of that, transplantation is also less costly for society in the long run [4].

HD is typically carried out in dialysis centers, while PD is carried out at home. There is no significant difference in quality of life among the dialysis modalities [1]. However, studies suggest that PD and home hemodialysis allow greater flexibility for patients and result in better psychosocial outcomes [5]. Some studies also found a better survival and quality of life for patients undergoing home dialysis compared to in-center dialysis. However, it is unclear whether this is causative or a reflection of a healthier population selected for home dialysis [6]. Cost differences between in-center dialysis and the home dialysis modalities vary significantly. There is evidence that home dialysis is the most economically efficient dialysis modality, also in terms of labor costs [7,8]. In the Netherlands, costs of in-center dialysis are marginally higher than the costs of the home dialysis modalities, approximately €71,000 vs €67,000 [4].

Between the two transplantation modalities, LDKT is preferable to DDKT, as it provides better graft and patient survival [9]. LDKT is also substantial less costly for society than DDKT [4]. Moreover, patients living with a functioning donor kidney are more likely to be part of the labor force than dialysis patients [10]. Unfortunately, access to transplantation is accompanied with difficulties. There is a scarcity of deceased kidney donors worldwide. To qualify for a DDKT, a patient is typically put on a waitlist and the waiting time starts of the first day of dialysis. The average wait time is approximately 2-4 years in Europe [11]. As the supply of deceased kidney donors has shown to be constant over many decades, LDKT is the only transplant modality at this time to have a clear potential for growth [12].

Although superior in terms of outcomes, access to LDKT is not without difficulties [13]. The extent to which patients are supported by professionals in finding a living donor varies greatly. Obstacles to find a donor include a lack of knowledge about the treatment options and difficulty initiating a conversation to ask family and friends to donate their kidney [13,14]. In the last two decades, several successful initiatives have been undertaken to address these difficulties in access [15]. Most notably, home-based educational interventions have shown to increase the number of LDKTs [16,17]. Innovative allocation programs, such as kidney exchange programs, have increased the possibilities for patients to receive a donor kidney despite blood or tissue incompatibility [18,19]. Currently, so-called 'HLA-incompatible' and 'ABO-incompatible' direct transplantations are also possible [20].

Preemptive transplantation is a transplantation that is performed as the first treatment option for patients. Preemptive transplantation is associated with superior (graft) survival, as the lasting effects of health deterioration by dialysis are avoided [21]. For these reasons, the guidelines for nephrology state that the preferred treatment option for patients eligible for transplantation is a preemptive

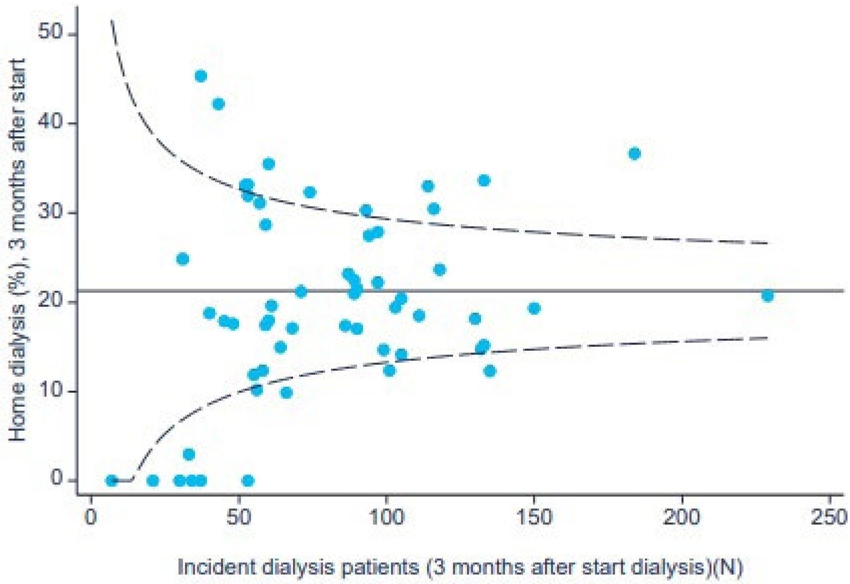

Figure 1 Center variation in percentage home dialysis three months after start dialysis. Home dialysis includes peritoneal dialysis and home hemodialysis. Data is adjusted for age, sex, SES, and primary kidney disease categories. Inclusion period 2018-2020 [26].

Second, even though access to LDKT has improved in recent years, due to improved allocation programs and medical innovations, the LDKT-rate has either stabilized or declined slightly in many developed countries [27,28]. There are no apparent reasons for this trend. Third, although preemptive transplantation is the preferred treatment, there is a large variability in the referral rate for preemptive transplantation [29]. For instance, in the Netherlands, the variation in referral rate among hospitals ranges between 0% to 40% of their incident patients, see Figure 2 [26].

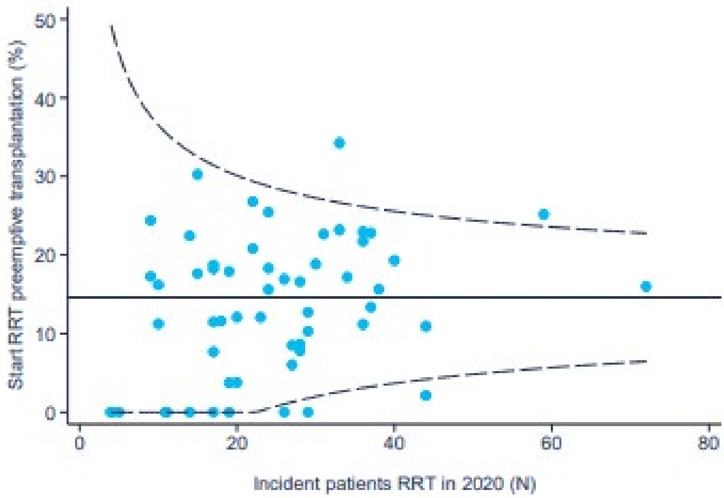

Figure 2 Center variation in percentage preemptive transplantations in incident KRT-patients in 2020. Adjustments were performed for age, sex, SES, and primary kidney disease categories [26].

In this article, we argue that the decrease in the number of home dialysis patients, the stabilization of the LDKT-rate, and the variation in referral rates for preemptive transplantation are mainly the result of current healthcare policy. We argue that there is overutilization of in-center dialysis and that demand for KRT is moderated by suppliers. The overutilization is the result of overcapacity of in-center dialysis facilities and financial incentives. Consequently, current policy leads to suboptimal care for ESKD-patients and excessive healthcare expenditures. In this paper, we suggest policy changes that may improve care for patients.

Methods and materials

To justify these recommendations, we looked at international research on the utilization rates of kidney replacement therapies in countries with a developed healthcare system. Literature that focused on organizational, policy-related and economic aspects of access to dialysis and transplantation care was selected. To support our claims further, Dutch publicly available records were used. Data on incidence, prevalence and the number of dialysis centers were calculated using empirical data from the Dutch Renal Registry 'Renine'. The Renine database contains information concerning all Dutch patients who underwent a non-experimental form of KRT. Data was analyzed using IBM-SPSS Statistics version 25 (SPSS Inc., Chicago). Findings were reported along the lines of the effects of capacity and financial aspects on the KRT-program.

Results

The role of capacity

In 1959, 'Roemer's Law' was formulated, which states that a "bed built is a bed filled" [30]. This claim was supported by other studies that found compelling evidence for a positive relationship between bed availability and healthcare utilization rates [31,32]. This observation is linked to 'supplier-induced demand', which refers to the notion that hospitals fill their beds regardless of the underlying demand for hospital care, i.e. that healthcare professionals do not always act as perfect agents for patients [33]. We argue that this mechanism is present in the current KRT-program, which has led to a decrease in the number of home dialysis patients, less attention to (preemptive) transplantation and lower referral rate.

DIALYSIS CAPACITY

Dialysis capacity has already been linked to induced demand. A North-American study reported that a rapid increase in the number of in-center dialysis facilities creates incentives to keep operating at capacity and, consequently, reduces the number of patients on home dialysis [25]. A similar trend can be found in the Netherlands. In 2000, a policy regulation came into force which deregulated the construction of new dialysis centers [34]. The rationale behind this deregulation was to improve access to in-center dialysis, as a substantial number of the patients had to travel a considerable distance to reach the nearest dialysis center. This was objectionable given that dialysis is a time-consuming, tiring and frequent treatment. This deregulation indeed improved access, as it led to a doubling of the number of dialysis centers, from approximately 50 in 2000 to more than 100 in 2017, while the incidence rate increased substantial less. This is visualized in Figure 3.

Parallel to this rapid increase in dialysis centers, there was a decrease in patients undergoing home dialysis. In 2000, 30% of the dialysis patients underwent a form of home dialysis, while in 2012 this percentage was 19%, which stabilized thereafter. Initiatives were undertaken to reverse this trend, but so far these have been unsuccessful [35]. There does not seem to be an apparent reason for this decrease as there were no significant changes in financing, production or delivery of home dialysis in this period. One hypothesis is that patients were directed towards in-center dialysis to prevent empty beds, indicating the presence of induced demand. Dutch Members of Parliament were aware of the trend, and expressed

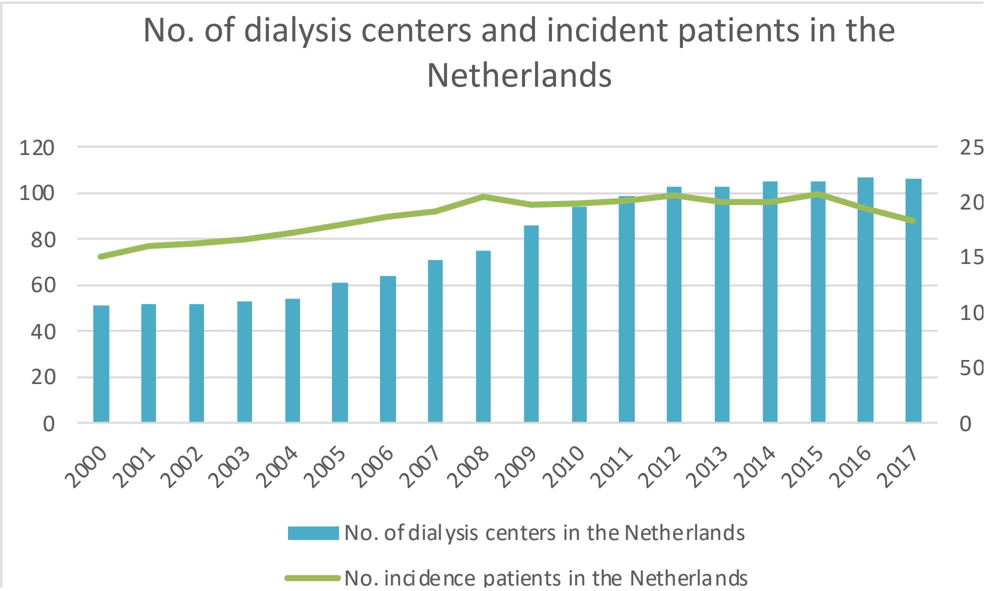

Figure 3 The number of dialysis centers in the Netherlands (primary Y-axis), and the number of incident patients (secondary Y-axis). Source: Dutch Renal Registry 'Renine'.

their concern, as it could endanger the freedom of treatment choice for patients, and a potential loss of quality of home dialysis care due to lower utilization[36].

The deregulation of the construction of new dialysis centers most likely led to a disproportionate increase in the utilization rate of in-center dialysis. One could argue that this has led to suboptimal care for patients. One solution to this induced demand is reducing the capacity of in-center dialysis. If an increase of dialysis beds resulted in overutilization, a decrease of capacity may lead to a lower utilization rate. Reducing (hospital) beds has proved to be an effective strategy to reduce overutilization in healthcare, as several European countries have cut down on the number of hospital beds in the past to reduce utilization of hospital care [37]. By reducing the capacity of in-center dialysis, nephrologists would be stimulated to look for alternatives beyond in-center dialysis, such as home-dialysis and (preemptive) transplantation.

Reducing capacity can be achieved in several ways by various actors. First, health insurers may restrict or stop reimbursement contracts with hospitals that have inadequate referral rates. This may entice hospitals to look at alternatives beyond in-center dialysis and consequently reduce their capacity. Reducing capacity may also be government-led, for instance, by introducing a so-called 'certificate-of-needs' regulation, which may help in aligning the supply and demand for KRT.

Certificate-of-needs programs attempt to reduce the construction of unnecessary healthcare facilities and to limit the acquisition of costly equipment that provides little benefit for patients. Certificate-of-needs programs are associated with a significant reduction in healthcare capacity, up to 10% [38].
Some considerations should be taken into account when arguing for a decrease of the in-center dialysis capacity. For instance, it is expected that the global incidence of patients with ESKD is going to increase due to the ageing population and accompanying comorbidities [39]. Although over the last decade the incidence rate in the Netherlands did not increase, it is not to say that this stability will continue in the future. Especially considering the negative impact of the COVID-19 pandemic on kidney care. In the Netherlands, there was a scarcity of ICU-beds which led to a substantial drop in the number of kidney transplantations. Consequentially, the waitlist for transplantation has increased. Moreover, infections with COVID-19 may result in kidney damage, which is especially troublesome for patients with kidney failure when infected [40]. The ageing population and the aftermath of the pandemic may lead to an increase in the demand for dialysis beds. We therefore argue for a lower ratio of dialysis beds to incidence rate. Furthermore, travelling distance for patients to dialysis centers should be kept to a minimum, as the treatment is already time-consuming and burdensome for patients. Finally, one has to bear in mind that some patients prefer in-center dialysis to home dialysis. Reasons for this include that some patients 1) do not want to 'hospitalize' their home, 2) do not want to commit time required for training for home dialysis, and 3) prefer the social function of in-center dialysis [41]. These factors should be taken into account while reducing the capacity of in-center dialysis.

Recommendation

» *The ratio of capacity of in-center dialysis to incidence rates should be lowered.*

TRANSPLANTATION CAPACITY

In the Netherlands, solely the eight university hospitals are allowed to perform transplantations. As a reduction of in-center dialysis will likely lead to an increase in the number of (preemptive) transplantation referrals, this could potentially be troublesome for the current KRT-program. Particularly because many transplant centers already have a waitlist for LDKT, a trend that started even before the COVID-19 pandemic. This suggests that the main scarcity problem for LDKT at the moment is no longer the scarcity of willing kidney donors, but rather the capacity to transplant the available kidneys. This lack of transplant capacity is especially alarming, as it can be expected that the supply of kidney donors will further increase in the coming years [42]. Moreover, it can be expected that medical and allocation innovations will further increase the eligibility of patients and donors for transplantation, such as improved HLA- and ABO-incompatible transplantations, and improved exchange programs. All these development are likely to lead to greater availability of kidneys for transplantation, and consequently, lead to an even longer waitlist for LDKT. For some patients this could result in missing out on a preemptive transplantation.

We therefore suggest to increase the total transplant capacity. Preferably, the capacity will be increased within the current transplant centers. Mainly because centralization of treatment of complex surgeries is associated with better quality of care and lower costs [43]. In the case that the transplant centers will not have sufficient opportunities to increase their capacity, large regional hospitals may be able and allowed to conduct transplantations.

Recommendation

» *Capacity of transplant facilities should be increased.*

Financial aspects

One of the reasons why physicians induce demand is financial self-interest [44]. It is well established that physicians/hospital managers respond to financial incentives and are able to influence demand to adhere to these financial incentives [45]. It therefore makes sense to change incentives for physicians. For example, by incentivizing home dialysis and transplantation and/or to change payment methods for physicians. Below, we discuss possible changes for financial rewards.

FINANCIAL (DIS)INCENTIVES

Reimbursement rates for the different dialysis modalities differ significantly across countries [46]. A recent study on dialysis reimbursement in 81 countries show that most healthcare systems favor the use of in-center dialysis. But even in countries where home dialysis is better reimbursed, the percentage of patients on home dialysis is low [47]. This is also the case for the Netherlands; most home dialysis modalities are better reimbursed than in-center dialysis, while the use of home dialysis is relatively low [4].

Incentivizing treatment options by increasing the financial rewards for physicians is an established strategy. This strategy is also used in the KRT-program to promote home dialysis. A literature review on whether financial incentives could increase the use of home dialysis shows effect, albeit limited [48]. This suggests that changing financial incentives alone will not always be sufficient and should be accompanied with other policy changes. Although the use of financial incentives has relatively limited effect, we still argue that behavior that follows the guidelines should be rewarded, and hence, referral for transplantation and home dialysis should be incentivized.

Financial disincentives may have a larger impact on the utilization of in-center dialysis than positive incentives. Empty dialysis beds are costly for nephrologists and hospitals. A survey among US nephrologists showed that a substantial portion of the nephrologists acknowledge the detrimental financial impact of transplantation on nephrologists' practice as it leads to empty in-center dialysis beds [49]. This financial impact is also present in the Netherlands, as physicians are typically involved in independently organized per-specialty partnerships, the so-called 'maatschap-structure' [50]. Consequently, empty dialysis beds directly affect a physician's income. A reduction in income is difficult to accept, even if the rationale of such a reduction is based on the best outcome for patients and society. 'Prospect theory' predicts that physicians respond to financial disincentives rather than to positive incentives, as the theory suggests that people have a strong aversion to loss [51]. This may explain the limited effects of incentivizing home dialysis and transplantation. It seems therefore vital to diminish and/or contain the financial disincentives of redundant beds.

Reducing capacity of in-center dialysis may be an effective strategy to reduce the total financial disincentives of empty beds. Incentivizing referrals for transplantation and/or home dialysis may also influence physician behavior. Another strategy is to detach the physicians' income from redundant dialysis beds.

Recommendations

» *Incentivize preemptive transplantation and home dialysis.*

» *Remove disincentives of empty in-center dialysis beds.*

PAYMENT SCHEMES

The interests of doctors and hospitals do not necessarily always align with the interests of patients and society [52]. It makes therefore sense to devise a payment system in such a way that the interests of physicians, patients and society are more aligned. In many countries, physicians are paid for every unit of healthcare they produce; the fee-for-service method. A fee-for-service payment system has been internationally associated with induced demand and overutilization of care [53]. Fee-for-service has also specifically been linked to overutilization of in-center dialysis.

A study in the US showed that the transition from a capitation-based payment system to fee-for-service resulted in more patients undergoing in-center dialysis and fewer patients on home dialysis [54].
The Netherlands also has a type of fee-for-service payment system, although the Dutch government intends to replace this payment system with a salaried employment for physicians to reduce wrongly placed financial incentives. Indeed, salaried employment is associated with improved quality of care, while minimizing supplier-induced demand. However, it is also associated with reduced productivity [55]. Capitation-based payment may also be considered, as it is also associated with a reduction in supplier-induced demand, but it may result in rejecting or referring out the relative less healthy patients [56]. In kidney care this may lead to adverse effects for patients who are not eligible for transplantation or home dialysis.
Research on payment schemes for physicians to balance cost containment and quality of care is widespread, but the perfect scheme has not yet been found. Designing a system in which medical decisions are not affected by financial compensation is complex and there is no empirical evidence of an existing remuneration or payment scheme that is perfectly aligned with the interests of patients and society. Internationally, there is consensus that a blended payment scheme, with characteristics of fee-for-service with a salary or capitation component is the best way forward to contain costs while maintain quality and productivity [57].
Improving quality in healthcare may also be done by introducing a pay-for-performance (P4P) component to a payment scheme. A P4P-system rewards physicians on achieving certain clinical targets and quality goals. Ideally, a P4P-system is 'decoupled' from base payments and should be tailored to the specific setting of implementation [58]. In kidney care, one of the performance targets may be a minimal referral rate for transplantation or home dialysis, adjusted for patient-mix. This may incentivize the hospitals that have low referral rates to look beyond in-center dialysis. Although theoretically appealing, evidence of the effectiveness of a P4P-system is currently lacking. Empirical evidence is needed to confirm the effectiveness of P4P in kidney care.

Recommendations

» Payment schemes for physicians should be devised in such a way that medical decisions are less affected by financial compensation.

» Empirical research should be conducted to confirm the effectiveness of a pay-for-performance component.

Discussion

In this paper, we argued that financial disincentives and overcapacity are the main causes for overutilization of in-center dialysis. It is well established that physicians respond to financial incentives, however, some may argue that alternative explanations for the overutilization of in-center dialysis exist beyond supplier-induced demand. Below, we will discuss some of these explanations.

Alternative explanations

Although physicians respond to financial incentives, they are bound by their intrinsic ethical restraints, such as the do-no harm principle. Research has shown that this is more important in the decision-making process for physicians than financial incentives [53]. This line of reasoning implies that some nephrologists are less aware of the harmful effects of dialysis, even though research has repeatedly shown that dialysis has a lasting detrimental effect on patients, even after a patient undergoes transplantation [59]. Physician education on the medical and psychosocial consequences of the different KRT-options can therefore help to improve the current KRT-program. Some studies indeed suggest that the underutilization of preemptive transplantation can be partly explained by a lack of knowledge on timely referral [60]. A study in the US suggests that nephrology trainees perceive low and moderate levels of preparedness for managing home dialysis [61]. A study in Europe also suggests that inadequate physician education is more likely to be the cause of low utilization than, for instance, patient-mix [62]. This would warrant improved physician educational programs.

Some scholars argue that supplier-induced demand is nothing more than using the available capacity to its limit. Physicians may believe this is the most appropriate thing to do as a healthcare professional, as not using available care can be seen as a waste [63]. This reasoning underlines that the overutilization is physician-driven, and one cannot rely on optimal utilization of current capacity by physicians. This does not just result in suboptimal care, but unrestricted use of resources in one healthcare sector will have consequences in other sectors. It is the society responsibility of healthcare professionals to take these considerations into account.

Alternatively, a more cynical explanation of the difference in utilization of in-center and home dialysis may exist. Some global listed companies make substantial profits on in-center dialysis, and have financial interests in promoting the use of in-center dialysis, while preventing the use of home dialysis. The magnitude of commercial forces likely differs between countries and healthcare systems. The role of these commercial interests in the overutilization of in-center dialysis should be investigated further.

Future research

Although we found indications for the presence of supplier-induced demand in the KRT-program, we did not present empirical evidence for these claims. More research on the relation between practice variation and financial incentives or payment schemes, would support the argument for supplier-induced demand greatly. Future research on the effect of a blended payment system and P4P-components to promote productivity and quality is also needed. From a policy perspective, it is important to determine how much the capacity of in-center dialysis should be reduced. In many countries, the incidence of patients with ESKD is increasing. Severely reducing the capacity may lead to unwanted results, as for a significant portion of the patients in-center dialysis is the only viable treatment option. Thus, reducing capacity of in-center dialysis should be done carefully.

Conclusion/Policy recommendations

Patients with ESKD do not always have equal access to all treatment options. This inequality is accompanied with a decrease in life expectancy and quality of life for patients, and larger healthcare expenditures for society. We argued that the demand for in-center dialysis is lower than currently supplied, and that operating at an overcapacity is financially incentivized. From our analysis, we conclude that limiting the relative capacity of in-center dialysis beds is the most effective strategy to better align supply and demand. Eliminating financial disincentives of empty in-center dialysis beds should accompany such reduction. In parallel, transplantation capacity should be increased. As long as the remuneration system for care for ESKD is based on a fee-for-service for physicians and dialysis centers, reduction of the dialysis capacity and eliminating the financial incentives are the only health policies that could improve kidney care and reduce the unequal access of all treatment options.

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CHAPTER 6

General discussion

In this thesis, we showed that the previous results of the *Nierteam aan Huis* intervention are generalizable, and that implementing the intervention throughout the Netherlands is feasible. The *Nierteam aan Huis* intervention is an effective way to improve knowledge and communication of patients and their social network, and consequently, to increase the living donor kidney transplantation (LDKT) rate (**chapter 3**). Furthermore, we showed that *Nierteam aan Huis* is cost-effective compared to care-as-usual: in **chapter 4,** we showed that *Nierteam aan Huis* is not only an effective intervention, but also a cost-saving intervention. Because of these results, the financial provisions have been put in place for the intervention to be incorporated into standard care, and as of January 2021, hospitals can be reimbursed by health insurers for carrying out the *Nierteam aan Huis* educational program.

Although structural financial support for the intervention has been put in place, there is up to now relatively low continuation after the project financing ceased. Three transplant regions are currently carrying out the *Nierteam aan Huis* program, and even within these regions, not all regional hospitals are participating in *Nierteam aan Huis*. Besides the difficulties that hospitals face due to the COVID-19 pandemic, it is likely that finances and policy factors play a role in the uptake of the program, as explored in **chapter 5.** In that chapter, we discussed the overutilization of in-center dialysis and underutilization of transplantation as a result of 'supplier-induced demand'. We argued that there are incentives to refer patients to in-center dialysis rather than to home-dialysis or preemptive transplantation, because of the high financial risks related to empty in-center dialysis beds. As patients are more likely to pursue LDKT after a *Nierteam aan Huis* intervention, these financial risks may hamper the uptake of the intervention into standard-care. Thus, a reduction of the relative capacity of in-center dialysis and an increase of the capacity of transplantation facilities may also help in the uptake of the intervention into standard-care.

Current challenges for Nierteam aan Huis

Other reasons may also play a role in the difficulties of uptake of *Nierteam aan Huis*. There are considerable differences in the structure and organization of *Nierteam aan Huis* between the implementation project and current implementation of standard care. Prior to *Nierteam aan Huis* implementation project, hospitals were solely responsible for the education of their own patients regarding the treatment options. There was no standardized educational program. Some hospitals were already offering patients a form of home-based education, while other hospitals gave patients leaflets and/or some education during outpatient clinics or held information evenings for patients and their families. *Nierteam aan Huis* is an addition, not a replacement, to these educational programs of the hospitals. In contrary to the implementation project, where all hospitals had their own *Nierteam*, the nationwide implementation of *Nierteam aan Huis* is more centralized and there is one *Nierteam* per transplant region. The Netherlands is divided in 7 transplant regions, and within these regions, the university hospitals (transplant centers) are responsible for the *Nierteams*. The current protocol states that there always needs to be an educator present during an intervention who is linked to a transplant center. The rationale behind this structure is to promote consistency in the implementation of the intervention within the regions. This entails more collaboration between the hospitals and it will take time to reach sustainable implementation. Collaboration may be hampered by the fact that regional hospitals do not have the sole responsibility anymore of educating their own patients. This can be perceived as a loss of autonomy for hospitals, and indeed, can evoke resistance among some regional hospitals, which may also hamper the uptake of the intervention into standard-care.

Next to the centralized coordination, the *Nierteam aan Huis* reimbursement structure is also centralized. The healthcare insurer reimburses the university hospitals for the interventions. In the cases that regional hospitals carry out the work for an intervention, i.e. by providing an educator for an intervention, they are compensated by the university hospitals instead of directly by health insurers. This also entails enhanced collaboration between regional hospitals and university hospitals, and it may take some time to harmonize the collaboration. This structure also diverges from the situation prior to the implementation project, as the regional hospitals were reimbursed for their own education activities directly by health insurers. A structure that depends on cooperation and finance may be problematic when autonomy is preferred. Organizations tend to avoid interorganizational cooperation which compromise their autonomy and financial liability [1]. Thus, although significant progress have been made in the nationwide implementation, the above complications need addressing in order to promote widespread.

All these barriers may mitigate the (cost-) effectiveness of *Nierteam aan Huis*. I would therefore argue that centralized policy measures have to be taken to achieve sustainable implementation of *Nierteam aan Huis*, and consequently improve care for patients with end-stage kidney disease. There needs to be multidisciplinary collaboration to solve the issues of the kidney replacement therapy program. National, centralized policy measures are necessary as the incentives to produce more healthcare for financial efficiency are sometimes more appealing than incentives to improve care or to provide quality care [2]. Thus, I argue that policymakers at a central level should actively collaborate with the clinical field in developing policies concerning kidney care, and create conditions for physicians and hospitals to improve kidney care.

Alternative policies

In chapter 5, we explored the impact of a potential policy that could be initiated by policymakers: removing dialysis beds in the kidney replacement therapy program. This might be seen as a rather crude method when alternative, less controversial, methods exist. Some might argue that dialysis beds should not be reduced at all, as the global incidence of kidney failure is expected to rise due to the ageing population and consequential comorbidities [3]. Although in the last decade the incidence rate in the Netherlands did not increase, it is not to say that this stability will continue in the future. Especially considering that the COVID-19 pandemic also had a negative impact on kidney care. First, due to the scarcity of ICU-beds the number of kidney transplantations has dropped significantly. Consequential, the waitlist for transplantation has increased. Second, infections with COVID-19 may result in kidney damage, which is especially troublesome for patients with kidney failure when infected [4]. This could lead to an increase in the demand for dialysis beds. However, even if the incidence of kidney failure would increase, we would still argue that the *ratio of dialysis beds to incidence rates* should be lowered. However, this does not mean that we do not suggest that other solutions are by definition ineffective. Below we explore the most important alternative policies to improve access to transplantation.

Changing tariffs

One possibility to improve the incentives for transplantation is to change the tariffs for referrals to transplantation. This may incentivize hospitals to refer more patients for a (pre-emptive) transplantation, or a *Nierteam aan Huis* intervention. Such an increase in financial rewards can be accompanied with a decrease in the reimbursement for in-center dialysis. Thus, rewarding best clinical practice and promote quality care.

Unfortunately, as was also mentioned in chapter 5 of this thesis, research has shown that incentivizing home dialysis has only a limited effect in the utilization of in-center dialysis [5]. This is also likely for transplantation referrals. Again, this may be partly due to the high financial disincentives that dialysis centers face when their beds remain empty. Moreover, the expenses of both *Nierteam aan Huis* and referrals for transplantations are insignificant compared to the costs of an empty dialysis bed. Consequently, increasing the tariffs of (pre-emptive) referrals for transplantation and *Nierteam aan Huis* would have to be considerable in order to compensate the empty beds and generate a favorable effect for the patient. Such massive 'overpricing' may even result in uncontrollable and unwanted results, such as 'overreferrals'. In other words, sole implementation of this strategy does not seem feasible.

Physician and patient education

Preliminary, unpublished results of a study that investigated the factors influencing access to transplantation [6] suggest that there is lack of standardized protocol on referrals for (pre-emptive) transplantation. This implies that the procedures around the care for patients with end-stage kidney disease differ per hospital. A way to overcome these disparities is by improved physician education, a standardized protocol, and more quality standards. The guidelines on kidney care need to be straightforward for all healthcare professionals. Standardized training and education for healthcare professionals to promote best practice should be encouraged. However, it is worth noting that such guidelines and programs to educate physicians about the guidelines already exist in the Netherlands. The national physician education is recognized as having high quality and is supported by the scientific communities of the physicians. Nevertheless, this quality implementation has not lead to full implementation of the guides of the same scientific communities of the physicians, therefore there is still room for improvement.

More patient education in addition to *Nierteam aan Huis* may also be a strategy to overcome the large information gap between physicians and patients, which is an important cause of supplier-induced demand. However, it is difficult to close the information gap between patients and doctors. The effectiveness and cost-effectiveness of additional educational efforts need to be tested in a research setting before implementation. So far, it remains unsure whether more patient education, beyond *Nierteam aan Huis*, will improve access to transplantation. Nevertheless, there are cues that patient education might be effective: there is evidence that some patient groups experience more disparities in access to transplantation than others. For instance, research has shown that ethnic minorities in the Netherlands have limited access to living donor kidney transplantation [7]. Therefore extra efforts to promote the possibilities of donation for these patient groups has the potential to be part of the solution for improved access to transplantation [8].

Increasing deceased donation

Another possibility to increase the number of available kidneys is to promote deceased donor kidney transplantation (DDKT). For years, the Dutch policy was to promote DDKT by public campaigning. However, the number of DDKTs remained remarkably stable over the years. In 2021, there was a legal change in the way the general public is registered as a potential donor for the DDKT program. Until recently, the Netherlands had an opt-in donor system that implied that citizens had to actively register as a deceased donor. In the case that one did not register anything, it was assumed that the person did not want to become a donor, unless the relatives of the deceased person stated that her/she had wanted to donate their organs. In July 2021, this 'opt-in' donor system was replaced by an 'opt-out' donor system. This implies that if citizens do not register anything, it is seen as 'no objection' for DDKT. The rationale behind this change was that many people were not engaged with the donation question and did not register as a donor, even though they would not have any objections. The goal was to increase the number of available organs for transplantation and make deceased organ donation the societal norm.

It took many years to get this new donor system ratified by Parliament. Many political parties had ethical objections to such an opt-out donor system. Consequently, in order to get the regulation to be ratified, many concessions were made along the way. Eventually, Parliament ratified a 'soft' opt-out system. This soft op-out system means that relatives of a deceased person can still object even if the patients did not file any objection to donation. Considering that the death of a loved one is an emotional moment, it is imaginable that a substantial portion of relatives will still object deceased donation: those relatives are not in position to take the risk of acting against any unspoken wishes of the loved one just deceased. There are indeed some cues that the effect of the policy chance are positive, but limited. In Wales a similar policy change was implemented, and preliminary result show a modest positive effect [9]. It remains to be seen if this adapted policy for deceased donation will have the desired effect of a substantial increase of transplantations in the Netherlands.

There are also other ways to achieve an increase in the number of deceased donation beyond the legal registration. There is evidence that by improving the communication with the family of the potential donor for DDKT may increase the number of DDKTs [10]. Moreover, not all deceased potential donors can indeed donate their kidney, due to the lack of favorable medical conditions needed for a successful transplantation. Therefore, a way to increase the number of DDKTs is by optimizing the number of organs that can be used for donation. The British Transplant Society formulated several strategies to maximize this potential by a) improving the donation experience for families and by b) improving organ utilization and quality. Improvement of the donation experience for families and donors can be done by recognizing and supporting donors and donor families who have donated organs. To improve the number of kidneys considered suitable for transplantation, there are effective innovations. For instance, a new perfusion technology leads to better clinical outcomes for deceased organ donation. This new perfusion technology can reduce damage to a kidney during transport and can even provide a mechanism to repair and recover donated kidneys. This way more organs can be used for donation. This strategies might be successful in improving the DDKT rate in the Netherlands, as it has done in the United Kingdom [8].

Medical innovations

Medical innovations may also play a role in improving access for patients to LDKT. Recently, there are impressive medical innovations that increased the possibilities for patients to receive a living donor kidney despite blood or tissue incompatibility. For instance, HLA-incompatible and ABO-incompatible transplantations are now possible [11]. These breakthroughs are a great step forward; especially considering that in the early days of kidney transplantation patients could only receive a kidney from a genetically related family member. These medical innovations make it is possible to allow incompatible transplantations, which will increase the effectiveness of the use of the scarce donors. Nevertheless, these solutions will not substantially increase the number of donations, which limits their contribution overcoming the scarcity of donor organs. Needless to say, medical research should always be an important research pillar to improve transplantation outcomes.

Other alternatives

Xenotransplantation has been a promise for several decades to overcome the scarcity of donor organs. Recently, surgeons from a hospital in New York were able to conduct the first transplantation with a kidney from a pig in a patient who was brain dead. However, its implementation is hampered by the risk of zoonosis, that is the transmission of microorganisms from animals to humans. Moreover, there are ethical considerations in xenotransplantation, as some people hesitate

to breed livestock in order to harvest their organs. Potential risks to human and nonhuman donors, recipients, and third parties should all be thoroughly considered [12]. Thus, although promising for decades, it is unlikely that patients and physicians will be open for the possibility of xenotransplantation, as long as the risks are considerable [13].
There are some other, more controversial alternatives that may improve access to living donor kidney transplantation. For instance, commercializing organ donation may lead to a higher supply of available organs. However, commercialism has obvious ethical and legal objections. Another alternative may be to promote altruistic kidney donation to the waitlist by lowering the barriers for donation. In-depth discussions about these alternatives are beyond the reach of this thesis.

Conclusions

Above we explored the most important alternative policies to improve access to transplantation. Some of these alternatives have potential and can be implemented in a wide approach to improve access to transplantation. Other solutions have shown in the past that their effectiveness is limited. Therefore, the conclusion of the thesis must be that a psychosocial educational program to improve knowledge and communication on kidney replacement therapy is the most cost-effective innovation to increase transplantation in the population with end-stage kidney disease. The implementation of such program should be accompanied with a reduction of the ratio of dialysis capacity and the incidence rates, as the high capacity of dialysis beds induce disincentives for transplantation. Alternative innovations as discussed above may contribute in reducing the scarcity of donor organs. What is most needed now to enhance best practice, are policy changes to improve incentives for transplantation and a more centralized guiding of the education of the patients, as presented by *Nierteam aan Huis*.

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APPENDIX

Summary

Samenvatting

Dankwoord

About the author

PhD portfolio

Summary

Living Donor Kidney Transplantation (LDKT) is the optimal treatment option for patients with end-stage kidney disease. LDKT is associated with the highest quality of life and survival compared to other treatment options, especially compared to dialysis. Access to LDKT is troublesome for some patients and not all patients have equal access. Research in the Rotterdam transplant area has shown that a home-based educational intervention, the *Nierteam aan Huis* (Kidney Team at Home) intervention, is an effective strategy to improve access to LDKT. The *Nierteam aan Huis* intervention consists of two home visits. During the first home visit, educators familiarize themselves with the social network of the patients and prepare the patient for the group education. In the second visit, the group education takes place with the patient and their social network. During the education, the advantages and disadvantages of the various kidney replacement treatments are discussed and communication between the patient and the social network is encouraged. Two randomized controlled trials demonstrated that this intervention leads to increased knowledge and communication among patients and their network, as well as increased access to LDKT. This thesis investigated 1) the generalizability of previous findings on home-based education to other regions in the Netherlands, 2) whether the intervention can be successfully implemented while maintaining quality, 3) the cost-effectiveness of the intervention from a societal perspective, and 4) possible barriers that could have a moderated effect on the intervention.

In 2016, an implementation project commenced with eight hospitals to evaluate the feasibility, viability and generalizability of *Nierteam aan Huis*. To increase the chance of successful implementation, a quality assurance system was established. The quality assurance system consisted of training educators prior to the implementation of the educational intervention, regular supervision (every six weeks), and intervision (peer-to-peer) meetings (evert quarter). This allowed for monitoring the quality of the interventions, and thus, increased the likelihood that the results of previous studies would be generalizable.

The results of the project were favorable. The results of the previous studies were replicated: Virtually all patients and invitees improved their knowledge on kidney replacement therapy options, and communication between patients and the social network also improved in many cases. Moreover, the LDKT-rate in the project was similar to the LDKT-rate of the randomized controlled trials. In addition, there was a positive relationship between protocol adherence and LDKT-activity, which shows the importance and merit of a protocolled approach. The implementation project also showed a stable participation rate throughout the whole project and relatively low costs. This showed that nationwide implementation of the *Nierteam* *aan Huis* intervention is viable and feasible.

Another important step to pave the way for nationwide implementation of *Nierteam aan Huis* into standard care was to assess the cost-effectiveness of the intervention compared to standard care. In the Netherlands and throughout the world, healthcare costs are rising. It is evident that *Nierteam aan Huis* is associated with additional costs in the form of salary for the educators, travel costs, professional translators and costs associated with the quality assurance system. It was crucial to evaluate whether these extra costs are effectively allocated to this programme. Kidney care is relatively expensive. Costs of dialysis lies between €80,000 and €100,000 per year, and the costs of a transplantation are between €60,000 and €100,000. However, after a successful transplantation, the costs drop significantly in the subsequent years compared to dialysis care. Healthcare costs for patients living with a functioning donor kidney are approximately €20,000 per year. Thus, a transplantation is also the preferred treatment option for society. Especially considering that patients living with a functioning donor kidney are more likely to have a job than patients who undergo dialysis.

Results of the cost-effectiveness analysis showed that the additional costs of the *Nierteam aan Huis* intervention were entirely overshadowed by the savings as a result of more transplantation and less dialysis. Furthermore, it was found that with nationwide implementation, substantially more life years and quality of life were gained. Thus, we showed that *Nierteam aan Huis* is a cost-effective approach to improve access to living donor kidney transplantation. Taken together, these results demonstrate that national implementation is both feasible and cost-effective, which leads to the recommendation for implementation in standard care.

Unfortunately, some potential hurdles and barriers may moderate the effects of nationwide implementation of the intervention. One of these barriers is the overutilization of dialysis care. This is partially due to the fact that dialysis equipment is expensive, making an empty dialysis bed costly for hospitals and dialysis centers. In this thesis, evidence was found for supplier-induced demand in the kidney replacement therapy program. Supplier-induced demand refers to the notion that hospitals fill their beds regardless of the underlying demand for hospital care, i.e. that healthcare professionals do not always act as perfect agents for patients. In this case, it means that nephrologists and dialysis centers may not refer patients in a timely manner for (pre-emptive) transplantation or discuss the possibility of home dialysis in order to ensure that their dialysis beds are filled. If implemented in standard care, it may also mean that *Nierteam aan Huis* is not offered to all patients who may benefit from it.

Overutilization of dialysis is worrisome as it leads to less life years and higher healthcare expenditures. We therefore formulated two policy recommendations. First, we suggest to decrease the ratio of total capacity of in-center dialysis to the incidence rate, while simultaneously increasing the transplantation capacity. This would stimulate nephrologists to look for alternatives beyond in-center dialysis, such as home-dialysis and (preemptive) transplantation. It is worth noting that this should be done carefully, especially considering the impact of the COVID-19 pandemic on kidney care, a possible increase of the incidence of kidney failure, and an ageing patient population and consequential comorbidities. Second, we recommend that policymakers should investigate the effects of different payment schemes for physicians and adapt the incentives for dialysis care accordingly. This would improve access to LDKT for patients, improve the quality of life for the average patient, and eventually will lead to lower healthcare expenditures.

Kidney care has improved a lot in the last decades. Medical innovations have been impressive; ABO- and HLA-incompatible transplantations for some patients are now possible. Psychosocial interventions and psychological care for patients, their social network and potential donors are continuously improving, and the introduction of *Nierteam aan Huis* into standard-care is a new chapter for kidney care. To improve kidney are even further, we argue for a greater focus in research on organizational and policy factors in order to further improve kidney care.

Samenvatting

De beste behandeling voor vrijwel alle patiënten met eindstadium nierfalen is transplantatie met een nier van een levende donor. Deze behandeling geeft de beste kwaliteit van leven en overlevingskans, zeker ten opzichte van nierdialyse. De toegang tot transplantatie van een levende donor wordt door sommige patiënten als moeilijk ervaren. Immers, patiënten moeten in de meeste gevallen zelf een donor vinden en veel patiënten vinden dit lastig. Onderzoek in de Rotterdamse transplantatieregio heeft uitgewezen dat een thuisvoorlichting, de *Nierteam aan Huis* interventie, een effectieve manier is om patiënten hiermee te helpen. De *Nierteam aan Huis* interventie bestaat uit twee bezoeken bij een patiënt thuis. In het eerste bezoek wordt er kennisgemaakt met de patiënt en wordt het sociale netwerk in kaart gebracht. In het tweede thuisbezoek vindt er een voorlichting plaats met de patiënt en het sociale netwerk. Tijdens deze voorlichting worden de verschillende behandelvormen besproken en getracht om de communicatie tussen patiënt en het sociale netwerk te bevorderen over de behandelvormen. Dit proefschrift onderzocht 1) of de resultaten van eerdere studies van de thuisinterventie generaliseerbaar waren naar andere regio's in Nederland, 2) of de interventie geïmplementeerd kan worden met behoud van kwaliteit, 3) of de interventie kosteneffectief is, en 4) of er mogelijke barrières zijn in het nierfunctievervangende therapie programma die invloed kunnen hebben op de effectiviteit van de interventie.

In 2016 is er een implementatieproject gestart met acht ziekenhuizen om te toetsen of het haalbaar is om *Nierteam aan Huis* landelijk te implementeren. Om de kansen voor een succesvolle implementatie te vergroten, is er een kwaliteitssysteem opgetuigd. Dit kwaliteitssysteem bestaat uit een gestandaardiseerde training voor alle voorlichters, regelmatige supervisie voor de voorlichters (elke 6 weken), en een verplichte intervisie met de voorlichters van alle *Nierteams* (4 keer per jaar). Daarnaast worden patiënten na afloop van de interventie gevraagd om de kwaliteit van de voorlichting en voorlichters te evalueren. Dit kwaliteitssysteem maakt het mogelijk om de kwaliteit van de interventies te monitoren, en vergroot daarmee de mogelijkheid om de resultaten van de eerdere studies te herhalen.

De resultaten van het project waren gunstig. De uitkomsten van de eerdere studies werden bevestigd: Nagenoeg alle patiënten en leden van hun sociale netwerk lieten een stijging in kennis van nierfunctievervangende therapieën zien en communicatie tussen patiënten en het sociale netwerken verbeterde ook in veel gevallen. Daarnaast was het percentage patiënten dat een transplantatie onderging naar aanleiding van de interventie ongeveer gelijk aan de percentages van de eerdere studies. Ook werd er een positieve relatie gevonden tussen de mate

waarin voorlichters zich aan het protocol hielden en transplantatie activiteit van de patiënten. Dit laat het belang en toegevoegde waarde van een geprotocolleerde aanpak zien. Het implementatieproject kende een constante participatiegraad gedurende het project. Tezamen met de relatief lage kosten van de interventie, lieten deze uitkomsten zien dat landelijke implementatie haalbaar is.
Een andere belangrijke stap om de weg te plaveien voor landelijke interventie, was om de kosten en effecten van Nierteam aan Huis af te zetten tegen huidige kosten en effecten van standaard zorg. In alle delen van de wereld stijgen zorgkosten, en kosteneffectiviteitsanalyses worden steeds belangrijker om zorgkosten te verantwoorden. *Nierteam aan Huis* brengt extra kosten met zich mee. Immers, de interventie bestaat uit twee thuisbezoeken bij een patiënt door twee zorgprofessionals, bovenop de standaard zorg en het kwaliteitssysteem ook extra kosten met zich mee. Het was daarom cruciaal om te toetsen of deze extra kosten goed worden besteed met *Nierteam aan Huis*.
Zorgkosten voor patiënten met eindstadium nierfalen zijn hoog. De kosten van dialyse liggen tussen de €80.000 en €100.000 per jaar per patiënt. De kosten van een transplantatie ligt ergens tussen €60.000 en €100.000. Na een succesvolle transplantatie dalen de kosten echter fors in vergelijking met de kosten van dialyse. Patiënten die leven met een niertransplantaat maken ongeveer €20.000 aan zorgkosten per jaar. Dus naast de voordelen van transplantatie voor een patiënt, heeft transplantatie ook maatschappelijke voordelen. Temeer omdat patiënten met een niertransplantaat beter in staat zijn om aan het arbeidsproces deel te nemen dan patiënten die drie keer per week dialyseren. Uit onze kosteneffectiviteitsanalyse blijkt dan ook dat de extra kosten die *Nierteam aan Huis* met zich meebrengen ruimschoots opwegen tegen de besparingen van meer transplantatie en minder dialyse. Daarnaast is gebleken dat met landelijke implementatie er substantieel meer levensjaren en gezondheidswinst worden gewonnen. *Nierteam aan Huis* is dus een kosteneffectieve manier om toegang tot transplantatie te vergroten. Dit resultaat liet de noodzaak zien van snelle landelijke implementatie.
Er zijn echter enkele potentiële verstorende factoren die de effectiviteit van *Nierteam aan Huis* negatief kunnen beïnvloeden. De voornaamste factor is het overmatige gebruik van dialysezorg. Dit wordt deels veroorzaakt door het feit dat dialyseapparatuur hoge kosten met zich meebrengt, wat ervoor zorgt dat een leeg dialyse bed duur is voor ziekenhuizen en dialysecentra. In dit proefschrift wordt aangetoond dat er indicaties zijn van aanbodgestuurde zorg. Aanbodgestuurde zorg houdt in dat een ziekenhuis een bed vult ongeacht de onderliggende vraag

naar deze zorg. In het geval van nierfunctievervangende therapie betekent dit dat zorgprofessionals patiënten doorverwijzen naar dialyse zonder de opties van transplantatie goed te overwegen en door te nemen met de patiënt.
Dergelijk aanbod gestuurde zorg is niet goed voor de patiënt en de maatschappij, want meer dialyse dan nodig zorgt voor minder levensjaren en kwaliteit van leven voor de patiënt en hogere zorgkosten voor de maatschappij. Pogingen om via richtlijnen, consensusvorming en prijsafspraken aanbodgestuurde dialysezorg te verminderen hebben tot nu toe nog niet het beoogde effect gehad. Daarom wordt in dit proefschrift aanbevolen om de relatieve capaciteit van dialysezorg te verminderen en tegelijkertijd de capaciteit van transplantatiefaciliteiten te verhogen. Hierdoor zullen zorgprofessionals eerder geneigd zijn om te kijken naar de mogelijkheden rondom transplantatie. Voorzichtigheid is echter geboden, gezien de impact van de COVID-19 pandemie op de nefrologische zorg, een vergrijzende patiënt populatie met bijbehorende comorbiditeiten en een mogelijke toename van de incidentie van patiënten met nierfalen. Vandaar dat er ook wordt gesproken over het verminderen van de 'relatieve capaciteit'. Een tweede aanbeveling is dat beleidsmakers de effecten moeten onderzoeken van andere betalingswijzen voor artsen en financiële prikkels rondom de behandelmogelijkheden zullen moeten verleggen. Dit zal toegang tot transplantatie verbeteren, meer kwaliteit van leven genereren, en uiteindelijk leiden tot lagere zorgkosten.

Zorg voor patiënten met nierfalen is enorm verbeterd in de laatste decennia. Medische innovaties zijn indrukwekkend geweest; zo is het tegenwoordig mogelijk om 'door de bloedgroep heen' te transplanteren. Psychosociale interventies en psychologische zorg voor patiënten worden continu verbeterd en met de introductie van *Nierteam aan Huis* in standaard zorg is er een nieuw hoofdstuk aangebroken. Wel zal er meer focus moeten worden gelegd op organisatorische en beleidsmatige factoren om de zorg voor patiënten met eindstadium nierfalen verder te verbeteren.

Dankwoord

Dit proefschrift was er nooit geweest zonder de inzet en hulp van velen. Ik wil dan ook graag iedereen bedanken die op enigerlei bij heeft gedragen aan dit proefschrift. Tot een aantal mensen wil ik mijn woord van dank in het bijzonder richten.

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"She has wisdom and knows what to do"

Steef, 2022

About the author

Steef Redeker was born on May 11 th , 1989 in Delfzijl, the Netherlands. He attended secondary school at the Ommelander College in Appingedam, where he graduated in 2007. In 2008, he started his bachelor's in Political Science at Leiden University and obtained his degree in 2013. Thereafter, Steef obtained his Master degree in Conflict & Cooperation at the Leiden University. In 2016, he started with his PhD-project at the department of Psychiatry, section Medical Psychology and Psychotherapy under the supervision of Dr. S.Y Ismail, Dr. E.K. Massey and Prof.dr. J.J. van Busschbach. During PhD-project, he was involved in teaching communication skills to medical students and contributed to the minor Medical Psychology. In 2019, Steef obtained his Master Degree in Health Economics, Policy and Law at the Erasmus University, in Rotterdam. He is currently working as a senior advisor at the Dutch Healthcare Institute in Diemen.

PhD Portfolio

SUMMARY OF PHD TRAINING AND TEACHING

Name PhD student Steef Redeker
Erasmus MC Department Psychiatry, section of Medical Psychology and Psychotherapy
PhD period 2017-2021
Promotor(s) Prof.dr. J.J. van Busschbach & Prof.dr. M.E.J. Reinders
Co-promotor(s) Dr. S.Y. Ismail & Dr. E.K. Massey

1. PhD training

	Year	Workload (Hours/ECTS)
General courses		
PubMed Systematic Research	2017	8 / 0.3 ECTS
EndNote Course	2017	4 / 0.1 ECTS
CPO Course	2017	8 / 0.3 ECTS
PhD Day 2017	2017	6 / 0.2 ECTS
Scientific Integrity	2017	8 / 0.3 ECTS
Specific courses (e.g. Research school, Medical Training)		
Decision Analytic Modelling for Economic Evaluation (York, UK)	2017	40 / 1.4 ECTS
Master of Science in Health Economics, Policy& Law (Erasmus University, Rotterdam)	2017-2019	60 ECTS
Advanced Decision Analytic Modelling (York, UK)	2019	16 / 0.6 ECTS
Seminars and workshops		
ISPOR Boston – Short Courses	2017	16 / 0.6 ECTS

(Inter)national conferences & Presentations		
• BOOT Zeist, the Netherlands	2017	
• Lola HesG Rotterdam, the Netherlands: 1 Oral presentation	2017	
• ISPOR Boston, United States	2017	
• Lola HesG (Hoenderloo): Discussant and chair	2017	
• BOOT Rotterdam, The Netherlands: 1 Oral presentation	2018	
• NND, Veldhoven, the Netherlands	2018	
• BOOT Amsterdam, the Netherlands: 1 Oral presentation	2019	
• ELPAT, Krakow, Poland, 1 Oral presentation	2019	
• NND, Veldhoven, the Netherlands, 1 Oral presentation	2019	
• Regionale Nascholing, Rotterdam, the Netherlands, 1 Oral presentation	2020	
• 1e Twents Nefrologie Symposium, 1 Oral presentation	2020	
• BOOT Roermond, the Netherlands, 1 Poster presentation	2020	
• NND (online): 1 Oral presentation	2021	
• ESOT Torino, Italy, 1 Oral presentation, 1 Poster presentation	2021	
Other		
Training ‘Omgaan met Groepen’	2017	3 / 0.1 ECTS
Training ‘Coaching for medical students’	2018	8 / 0.3 ECTS
Training ‘Teach the Teacher’	2019	8 / 0.3 ECTS

&

2. Teaching

	Year	Workload (Hours)
Lecturing		
Communication & Professionalization for medical students	2017-2019	200 hours
Minor Medical Psychology	2018-2020	30 hours
NIHES course 'Failed Interventions'	2020-2022	15 hours
Supervising Master's theses		
Supervising 2 masterstudents	2019-2020	
Other		
Coaching medical students	2018-2020	28 hours

3. Other publications

1. Kloss K, Ismail S, Redeker S, et al. Factors influencing access to kidney transplantation: a research protocol of a qualitative study on stakeholders' perspectives. BMJ Open. 2019; 9: e032694.
2. Peters CML, de Vries J, Redeker S, et al. Cost-effectiveness of the treatments for critical limb ischemia in the elderly population. Journal of Vascular Surgery. 2019; 70: 530-38.e1.