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## Patient-relevant outcomes after kidney transplantation

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# Chapter 6

Outcomes after kidney transplantation, let's focus on the patients' perspectives

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## **Abstract**

Graft function and patient survival are traditionally the most used parameters to assess the objective benefits of kidney transplantation. Monitoring graft function, along with therapeutic drug concentrations and transplant complications, comprises the essence of outpatient management in kidney transplant recipients (KTRs). However, the patient's perspective is not always included in this process. Patients' perspectives on their health after kidney transplantation, albeit subjective, are increasingly acknowledged as valuable health care outcomes and should be considered in order to provide patient-centered health care. Such outcomes are known as patient-reported outcomes (PROs; for example, health-related quality of life and symptom burden) and are captured using patient-reported outcome measures (PROMs). So far, PROMs have not been routinely used in clinical care for KTRs. In this review, we will introduce PROMs and their potential application and value in the field of kidney transplantation, describe commonly used PROMs in KTRs, and discuss structural PROMs implementation into kidney transplantation care.

## Introduction

In the past 60 years, kidney transplantation has been established as the preferred renal replacement therapy for most patients with end-stage kidney disease[1]. Many studies have shown its survival benefits compared to dialysis[1-3]. However, in an era where patient-centered health care is continuously gaining importance, patients' perspectives about their health should be taken into account in addition to clinical outcomes to understand the merit of treatments and to guide treatment decisions. Such perspectives, captured in patient-reported outcomes (PROs), can be structurally measured employing validated patient-reported outcome measures (PROMs)[4]. Studies have shown that PROMs can improve health care in patients with chronic conditions such as cancer[5, 6]. In a recent nationwide Dutch study conducted by our research group, PROMs were implemented into standard dialysis care to routinely measure health-related quality of life (HRQOL) and symptom burden[7]. In kidney transplantation, PROs have been advocated as core outcomes in research by the Standard Outcomes in Nephrology (SONG) initiative[8]. However, PROMs have not yet been widely used in clinical care for kidney transplant recipients (KTRs). To raise awareness of the clinical use of PROMs in kidney transplantation care, we will describe the potential application and benefits of PROMs in clinical practice, introduce commonly used PROMs in kidney transplant research, and describe an initiative to implement PROMs in incident Dutch KTRs.

### General concept: PROMs

PROMs are validated questionnaires to measure patients' appraisal of their health and functioning, which can either be generic or disease-specific. Generic PROMs are not specific to any particular disease or condition. Therefore, generic PROMs are suitable for use among patients with multi-morbid conditions and can be used in different populations to facilitate the comparison of outcomes between patient groups. A disadvantage is that generic PROMs don't necessarily cover the prevalent health issues specific to a condition of interest and might include less specific questions. Consequently, they may be less sensitive to detect important changes in outcomes when administered in specific patient groups. Disease-specific PROMs focus on a specific disease or treatment and are more suitable to detect disease-specific changes in a particular patient group and can provide valuable information for targeted interventions. Generic and disease-specific PROMs are often combined to map all outcomes of interest[4, 9-11]. For example, in the aforementioned nationwide study in the Dutch dialysis population, a generic PROM (the 12-item Short-Form Health Survey, SF-12) is used to measure HRQOL and a disease-specific PROM (the Dialysis Symptom Index, DSI) is used to assess symptom burden[7]. To date, a variety of PROMs have been developed to

measure different PROs, including HRQOL, symptom burden, illness perceptions, functional status and health behaviors[4].

## Potential benefits of PROMs for kidney transplantation care

### To facilitate patient management and improve outcomes

Due to the immunosuppressive treatment and its side effects, KTRs experience a high symptom burden and compromised levels of HRQOL[12, 13]. When ignored, they can eventually influence graft and patient survival[14, 15]. Literature suggests that underdiagnosis and undertreatment of symptoms is a common problem in both patients treated with dialysis and KTRs[16-19]. For example: a single-center audit of depression screening in a UK outpatient clinic has revealed underdetection of depressive symptoms among KTRs (screening rate: 13.8%; the prevalence of depressive symptoms: 22.4%)[18]. In a survey among nephrologists, 96% of the respondents only addressed sexual dysfunction – another common symptom among KTRs – during consultations in less than half of their transplant patients, with the biggest barrier being that patients did not express such concerns spontaneously[19]. The implementation of PROMs can complement the existing laboratory or radiological measurements, hereby enabling a more comprehensive evaluation of a patient's health[20]. **Table 1** lists some of the current evidence on the benefits of PROMs regarding the management of patients with chronic kidney disease[8, 20-25]. Results from randomized trials have echoed the clinical benefits of PROMs for patient management, showing a positive association between symptom screening using PROMs and improved patient survival and HRQOL compared to standard care in cancer patients[26, 27]. Routinely measured PROs also have prognostic value, which allows early adjustment in treatment strategy to achieve better health outcomes in patients. In a recent post-hoc analysis of trial data, KTRs with “always good” and “poor-to-improved” HRQOL trajectories within the first 3 years after transplantation had a similar risk of graft failure while the risk in the subgroups with “always fair” and “always poor” HRQOL were 4-fold and 19-fold higher compared to their counterparts with “always good” HRQOL[15]. Such information can be used to identify high-risk patients and consequently modify treatment strategies or provide additional support. Furthermore, PROMs have been recommended to monitor adherence to immunosuppressants, a vital modifiable risk factor for graft failure in KTRs, combined with laboratory tests[28]. After identification of non-adherent patients by means of validated PROMs, active interventions (e.g., establishing a reminder system) can be used to improve medication adherence[29]. Finally, it is important to note that, contrary to the concern about inadequate time in the consultation room, discussing PROs with patients doesn't necessarily prolong the clinical visit[30].

**Table 1.** Benefits and necessity of PROMs identified in nephrology care.

Author (year)	Study design	Study population	Identified benefits or necessity of PROMs
Evans et al., 2020[20] <sup>a</sup>	A multi-center, longitudinal, mixed-method study	Patient on hemodialysis and health professionals	Facilitate standardized symptom screening; Improve awareness of symptoms in patients and health professionals; Empower patients to raise questions with health professionals.
Aiyegbusi et al., 2019[21] <sup>a</sup>	A single-center qualitative study	Patients with stage 4 or 5 not on dialysis and health professionals	Facilitate patients and health professional communication; Allow timely identification of otherwise neglected health problems; Facilitate self-management in patients and potentially reduce clinical visits; Allow health professionals to address health problems prioritized by patients.
Schick-Makaroff et al., 2019[22] <sup>a</sup>	A multi-center qualitative study	Patients on dialysis and health professionals	Allow intervention for identified health problems; Direct interdisciplinary follow-up or further assessment.
Morton et al., 2019[23] <sup>a</sup>	A cross-sectional survey study	Health professionals from renal units	Inform clinical care.
Schick-Makaroff and Molzahn et al, 2017[24] <sup>a</sup>	A multi-center, longitudinal, mixed-method study	Patients on dialysis and health professionals	Allow health professionals to address health problems prioritized by patients; Direct interdisciplinary follow-up; Improve awareness of health problems in patients; Bring positive changes of medical care to patients.
Verberne et al. [25], 2019	International consensus workshop	Kidney disease experts and patient representatives	PROMs identified as one of the standard set of value-based outcome measures.
Tong et al., 2017[8]	International consensus workshop	Kidney disease experts and patient representatives	PROs (e.g. life participation) recommended as an essential component of the core outcome set.

<sup>a</sup>Most important qualitative and quantitative studies that have investigated the impact of PROMs in patients with kidney disease and/or relevant health professionals. Abbreviations: PROMs, patients reported outcome measures; PRO, patient-reported outcome.

## To improve patient participation

Active patient participation in their care delivery is important for KTRs, as they have chronic conditions with a high treatment burden (e.g., taking multiple medications to prevent rejection and for comorbidities and complications caused by chronic immunosuppression). A recent qualitative study investigating determinants for patient participation showed that, among other factors, patients' knowledge and understanding of their health is essential for patient participation. Another important determinant is the availability of tools and routines

(e.g., PROMs and protocols) that health care professionals can use to encourage patients to be more actively involved in their own health care[31]. Notably, PROMs implementation provides the opportunity to improve patient participation for both patients and professionals. PROMs completion can prompt patients' understanding of their medical conditions (i.e. illness insight), facilitate patient-provider communication, and therefore form a basis for better self-management and engagement in the process of shared (clinical) decision-making[20, 32, 33]. Please also see **Table 1** for the supportive evidence of PROMs use in nephrology care.

### **To evaluate the value of transplantation**

Patient survival and graft function are widely used to evaluate kidney transplant care. However, despite a well-functioning graft, KTRs can experience unsatisfied and impaired levels of HRQOL[8, 34]. Therefore, it is essential to assess outcomes reported by patients. Furthermore, due to the growing number of elderly patients accepted for kidney transplantation and the increased use of extended criteria donor kidneys over the recent decades[35, 36], the survival benefit of transplantation may not be present in all subgroups of KTRs. A recent national Dutch registry study pointed out that the five-year survival of elderly KTRs with an elderly deceased donor, especially after cardiac death, was comparable to that of dialysis patients on the waiting list[37]. Notably, elderly recipients did report a better HRQOL after transplantation in another previous study[38]. Such findings stress the need for health care professionals to look beyond clinical outcomes to evaluate the benefits of kidney transplantation. In the emerging value-based health care theory, which emphasizes patient-relevant outcomes relative to the medical cost, PROMs are instrumental in assessing the overall value of care by incorporating the patient's voice[39]. According to the International Consortium for Health Outcomes Measurement (ICHOM) chronic kidney disease working group, a PROM to measure HRQOL is part of the recommended standard set of outcomes for health care along with patient survival, disease burden (i.e. hospitalization and cardiovascular events) and treatment modality-specific outcomes (i.e. graft function, graft survival, acute rejection, and malignancies) in KTRs[25].

### **To guide decision-making and policy-making**

PROs are important outcomes that should be taken into account to guide shared decision-making. For instance, doctors and patients can choose the most suitable renal replacement therapy not only based on patient survival but also HRQOL. Furthermore, stakeholders within the transplant community have argued that the current organ allocation policy that values longevity is outdated, and a comprehensive evaluation involving post-transplant HRQOL, functional status, and the cost is more relevant[40]. Prediction models comprising both

clinical and patient-reported outcomes can be developed to facilitate the above process. Despite that PROs have been adopted as an outcome in kidney transplant research, large longitudinal studies in incident patients with a long-term follow-up are still lacking to support the use of aggregated PROMs information in clinical practice.

## **PROMs for kidney transplantation**

In the field of chronic kidney disease (CKD) and kidney transplantation, different international working groups have emphasized the importance of PROMs in clinical practice[25, 41]. As the most frequently measured PRO, many PROMs have been developed or validated to measure HRQOL, including those for kidney transplant recipients. In this review, we will narratively introduce generic and disease-specific PROMs for HRQOL and PROMs for symptom burden – a main determinant of HRQOL.

### **PROMs for HRQOL in kidney transplantation**

A working group with geographical diversity was assembled in 2016 by ICHOM to select a set of PROMs for patients with CKD on conservative treatment, on dialysis and after kidney transplantation. The invited health care professionals and patient representatives concluded that the following six HROQL domains were required to sufficiently capture HRQOL: general HRQOL, physical function, daily activity, pain, fatigue and depression. In total, three generic PROMs were recommended by the workgroup to measure HRQOL: the 36-item Short-Form Health Survey (SF-36), the RAND 36-item Health Survey (RAND-36), and the combination of Patient-Reported Outcomes Measurement Information System (PROMIS)-Global Health and the 29-item PROMIS (PROMIS-29)[25]. In a European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) experts consensus meeting involving 45 European renal registries, the SF-12 was selected as the preferred generic PROM to measure HRQOL in practice due to its efficiency routinely[41]. The SF-12 was developed as a shorter version of the SF-36. In a reliability and validity study, the SF-12 reproduced similar physical and mental HROQL summary scores as the SF-36 but less comparable scores for the separate HRQOL domains[42]. Finally, the validated EuroQol 5-Dimension (EQ-5D) was recommended by the same ERA-EDTA consensus meeting to assess health status and to study the cost-value as it provides the utility data required for such analysis[41].

The ICHOM workgroup also identified two kidney disease-specific PROMs to measure HRQOL, namely: the Kidney Disease Quality of Life-Short Form (KDQOL-SF) and its shorter version: the Kidney Disease Quality of Life-36 (KDQOL-36). Even though both PROMs cover the required HRQOL domains, they were not recommended by ICHOM to measure HRQOL because they also contain kidney disease-specific domains (e.g., symptoms, the burden of kidney disease



and effects of kidney disease)[25, 43, 44]. However, the KDQOL-36 was recommended by the ERA-EDTA experts consensus meeting to routinely measure disease-specific HRQOL[41]. Finally, there are also validated kidney transplant-specific HRQOL PROMs, including the Kidney Transplant Questionnaire (KTQ)[45] and the End-Stage Renal Disease - Symptom Checklist - Transplantation Module (ESRD-SCL-TM)[46]. **Table 2** shows detailed information of the aforementioned generic, disease-specific and kidney transplantation-specific PROMs for HRQOL[42, 44-50].

## **PROMs for symptom burden in kidney transplantation**

KTRs have a high symptom burden[13]. The ERA-EDTA experts consensus meeting emphasized the importance of monitoring patients' symptom experience, although no agreement was achieved over a preferred PROM to measure symptom burden[41]. The ICHOM workgroup did not recommend a PROM for symptom burden either but did encourage health care professionals to measure symptom experience[25]. There are several suitable and validated PROMs to measure symptom burden in KTRs that will be discussed below.

The Modified Transplant Symptom Occurrence and Symptom Distress Scale - 59 Items Revised (MTSOSD-59R) aims explicitly to measure the side effects of immunosuppressive therapy and is suitable for mapping symptom burden in KTRs. This 59-item checklist is an updated revision of MTSOSD-45, complemented with side effects of the newer generation of immunosuppressants such as tacrolimus, mycophenolate-based formulations, everolimus and belatacept. The MTSOSD-59R measures both symptom occurrence and symptom distress[51].

The Gastrointestinal Rating Scale (GSRs) is a PROM that covers gastrointestinal symptoms due to the immunosuppressive regime. Five symptom clusters measured by this 15-item PROM are: reflux, abdominal pain, indigestion, diarrhea and constipation[52]. Compared to the two previously mentioned PROMs, the GSRs has a narrower symptom spectrum as it only focuses on symptoms related to the digestive system.

The revised version of Edmonton Symptom Assessment System (ESAS-r) is a PROM primarily designed to measure symptom burden in patients receiving palliative care. It has been validated in both dialysis patients and KTRs, which enables potential use in longitudinal follow-up across different renal replacement therapies. This PROM measures the severity of the following nine symptoms: pain, tiredness, nausea, shortness of breath, lack of appetite,

**Table 2.** Generic, kidney disease-specific and kidney transplantation-specific HRQOL PROMs.

Target population	Number of items	Time indication to complete (minutes)	Licensing	Domain Coverage	HRQOL scores
<i>PROMs recommended by the ICHOM CKD working group</i>					
PROMIS Global health[47] <sup>a</sup>	10	5	None	Overall physical health, mental health, social health, pain, fatigue, and overall perceived HRQOL.	Summary score for mental and physical HRQOL.
PROMIS-29[48] <sup>a</sup>	29	10	None	Depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social roles and activities.	Domain scores.
SF-36[42]	36	10	License fee	Vitality, physical functioning, bodily pain, general health, physical role functioning, emotional role functioning, social role functioning, and mental health.	Domain scores and summary score for mental and physical HRQOL. Identical to SF-36.
RAND-36[49]	36	10	None	Identical to SF-36.	Summary score for mental and physical HRQOL.
<i>PROMs recommended by the ERA-EDTA consensus meeting</i>					
SF-12[42]	12	5	License fee	Identical to SF-36.	Summary score for mental and physical HRQOL.
EQ-5D[50]	6	5	License fee	Mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and a VAS for global health	Utility score and EQ-VAS score. HRQOL score.
KDQOL-36[44]	36	15	None	SF-12 and disease-specific domains: symptoms, burden of kidney disease, and effects of kidney disease.	Domain scores and summary score for mental and physical HRQOL.
<i>Commonly used kidney transplantation-specific PROMs</i>					
KTQ[45]	25	15	None	Physical symptoms, fatigue, uncertainty/fear, appearance, and emotions.	Domain scores.
ESRD-SCL[46]	43	10	None	Physical capacity, cognitive capacity, cardiac and renal dysfunction, side effects of corticosteroids, increased growth of gum and hair, and transplantation-associated psychological distress.	Domain scores and a global HRQOL score.

<sup>a</sup>The two questionnaires should be used in combination to cover all 6 domains (general HRQOL, physical function, daily activity, pain, fatigue and depression) prioritized by the working group. The first 4 items for each questionnaire were adapted from a published article[53]. Abbreviations: CKD, Chronic Kidney Disease; EQ-5D, EuroQol 5-Dimension; ESRD-SCL, End-Stage Renal Disease-Symptom Checklist; ERA-EDTA, European Renal Association – European Dialysis and Transplant Association; ICHOM, International Consortium for Health Outcomes Measurement; KDQOL-36, Kidney Disease Quality of Life-36; HRQOL, health-related quality of life; KTQ, Kidney Transplant Questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System; Patient Reported Outcome Measures, PROMs; SF-36, 36-Item Short-Form Health Survey; SF-12, 12-Item Short-Form Health Survey; VAS, Visual Analogue Scale.

**Table 3. Validated symptom PROMs for kidney transplant recipients**

PROMs	Target population	Number of items	Time indication to complete (minutes)	Licensing	Symptom scores
<i>PROMs to measure symptom/symptom burden</i>					
MTSOSD-59R[51]	Under immunosuppressive treatment	59	10-15 <sup>a</sup>	None <sup>b</sup>	Symptom occurrence and symptom distress
MTSOSD-45[51]	Under immunosuppressive treatment	45	10 <sup>a</sup>	None	Symptom occurrence and symptom distress
GSRs[52]	Under immunosuppressive treatment	15	5 <sup>a</sup>	None	Scores for each symptom cluster (reflux, abdominal pain, indigestion, diarrhea and constipation)
ESAS-r[53]	Kidney disease	9	5 <sup>a</sup>	None	Global, physical and emotional symptom scores
<i>HRQOL PROMs with domains to measure symptoms</i>					
KDQOL-SF[44]	Kidney disease	82 (12 <sup>c</sup> )	15	None	Symptom score
KDQOL-36[44]	Kidney disease	36 (6 <sup>c</sup> )	25	None	Symptom score
ESRD-SCL[46]	Kidney transplantation	43 (18 <sup>c</sup> )	10	None	Domain scores (side effect is corticosteroids, increased growth of gum and hair, Transplantation-associated psychological distress)
<i>Examples of PROMs for one specific symptom</i>					
PSQI[54]	Non-specific	19	5-10	License fee	Global PSQI score and domain scores (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction)
HADS[55]	Non-specific	14	2-5	License fee	Global HADS score
BDI[55]	Non-specific	21	2-5	License fee	Global BDI score

<sup>a</sup>Time indication to complete the PROM was extrapolated based on our experience with the Dialysis Symptom Index, a 30-item PROM to measure both symptom occurrence and symptom distress.

<sup>b</sup>Permission and conditions to use the BAASIS© can be obtained from [sabina.degeest@unibas.ch](mailto:sabina.degeest@unibas.ch)

<sup>c</sup>Number of items to measure symptoms.

Abbreviations: BDI, Beck Depression Inventory; ESAS-r, Revised version of Edmonton Symptom Assessment System; ESRD-SCL, End-Stage Renal Disease-Symptom Checklist; GSRs, Gastrointestinal Symptom Rating Scale; HADS, Hospital Anxiety and Depression Scale; KDQOL-36, Kidney Disease Quality of Life-36; KDQOL-SF, Kidney Disease Quality of Life Short Form; MTSOSD-45, Modified Transplant Symptom Occurrence and Symptom Distress Scale – 45 item; MTSOSD-59R, Modified Transplant Symptom Occurrence and Symptom Distress Scale - 59 Items Revised; PSQI, the Pittsburgh Sleep Quality Index.

drowsiness, depression, anxiety and general well-being. It generates three summary scores: the global, physical and emotional symptom scores[53].

Notably, some of the previously mentioned PROMs to measure HRQOL also include items measuring symptom experience. The ESRD-SCL-TM contains specific items assessing the side

effects of corticosteroids (5 items), increased gum growth and body hair (5 items), and transplantation-related psychological discomfort (8 items)[46]. However, it only covers the side effects of commonly used immunosuppressants two decades ago. The KTQ and the KDQOL-SF/36 measure 6 and 12 symptoms, respectively[43-45]. Finally, there are also commonly used PROMs that measure only one specific symptom in KTRs. For example, the Pittsburgh Sleep Quality Index (PSQI)[54] is used to measure sleep disorders, and the Hospital Anxiety and Depression Scale (HADS) or the Beck Depression Inventory (BDI)[55] are used to assess depressive and anxiety symptoms. **Table 3** shows detailed information of the aforementioned PROMs measuring symptom burden[44, 46, 51-55].

## Implementation of PROMs in routine care

Despite the not yet available evidence of the effect of PROMs implementation on actual health outcomes (e.g. HRQOL or survival) in patients receiving dialysis treatment or KTRs, a number of studies have reported positive findings with regard to other outcomes (Please see **Table 1**). In recent years, there have been increasing attempts to implement PROMs in nephrology care, mostly in patients with CKD or patients treated with dialysis[7, 20, 56, 57]. Implementation of PROMs in clinical care is far more complicated than handing out a questionnaire to patients. Multiple factors can hinder the implementation and diminish the value of PROMs. For health care professionals, insufficient knowledge of the PROMs, limited time in the consultation room, failure to integrate PROMs in the standard workflow, absence of standard protocols to improve PROs, and a lack of administrative support (e.g., a lack of staff and electronic system) can discourage the use of PROMs[58, 59]. For patients, the major barriers include: the inability to complete PROMs due to poor health status or difficulties using an electronic device, perceived low value of PROMs, and too much time to fill out the PROMs[59]. Therefore, efforts during the design phase and the preparation phase are essential for the successful implementation of PROMs in clinical practice. In these phases, it is important to take at least the following steps: select suitable PROMs, decide on how to administrate the PROMs, develop the electronic system to facilitate its use during consultations, and train professionals how to interpret and intervene on the PROM-results[60].

When it comes to longitudinally monitoring PROs, the response rate also poses a challenge. A considerable variation in and downward trend of response rate for PROMs are often encountered in registry-based studies[61]. In the Dutch dialysis PROMs study, the response rate also varied greatly among the dialysis centers (ranging from 6% to 70%) and the response rate declined over time (28% at baseline compared to 21% at 3 and 6 months). The variation between medical centers was most likely related to differences in infrastructure and logistical

approaches (i.e. providing tablets) and engagement of health professionals. The relatively low baseline response rate is in line with a previous PROMs study in dialysis patients in Scotland[62], and could be seen as an indication to improve stakeholder engagement (e.g. increase awareness of PROMs in health professionals and patients)[7]. With regard to the decline in response rate over time, potential explanations include: 1) patients forget to complete the PROMs, 2) patients have a poor health status, 3) patients get insufficient support when completing the PROMs, 4) patients have (unrealistically) high expectations of PROMs implementation which may negatively influence its perceived value, 5) health professionals do not discuss and/or (adequately) respond to the PROM-results (e.g. due to a lack of efficient treatment or multidisciplinary care)[20, 63, 64].

Previous studies suggest general measures to improve the response rate, including sending reminders to patients, providing PROMs in different formats (digital and paper version) and languages and facilitating PROMs completion during their hospital visit[61, 65]. In the Dutch dialysis PROMs study, 41% of the responders received support to complete the PROMs (i.e. reading the questions, translating questions and filling in patients' answers on their behalf) and providing tablets for patients to complete the PROMs during dialysis was associated with higher response rate[7]. Finally, building realistic expectations of using PROMs in patients and health professionals and providing adequate resources to respond to the PROM-results should also be addressed. However, from a value-based perspective, one could ask oneself the question whether maximal efforts should be made to improve the response rate as the costs will rise along with the increased efforts[65].

## **Implementation of PROMs in Dutch health care for KTRs**

Currently, PROMs (i.e. the SF-12 as generic PROM to measure HRQOL and the DSI as disease-specific PROM to measure symptom burden) are implemented in all Dutch dialysis centers to routinely measure PROs over time and to improve health outcomes of dialysis patients[7]. Following this initiative by our research group, we aim to take similar steps in KTRs by means of the Patient-reported OutcomeS In kidney Transplant recipients: Input of Valuable Endpoints (POSITIVE) study. To enable successful PROMs implementation in Dutch KTRs, several of the aforementioned factors were taken into account and will be discussed below.

First, the PROMs were carefully selected for KTRs with regard to the content and the time it takes to fill in the PROMs. To enable comparison with the dialysis population and to ensure longitudinal follow-up of patients across different CKD stages and across treatment modalities, we harmonized the KTRs PROMs with those administrated in the dialysis population. Thus, the SF-12 and the DSI are selected for the POSITIVE study to measure

generic HRQOL and CKD symptom burden. A recent mixed-method study has shown positive results in using the DSI to measure symptom burden in prevalent KTRs[66]. In addition to these two PROMs, the MTSOSD-59R is included in the POSITIVE study as a treatment-specific PROM for chronic immunosuppression to capture the full range of symptoms experienced by KTRs (i.e. CKD symptoms and medication side effects). Taken together, the Dutch kidney transplantation PROMs can be filled out in approximately 15 minutes (5 minutes for the SF-12[25], 5 minutes for the DSI[66], and 5 minutes for the complementary items from the MTSOSD-59R). Based on our experience, the time to read a PROM-report is approximately 1 minute (for both patients and health professionals) and the time to discuss PROM-results depends on the number of health issues that need to be addressed.

Second, to facilitate the use of PROMs by patients, digitalized and paper versions of the PROMs are available and will be provided according to patient's preference. PROMs are also available in different languages (i.e. Dutch but for example also English). All participating patients are asked to fill out the questionnaire at transplantation (during the hospitalization for transplantation); six weeks, six months and one year after kidney transplantation; and hereafter annually. A reminder is sent to patients if the PROMs are not filled one week before the scheduled time point.

Third, to encourage the clinical use of PROMs by healthcare professionals, an electronic module has been developed so that the PROM-report is easily accessible for nephrologists in their local hospital system. For medical centers with such measures to facilitate PROMS implementation are endorsed by studies in cancer patients[67, 68]. Continuous attention is also being paid (e.g. by means of presentations) towards increasing professionals' awareness and knowledge of PROMs and PROM-results (e.g. the e-module, how to interpret the results, etc.).

Fourth, to facilitate the discussion about PROs in the consultation room, a PROM-report is generated directly after PROMs completion and accessible for the patients and their doctors. The report contains information about the patient's HRQOL and symptom burden scores. Similar to the PROM-report used in the Dutch dialysis population (<https://www.nefrovisie.nl/proms-faq/>), HRQOL scores are presented with reference values (e.g. the Dutch general population) in bar charts and the response to each HRQOL-item and symptom-item is categorized into three levels based on their severity and colored accordingly: the red color indicates the highest burden caused by that specific item, orange indicates moderate burden, and green indicates the lowest burden. The graphical presentation and classification of PROs are believed to promote the interpretability and clinical actionability for providers[69, 70]. The report is filled out prior to consultation and

discussed at the upcoming clinical visit. In case of an alarming report (e.g. extremely low HRQOL or extremely high symptom burden), an extra telephone or video consultation can be arranged before the scheduled visit.

This ongoing POSITIVE study showcases the first steps to incorporate PROMs in kidney transplantation care and hereby also the next step in the implementation of PROMs into Dutch nephrology care. Future studies are needed to investigate the determinants for successful PROMs implementation in KTRs. **Figure 1** briefly illustrates the roadmap for this study.

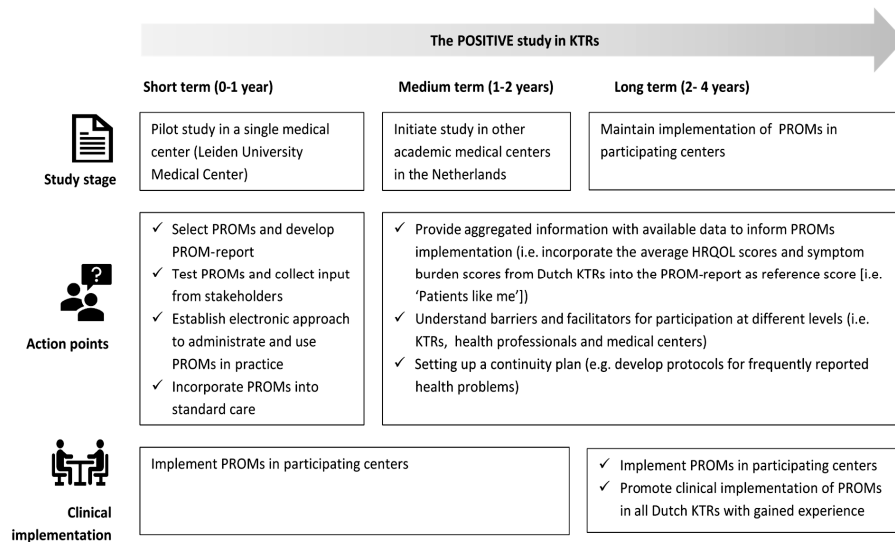


Figure 1. Road map of the POSITIVE study.

## Conclusion

PROMs are potentially powerful tools to assess PROs and improve the value of health care at an individual and population level. A number of PROMs to measure HRQOL and symptom burden are available for KTRs, although not yet commonly used in clinical practice. To the best of our knowledge, there is no agreement on a preferred HRQOL or symptom PROM for routine assessment in KTR. The decision to use a specific PROM should depend on the purpose and the population. To implement the PROMs in clinical practice, sufficiency preparation at an early stage and sufficient efforts to maintain the response rate are necessary.

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