Patient self-management in kidney transplantation: Definition, Measurement, and Intervention

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SUMMARY

While one-year graft survival rates for deceased donor transplants have soared from about 40% in 1975 to more than 90% in 2005 [1], the long-term perspective has changed very little. From 1996-2005, 10-year deceased donor graft survival has remained at about 40%, only slightly above that of the 1987-1995 period [1]. Furthermore, the gain in graft survival between 1988 and 1995, based on calculated real half-lives, has been reported as 4.7 or 8.4 months, for first or further deceased donor transplants, respectively. These numbers reveal that estimates of doubled half-lives from 1988 to 1995, which were based on projected half-lives, were far from accurate [2]. The remarkable short-term improvements have thus not translated into long-term advantages [1, 2].

Improving long-term post-transplantation outcomes should therefore be a priority of transplant recipient management. Investing in chronic illness management, which focuses on improving patient self-management and medication adherence, is a promising pathway in that direction.

Chronic illness management has lately emerged as a response to the reported dramatic global increase in chronic conditions [3]. A chronic condition is defined as one that is never completely cured [4] and that requires ongoing long-term management of the illness, coexisting morbidities, treatments, or measures to prevent further disability [3]. Such management imposes a heavy burden on current health care systems. The gravity of the situation is increased by the application of acute care models (i.e., prioritizing the treatment and cure of peoples' acute and urgent symptoms), which have limited effects on chronic conditions [3]. Effective chronic care models, i.e., care that improves chronically ill patient populations' conditions, are characterized by continuity of care, partnership with patients, families, and communities, support for patients in improving self-management skills, attention to preventive measures, decision-making support for healthcare providers, and availability of clinical information systems [3, 5-7]. Empirical evidence underlines the effectiveness of chronic illness management [8-10]. Of these,

models that incorporate patient self-management support show the most improved outcomes [3, 7, 11].

Patient self-management refers to actions performed by patients for themselves in daily life to manage their illness and treatment, and to avoid health deterioration [5, 12]. Related support consists of two components: the training of disease specific knowledge and technical skills, and the training of non-disease specific problem solving and other skills to assist behavior change [13]. A growing body of evidence in patients with chronic illness demonstrates that supporting patient self-management positively impacts outcomes [10, 14-19].

An essential component of patient self-management is managing the medical regimen, including adherence, i.e., "the extent to which a person's behavior (taking medications, following a recommended diet, and/or executing lifestyle changes) corresponds with the agreed recommendations of a healthcare provider" [8]. The scale and impact of medication adherence regarding patient outcomes have been widely demonstrated in chronic patient populations [20-22]. Recent literature reviews regarding kidney transplantation [23-25] demonstrate that non-adherence to immunosuppressive therapy is a major contributor to poor clinical outcomes. Given that inadequate medication adherence has critical implications on health outcomes, focusing prominently on adherence as an essential part of patient self-management is crucial to improve outcomes in the kidney transplant population.

The gaps in the literature guiding this research program were as follow: 1) as no conceptualization was available for patient self-management in the kidney transplant population, it was necessary to define one; 2) little information was available on the diagnostic accuracy of measurement methods to identify medication non-adherence in the kidney transplant population, 3) there was a need to test medication adherence enhancing interventions, as very little information was available on this patient group; and 4) there was a need to evaluate a technological intervention designed for patient use, as such information was lacking.

The work and studies incorporated in this research program to address these gaps used a variety of methods, including both quantitative and qualitative approaches. The studies are summarized as follows.

First, a comprehensive definition of kidney transplant recipient self-management has been developed, summarizing evidence from the transplant literature. This definition provides both detailed kidney transplant specific self-management activities and core skills that patients may acquire or further develop for successful self-management. It also provides a conceptual model using a care paradigm that regards the patient as a worker having expertise at managing the illness in daily life. This is a crucial aspect of chronic illness management. The model outlined here can be used as a basis for the development of systematic and comprehensive kidney transplant recipient self-management support. It furthermore constitutes a crucial first step to allow transplant clinics to shift from an acute to a chronic care model for long-term transplant recipient management.

Second, the literature summarized current understanding about medication non-adherence, and provided an overview of current knowledge regarding correlates of medication non-adherence, as well as of medication adherence enhancing interventions in the kidney transplant population. Further, to offer a concrete example on how to implement theory based adherence enhancing strategies into an individual situation, it reports on a case study [26].

Third, we used a cross sectional study to test the diagnostic accuracy of immunosuppression assay, patients' self-reports, clinicians' collateral reports, and constructed composite adherence scores using electronic monitoring as a reference standard for a convenience sample of 249 kidney transplant recipients (female: 43.4%; mean age 53.6 (SD: 12.7), median 7 years (IQR: 9 years) post-transplantation). Medication non-adherence prevalence, as assessed by electronic monitoring, was 17.3%. Across the measurement methods, prevalence rates varied from 12.4% for self-reports to 38.9% for composite adherence scores. Of all the measures, the composite adherence score yielded both the highest sensitivity (72.1%) and the highest likelihood ratio of a

positive test (2.74), while collateral reports of at least three clinicians showed the highest specificity (93.1%). While no measures showed high sensitivity alongside high specificity, combining measures increased diagnostic accuracy, indicating the relevance of combined measures for clinical and research purposes [27].

Fourth, we tested the efficacy of an educational/behavioral intervention and enhanced social support intervention to increase medication adherence in 18 non-adherent renal transplant recipients (age: 45.6±1.2 yr; 78.6% male). Using a pilot randomized controlled trial, the study showed a remarkable decrease in non-adherence in the intervention group (IG, n=6) and in the enhanced standard care group (EUCG, n=12) over the first three months (IG, χ^2 =3.97, df=1, p=.04; EUCG, χ^2=3.40, df=1, p=.06). The interventions appeared to add further benefit to medication adherence levels in the IG, as the greatest decrease in non-adherence was observed there. This result was not, however, statistically significant (at 90 days:, χ^2=1.05, df=1, p=.31), owing to insufficient sample size [28].

Fifth, we tested the content validity and usability of a computer based patient information and education tool (OTIS^{TM}), from the perspectives of clinicians and patients. Using qualitative methods and a purposive sample of 8 clinicians and 14 patients, the study identified deviations from current medical practice regarding the content, language, and information structure of OTIS^{TM}. Seven of the eight clinicians rated OTIS^{TM} as non-relevant for implementation in clinical practice and all patients encountered usability problems, mostly regarding the program's interface. Emerging categories from the patients' perspectives vis à vis content were knowledge acquisition, illness management, and partnership forming. The study demonstrated the need to establish the presented material's content validity and usability by involving clinicians and patients well before its clinical implementation phase [29].

The results of our research program contribute in five main ways to the evidence base regarding kidney transplant recipients' self-management, and, more specifically, adherence to post-transplantation medication taking. First, it described, for the first time, a comprehensive kidney transplant recipient self-management model, outlining disease

specific activities and non-disease specific patient core skills. Second, it summarized knowledge on current understanding, correlates of medication adherence, and post-transplant adherence enhancing interventions. Third, it added detailed knowledge on diagnostic accuracy of state-of-the art measures to identify medication non-adherence in renal transplant recipients. Fourth, it provided evidence and thus added to the very limited amount of available information, supporting the feasibility of enhancing medication adherence in non-adherent renal transplant recipients using a package of educational-behavioral interventions and social support. Finally, it suggested that in order to ensure and maximize benefits to its intended users, technological interventions for patient use need to be evaluated with regard to usability and content validity.

Future research should focus on further development and testing of the conceptual model presented here, with attention to relationships between the model variables, to develop and evaluate valid kidney transplant recipient self-management measures, and to test whether supporting such self-management results in improved long-term health outcomes.

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INTRODUCTION

Despite impressive scientific advances in immunosuppression and in other aspects in the transplant management, which have reduced the incidence of acute and chronic rejection, recent evidence shows that no significant improvement in long-term kidney transplantation outcomes has been achieved since the 1970's [1]. One-year post-graft survival rates for deceased donor transplants have improved impressively, from about 40% in 1975 to more than 90% in 2005. Yet, while this level of success can scarcely be improved [1], such remarkable progress has not translated into long-term advantages [2]. Improving long-term outcomes should therefore be afforded a top priority in transplant-related research. Refining chronic illness management, including patient self-management and medication adherence, offers excellent potential for progress.

This thesis contributes to this goal by taking preliminary steps towards developing a kidney transplant recipients' self-management program. It consists of 7 Chapters, of which three detail original studies. Chapters 3-5 have been published, and Chapter 6 has been accepted for publication, all in peer reviewed journals.

In the context of kidney transplantation, the idea of chronic illness management as a care model is new and relatively unexplored: to date, no comprehensively study exists on kidney transplant recipients' self-management. Therefore, Chapters 1 and 2 below provide the background and aims of this thesis, based on the literature on chronic illness and kidney transplant groups.

- **Chapter 1** provides a literature based introduction to the use of chronic illness management to improve kidney transplant outcomes. This includes an introduction to patient self-management and medication adherence. More specifically, the description of the kidney transplant recipient self-management model outlines sets of activities and core skills to achieve behavior change.
- **Chapter 2** describes the aims of the research program.

Furthermore, as transplant recipients' medication management /adherence occupies a central role, both within self-management and within the expertise of the research group which embedded this thesis, further studies were directed to examine medication regimen adherence (Chapters 3-5):

- **Chapter 3** summarizes correlates of medication adherence and adherence enhancing interventions, and provides a case study to illustrate the practicability of translating theory-driven interventions into specific situations;
- **Chapter 4** explores the measurement of medication adherence; and
- **Chapter 5** reports on an intervention study testing theory based adherence enhancing interventions in non-adherent kidney transplant recipients.

Additionally, given the increasing importance of information technology in healthcare, this research program also included steps towards employing computer-assisted learning in kidney transplant clinics.

- **Chapter 6** reports on a study evaluating a computer-based patient information and education tool designed to enhance patient self-management after kidney transplantation.

To conclude,

- **Chapter 7** discusses the research program as a whole by placing the findings in a broader research and clinical practice context, identifying methodological issues, and suggesting further steps to develop and strengthen kidney transplant self-management programs.

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Chapter 1

Chronic illness management as an instrument to improve long-term kidney transplant outcomes

1.0. Long-term kidney transplant outcomes

Long-term graft survival after kidney transplantation has remained practically unchanged for three decades, despite significant improvements in short-term graft survival and immunosuppression [1]. Based on data from the UCLA Kidney Transplant Registry (n=46.000, start 1969), the United Network of Organ Sharing (UNOS) Kidney Transplant Registry (n=80.000, start 1987) and 138,000 transplant cases from 1996-2005, Kaneku et al. reported on a thirty-year trend in kidney transplants. While first-year graft survival for deceased donor grafts improved impressively from about 40% in 1975 to more than 90% in 2005, the long-term perspective is strikingly different. From 1987-1995, ten year deceased donor graft survival improved slowly from about 35% to about 40%, with no further advancement since then [1]. Furthermore, based on the US Scientific Renal Transplant Registry database for transplants performed between 1988 and 1995, the increase in graft survival over this period, based on real half-lives, was 4.7 months in deceased donor transplants, and 8.4 months in first deceased donor transplants. Further, whereas projected half-lives of deceased donor transplants (including re-transplant recipients) increased from 7.9 years in 1988 to 13.8 in 1995, a Kaplan Meier analysis yielded significantly shorter actual half-lives, i.e., 6.0 years in 1988 and 8.0 in 1995 [2]. These numbers reveal that the expected doubling of half-lives from 1988 to 1995, based on projected half-lives, resulted from an overestimation. These findings indicate that the remarkable short-term improvements have not translated into a long-term advantage [2].

The leading cause of late graft failure is chronic allograft nephropathy, i.e., a progressive decline in renal function, with prevalence rates of 81-86% [1, 3]. Evidence suggests that this condition is multifactorial in origin, with both immunological (e.g., human leukocyte antigen mismatch, inadequate immunosuppression, previous episodes of acute rejection) and non-immunological risk factors (e.g., age, race, sex, hypertension, hyperlipidemia, cytomegalovirus infection, recurrent and de novo disease) contributing to the decline of

renal function [3, 4]. Additionally, patient death is the most significant adverse outcome after kidney transplantation. According to the UNOS, the known long-term leading causes of death in deceased donor kidney transplant recipients from 1993-2004 were cardiovascular disease (22%), infection (16%), malignancy (6.8%), cerebrovascular/hemorrhage (6.3%), trauma (0.6%), non-adherence (0.2%), graft failure (1%), and various other (19%) [4].

The suggested insignificant contribution of non-adherence to patient outcomes may be due to a lack of routine or standardized non-adherence assessment in research and clinical care, as it contrasts directly with evidence demonstrating the detrimental impact of non-adherence on clinical outcomes [5-7]. However, other sources (e.g., [8]) have also neglected the patient's role in managing kidney transplantation as a possible pathway to maintaining graft function, overall health and thus long-term patient and graft survival. Only Gordon et al. (2005) have recently suggested considering the patient's role in managing aspects of transplantation in daily life when developing long-term strategies. More specifically, they suggested that patient engagement and self-management activities may be vital in limiting the decline of graft function, thus shifting from a pure molecular perspective to a behavioral level [9].

As patient self-management is an essential characteristic of chronic illness management, the following paragraphs discuss first chronic illness management, thus providing a context for patient self-management, then elaborate the definition of patient self-management as it relates to kidney transplantation.

1.1. Chronic illness management

With the 2002 global report, "Innovative care for chronic conditions: building blocks for action," the World Health Organization alerted policy makers and health care workers of the dramatic global increase of chronic conditions, and of the challenges this increase would entail for current and future health care systems [10]. Current health care systems use an acute care model, which prioritizes the treatment and cure of acute and urgent symptoms. However, such a model is ineffective when dealing with chronic conditions,

i.e., conditions that are not completely curable [11] and that require ongoing management across years due to the illness, coexisting morbidities, treatment, or prevention of further disability [10]. Chronic conditions have lifelong influence on people's daily lives. It is estimated that up to 99% [12] of daily chronic illness management is left to patients and their families, who are undersupplied by acute care models, which focus on identifying and treating the urgent acute episodic health problems of the remaining 1% [10, 12, 13].

In contrast, effective chronic care models focus on maintaining or improving the health of chronically ill populations. They are characterized by a number of building blocks that refer to continuity of care, partnership with patients, families, and communities, support for patients in improving their self-management skills, attention to preventive measures, decision-making support for healthcare providers, and availability of clinical information systems [10, 13-15].

Empirical evidence underlines the effectiveness of chronic illness management. Improved outcomes are observed among chronically ill patients when the care system shifts from an acute/curative model to one of chronic management [15-18]. Models incorporating elements of patient self-management support show outcomes superior to those lacking such components [10, 19].

Thus, a care model incorporating self-management support is preferable for patients with chronic conditions [10]. It can be hypothesized that kidney transplant recipient outcomes will also benefit from the incorporation of patient self-management support into related clinical care, as the chronic condition definition also applies to this patient group. More specifically, although kidney transplantation is the treatment of choice for end stage renal disease [20], it requires lifelong medical treatment, and coexisting morbidities are common [21]. In addition to regular medication taking and transplant center follow-ups, this includes preventing or managing risk factors for cardiovascular disease and cancer, coexistent morbidities or side effects of immunosuppressive therapy, and self-monitoring of rejection and infection signs [22, 23].

However, in the kidney transplant population, patient self-management has not yet been described, and no programs yet exist to support it. The following paragraphs therefore discuss patient self-management by suggesting a definition of kidney transplant recipient self-management.

1.2. Defining patient self-management in kidney transplantation

In general, patient self-management refers to the actions patients perform for themselves in daily life to manage their illness and treatment, and to avoid functional decline and health deterioration [10, 14, 19]. Further, patient self-management implies the patient's active involvement in his/her own care. Regardless of his/her capacity for being "active", over the course of the illness, a patient develops expertise at managing it on a daily basis. This expertise nurtures and influences daily life decisions and should therefore be considered as important as that of the patient's healthcare team [12].

The impact of patients' expertise regarding chronic illness self-management on health outcomes has been investigated in various chronic patient groups. Several Cochrane reviews and other research on patients with chronic obstructive pulmonary disease [24], diabetes [25-27], asthma [18, 28, 29], epilepsy [30, 31], bipolar disorders [32], oral anticoagulation [33], arthritis [34, 35] and various other chronic diseases [36] demonstrate associations between supporting patients' chronic condition management and enhanced patient outcomes.

For example, Lorig et al. (2008) used a randomized controlled trial to test the impact of a 6-week community-based, peer-lead diabetes self-management program in 567 Spanish speaking adults with type 2 diabetes, on the participants' health status, health behaviors, and self-efficacy. At 6 months, compared with standard care subjects, intervention subjects demonstrated significant improvements in A1C (-0.4%), health distress, symptoms of hypo- and hyperglycemia, and self-efficacy ($p<0.05$). Additionally, intervention subjects demonstrated improved self-rated health and communication with physicians, and had fewer emergency room visits (-0.18 visits in 6 months, $P < 0.05$). Furthermore, all improvements persisted to 18 months, demonstrating long-term effectiveness on patient outcomes [25].

The effectiveness of self-management programs has also been demonstrated by others. Deakin et al. (2005) performed a Cochrane review to assess the effects of group based, patient centered training on clinical, lifestyle and psychosocial outcomes in subjects with type 2 diabetes. They found 11 studies involving 1532 participants. Self-management programs were effective in reducing glycated hemoglobin at four to six months (1.4%, $p<0.00001$), 12-14 months (0.8%, $p<0.00001$), and two years (1.0%, $p<0.00001$). Fasting blood glucose levels were reduced at 12 months (1.2mmol/l, $p<0.00001$); body weight was reduced at 12-14 months (1.6kg, $p<0.00001$); systolic blood pressure was reduced at four to six months (5 mm Hg, $p<0.01$); and diabetes knowledge was measurably improved at 12-14 months ($p<0.00001$). Furthermore, intervention subjects showed a reduced need for diabetes medication (odds ratio 11.8, $p<0.00001$) [27]. These results clearly demonstrate the effectiveness of self-management support using a group format.
Expert-led self-management support, whether focusing on individuals or on groups, has been shown to improve patient outcomes. For example, Morris et al. (2007) summarized 11 randomized controlled trials in patients with bipolar disorders to assess the effect of patient self-management support to recognize and manage early warning signs of manic, depressive and bipolar episodes. Six high quality studies reported on these outcomes. The time to the first recurrence of any type of episode (hazards ratio 0.57, 95% CI 0.39 to 0.82), the time to a manic/hypomanic episode, the time to a depressive episode, and the percentage of people functioning favored the intervention group, demonstrating the beneficial effect of patient self-management support in patients with bipolar disorders [32]. Moreover, this study agreed with others [37, 38] in suggesting that patient self-management support, including skill training components (e.g., recognizing signs and symptoms and acting appropriately), is effective in improving patient outcomes and may be superior to support limited to disease specific knowledge training. These studies provide clear empirical evidence that patient self-management support can effectively improve chronically ill patient outcomes.

Despite the growing body of evidence that chronic patient populations benefit from self-management support, most transplantation patients are still subject to an acute care paradigm focusing on complex immunological issues and the treatment of acute and

urgent post-transplantation problems. Self-management (i.e., an essential characteristic of chronic illness care) has not yet been described for the transplant recipient population.

1.2.0. Conceptual model of the renal transplant recipients' self-management

The conceptual model suggested below (see figure 1) offers an overview of a possible renal transplant recipient self-management paradigm, along with a description of its transplant specific components. This model uses three components that emerged from a qualitative hallmark study of the work chronically ill patient groups perform for themselves while living with their conditions: managing the medical regimen; managing emotions; and managing their (new) life roles [39].

The kidney transplant recipient self-management model outlined here has been extended to offer a detailed, illness specific description of its components. More specifically, descriptions of specific kidney transplant recipient self-management activities were guided by data-based evidence in the transplant literature, and/or clinical expertise in transplantation care in cases where available literature was insufficient. The scope of this dissertation is limited to a detailed description of one of the three components, i.e., managing the medical regimen. Further work has to be done to describe kidney transplant recipient self-management of emotions and new life roles.

Thus, renal transplant recipient self-management can be divided into the same three components as are used for other chronic illness populations (see figure 1): 1) managing the medical regimen, 2) managing emotions, and 3) managing (new) life roles. The (renal) transplant recipient's self-management occurs individually, may affect the family and/or the community, and is ideally a significant part of the patient's interaction with health care professionals (see outer circle). Furthermore, this self-management may start pre-transplantation (see arrow), with several aspects being more or less important at each respective stage.

The (renal) transplant recipient must also have or acquire a set of core skills [40] (see the various small circles). These are: 1) *problem solving:* isolating problems, gathering information, implementing solutions, and evaluating the results; 2) *decision making:* applying information and training to distinguish medically serious symptoms from less

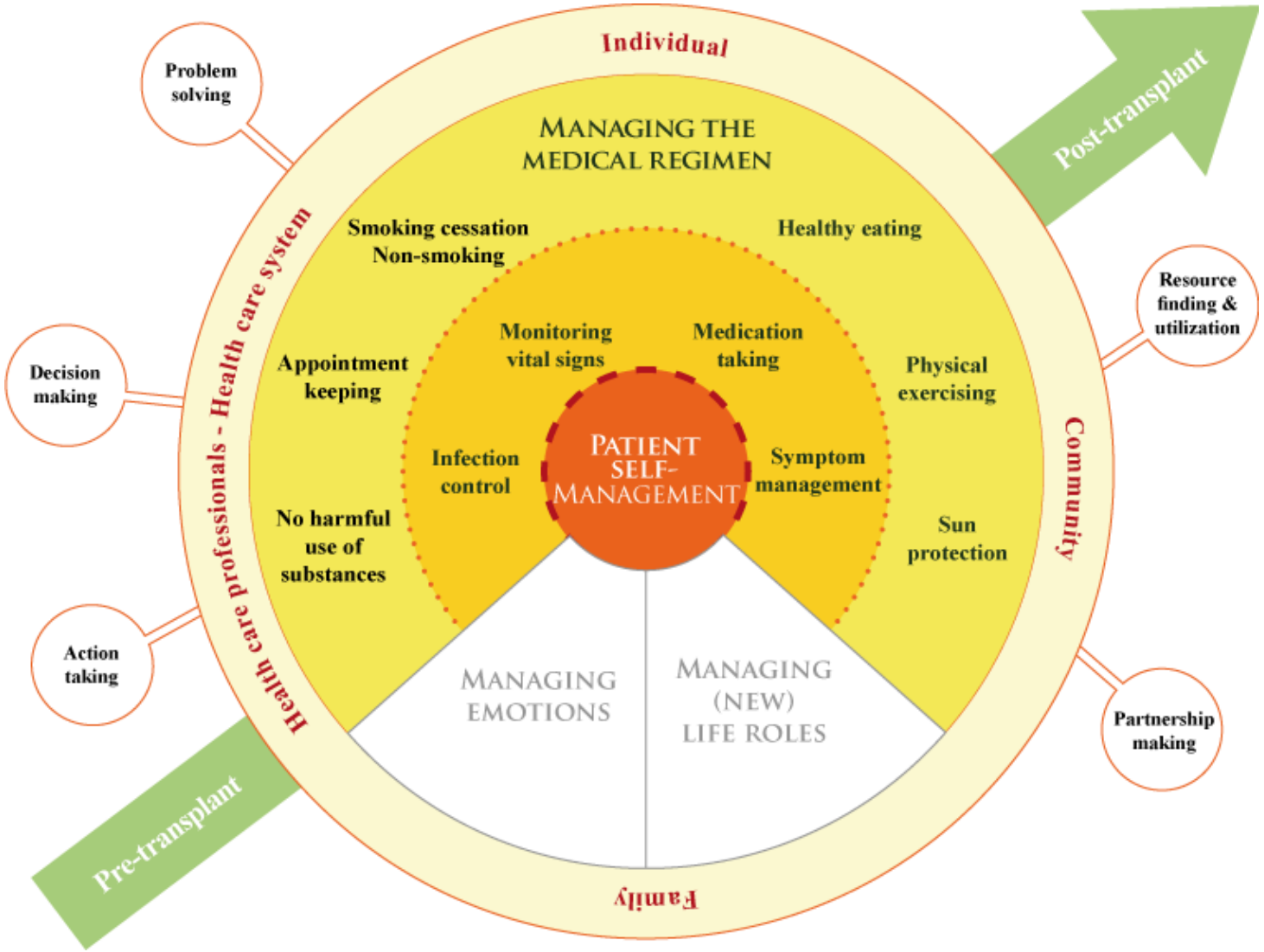
serious problems and acting appropriately; 3) *resource location and skill utilization:* navigating through health information sources and identifying the most relevant material; 4) *partnership building:* appropriately discussing developments regarding the course of the illness with health care providers to make informed treatment decisions; and 5) *action planning:* developing and implementing short-term action plans [40].

The conceptual model for managing the medical regimen contains two inner circles. Of these the inner most circle may assume a more central role to the kidney transplant recipient's self-management, and may have the greatest importance throughout the illness trajectory (e.g., immediately post-transplantation, long-term phase). For example, taking medications correctly is crucial at every phase. On the other hand, the outer circle illustrates self-management activities that ideally are incorporated before transplantation or immediately post-transplantation. However, if they are not ideally managed from an early stage, these activities may also be feasibly addressed some months post-transplantation, after the immediate acute phase has been successfully managed.
The conceptual model for patient self-management of the medical regimen includes four central components (see inner circle of managing the medical regimen in figure 1): 1) *infection control* (e.g., hygienic measures, self-monitoring for signs of infection), 2) *monitoring vital signs* (e.g., weight, blood pressure), 3) *medication* (e.g., a complex regimen of immunosuppressive drug therapy to prevent graft rejection and loss, as well as other medications to fight or prevent diseases, coexistent morbidities or side effects of immunosuppressive therapy), and 4) *symptom management* (e.g., self-monitoring of vital signs and symptoms, applying appropriate interventions for symptom alleviation). The outer circle of medical regimen management extends the central set to ten items: 5) *no harmful use of substances* (e.g., alcohol), 6) *appointment keeping* for regular follow-up visits, 7) *non-smoking or smoking cessation* (if applicable), 8) *healthy eating,* and 9) *physical exercise* to control weight and protect against cardiovascular disease, and 10) effective *sun protection* to guard against skin cancer.

To conclude, this conceptual model for renal transplant self-management is designed to provide comprehensive, systematic patient self-management support in transplant clinics.

Such support should be oriented towards assisting kidney transplant recipients to achieve a complex set of objectives: to become knowledgeable about their condition, treatment and self-management; to develop effective decision-making strategies; to develop problem-solving skills for challenging situations in daily life; to interpret and integrate clinical recommendations into daily practice; and to change to, adhere to and perpetuate behaviors that support favorable short- and long-term health outcomes.

Figure 1: Conceptual Model for Kidney transplant recipient self-management



While the aim of this research program was to move towards developing a kidney transplant recipient self-management program, three of the seven chapters study medication management as a central aspect of medical regimen self-management. More specifically, the research focuses on measuring and enhancing medication adherence after kidney transplantation. Therefore, the following paragraphs provide an evidence base regarding adherence to self-management activities, medication adherence measurement, and adherence to transplantation-related interventions.

1.3. Positioning adherence within patient self-management

Patient self-management is the offspring of a care paradigm wherein patients are regarded as experts in managing the many tasks necessitated by their illness. Adherence, on the other hand, has evolved from a traditional, paternalistic care paradigm, wherein clinicians, assuming that they knew best, made expert decisions for patients. In the past, patients assumed the more passive role of simply doing what they were told by their clinicians. The current definition includes a measure of patient input: adherence is now "the extent to which a person's behavior (taking medications, following a recommended diet, and/or executing lifestyle changes) corresponds with the agreed recommendations of a healthcare provider" [16]. The link between adherence and patient self-management lies in the patients' daily application of strategies *to manage adherence* to the medical regimen. Such strategies may be based on patient knowledge regarding the medical regimen, and their experience with self-managing. For example, taking medication on a daily basis in accordance with a medication regimen requires skills inherent to patient self-management: problem solving, decision making, resource location and utilization, partnership building, and action planning [40].

1.4. The challenge of adherence to the kidney transplant medical regimen self-management

As illustrated in the conceptual model, kidney transplant medical regimen self-management includes *medication taking, sun protection, non-smoking or smoking cessation*, *healthy eating, physical exercise, symptom management*, and *infection control*. As self-management of the medical regimen likely impacts patient outcomes, it is

important to have precise information regarding the risks of non-adherence. Recently, Dew et al. (2007) performed a meta-analysis of 147 studies in several organ transplant populations, and found that medical regimen non-adherence rates (i.e., cases per 100 persons per year) in kidney transplantation ranged from low (e.g., illicit drug use: 1.0; alcohol use: 1.4; tobacco use: 3.3; missing clinic appointments: 4.7) to high (e.g., failure to take immunosuppressive medications: 35.6; following diet: 30.8) [41].

The following paragraphs provide more details of medical regimen self-management in kidney transplantation.

1.4.1. Prevalence and consequences of self-management of adherence to the kidney transplant medical regimen

Adherence to the prescribed medication regimen has been researched extensively in various chronic and acute illness populations and has been found to be a major problem: up to 50% of patients take medications only at levels associated with poor clinical and economic outcomes [42-44].

Medication non-adherence is also a major problem in the kidney transplant population. Recent literature reviews [6, 41, 45] demonstrate that non-adherence to immunosuppressive therapy occurs in 36 cases per 100 patients per year [41] or in an average of 22-28% of adult kidney transplant recipients (range 8-65%) [6, 45]. Non-adherence accounts for 20% (range 2.5%-80%) of late acute rejections and 16% (range10%-64%) of graft losses.[6] The detrimental impact of immunosuppressive non-adherence on graft outcome was recently confirmed by Takemoto et al. (2007), who observed a 43-46% increased risk of graft failure for subjects with imperfect adherence rates, suggesting that adherence be perfect for optimal graft functionality [5].

Sub-optimal self-management is also prevalent in other aspects of the kidney transplant medical regimen. Limiting exposure to ultraviolet radiation, the main modifiable risk factor for skin cancer, requires photoprotective practices such as avoidance of sun exposure, use of protective clothing, and use of effective sunscreen for exposed body parts [22, 46, 47]. However, studies report that 25.9-62.3% of kidney transplant recipients do not apply any sun protection [47-49]. Further, only 18% of recipient samples usually

avoid the midday sun during holidays [50], and less than 50% wear protective clothing in the sun [47].

The risks are unambiguous. Neglect of photoprotective practices can contribute to poor patient outcomes, as immunosuppressive therapy increases the risk of skin cancer after transplantation. It has been reported that the frequency of squamous-cell carcinoma increases with time post-transplantation, reaching 40-70% of patients within 20 years [46]. Moreover, the risk of invasive squamous cell carcinoma has been reported to be 82-100 times greater for transplant recipients than for non-transplant populations [48, 51]. By year 6 post-transplantation, even after adjusting for aging, that risk factor (for patients aged < 50) will grow to 200 [48].

Non-smoking, healthy eating and regular physical exercise to maintain normal weight are further important self-management activities in view of cardiovascular and/or cancer risk, as well as post-transplantation co-morbidities. Recent studies showed that 12.1%-22% of adult kidney transplant recipients actually smoked tobacco [52-54], while 50-60% were overweight or obese [54, 55]. Furthermore, despite a lack of post-transplantation exercise data [56], Painter et al. (2002) documented that at 1 year post-transplant only 36% of kidney transplant recipients enrolled in the control arm of the study performed regular physical exercise [57]. Despite general agreement that physical activity benefits long-term cardiovascular health in healthy populations [58] as well as chronically ill ones, including kidney transplant recipients [56], evidence indicates that regular physical exercise generally occurs at a low rate after transplantation.

Smoking, non-adherence to healthy diets and regular physical exercise to maintain normal weight contribute to morbidity and mortality after kidney transplantation, as cardiovascular disease, infection and malignancy are among the leading long-term causes of death after kidney transplantation [4]. More specifically, 30-50% and 8% of deaths of kidney transplant recipients with functioning grafts are due to cardiovascular disease and cancer, respectively [59, 60]. Moreover, kidney transplant recipients have a 3.5-5% annual risk of a fatal or non-fatal cardiovascular event – 50 times greater than that of the general population [61]. Additionally, because of the trend toward more aged, frail and complex end stage renal disease patients, coexisting morbidities are common in kidney transplant populations. A recent study analyzing data from the Canadian Organ

Replacement Registry, showed that 22% of the 6324 study subjects had at least one co-morbidity (in addition to the presence of moderate or severe renal disease), with cardiac disease, diabetes, and malignancy the most common additional illnesses. In this kidney transplant population, increasing co-morbidities were predictive of poorer outcomes, a finding which is consistent across studies [21].

Finally, self-monitoring of vital signs and symptoms related to graft rejection and infections helps to prevent graft loss and major critical incidents such as severe and/or systemic infections, which number among the leading causes of long-term patient death [4, 62]. In heart transplant patients, the prevalence of non-adherence to self-monitoring ranged from 22% to 59% [63], No data have been published for this aspect of the medical regimen among kidney transplant recipients.

This literature review illustrates that aspects of medical regimen self-management largely impact kidney transplant recipients' health outcomes. These findings are similar to those of other chronic illness patient groups (e.g., diabetes, arthritis, bipolar disorders), where studies have demonstrated that investing in support for patient self-management effectively improved clinical outcomes (e.g., HbA1C, hypo-and hyperglycemia symptoms, body weight, systolic blood pressure; improved symptom management) [25, 27, 32]. All of these self-management activities therefore merit in-depth study regarding measurement, followed by the development of appropriate interventions. It is particularly important to isolate specific conditions that contribute to poor patient outcomes. However, the scope of this research program was limited to measuring and improving adherence to medication regimens.

Chapter 3 offers a practical approach to promoting medication adherence by providing an overview of non-adherence correlates, consequences, and adherence enhancing interventions. A case example illustrates a practical implementation of a medication adherence enhancing intervention.

1.4.2. The measurement of medication regimen adherence

As non-adherence to immunosuppressive drugs often results in poor kidney transplant recipient outcomes [5, 6, 45], accurate measurement of medication non-adherence is essential. Adherence can be measured via several direct or indirect methods, each of which has specific advantages and disadvantages (see table, NEJM, 2005;353;5, p.489).

Test	Advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and "white-coat adherence" can give a false impression of adherence; expensive
Measurement of the biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g., pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials
Measurement of physiologic markers (e.g., heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

Table from NEJM, 2005;353;5, p.489 [64]

In kidney transplantation, direct measure of medication adherence refer to immunosuppressive blood trough assay, routinely performed post-transplantation for most immunosuppressive drugs except azathioprin and prednisone, for which no blood assays are available. Some studies have used this method to measure medication non-

adherence [65-72]. Most studies, however, have relied on indirect methods, such as patient self-reports (e.g., surveys, questionnaires, interviews) [65-67, 69, 72-91], collateral reporting [65, 69]; pharmacy refill records [5, 68, 70]; pill counts [69, 91, 92]; and, more recently, electronic monitoring of bottle-openings [65, 84, 88, 93-100], to measure non-adherence.

Although studies have used a variety of methods [65, 68-72, 81, 84, 91], only one has assessed diagnostic values of kidney transplant recipients' non-adherence measures using electronic monitoring (of prednisolone intake) as a reference standard [65]. For that study, which focused on late medication, the highest scores for both sensitivity (85.7%) and specificity (72.5%) corresponded to confidential interviews by the researcher. Self-report questionnaires (i.e., the Morisky scale and medication adherence rating scale (MARS)), collateral reporting by nephrologists and by the researcher, and cyclosporine levels showed sensitivity ranging from 42.9% to 100% [65] (although the cut-off point necessary for 100% sensitivity misclassified half of the sample). For these collection methods, specificities were below 69% [65].

Given the clinical relevance of non-adherence to immunosuppressive drugs, the use of feasible and accurate measures is critical. This will require concise, clinically meaningful definitions of all domains to be measured. Once achieved, valid, cost-effective measurement of non-adherence will be a first step toward providing effective adherence enhancing interventions.

Chapter 4 assesses the diagnostic accuracy of different methods of measuring medication non-adherence. The study was a sub-analysis of the SMART study (Supporting Medication Adherence in Renal Transplantation) [101] and included a sample of 249 renal transplant recipients. Diagnostic accuracy of patient self-reporting, clinicians' collateral reports, and blood assay were determined using electronic monitoring as a reference standard.

1.4.3. Interventions to enhance medication adherence in adult transplant recipients

Unfortunately, no study has yet tested a comprehensive transplant self-management program. Ideally, though, patient self-management support should consist of two components – one for disease specific knowledge and skills, and one for non-disease specific skills, in order to assist in behavior change [19]. Self-management programs that include the skill development appear to yield results superior to those focusing mainly on information and education [37]. With this in mind, in addition to transplant specific knowledge regarding medical regimen management, a comprehensive transplant self-management program should integrate the training of core skills (e.g., problem solving) as defined in the conceptual model for kidney transplant recipient self-management.

More specifically, it should assist kidney transplant recipients and their families in managing their medical regimen, emotions, and (new) life roles, by either acquiring or further developing problem solving skills for challenging situations occurring in daily life. It should nurture decision making skills to help patients interpret signs and symptoms for their medical seriousness and acuity. It can help patients develop skills and strategies to locate resources, navigate health information pathways, and integrate clinical recommendations into daily life. Finally, taking into account the individual's home environment, employment situation and community, it should foster partnership building and action planning to adopt, adhere to and perpetuate behaviors that support favorable short- and long-term health outcomes.

Regarding improving medication adherence in chronic-illness patient populations, based on the limited available evidence assessing the impact of adherence enhancing interventions on patient outcomes, the current consensus is that effective interventions should share at least four characteristics: 1) they should be derived from randomized controlled trials; 2) they should build upon theoretical models explaining behavior change, 3) they should be multidimensional, combining educational and behavioral interventions with social support over a sustained period; and 4) they should use a multi-level approach simultaneously targeting risk factors on several different levels (e.g., the patient and the provider, or the policy maker and the health care system) [102, 103].

In adult kidney and other solid organ transplant populations, evidence is scarce on interventions to promote medication adherence. A broad variety of interventions have been proposed: educational approaches [68, 104, 105], internet-based interventions [106], financial support programs for medications [70, 107], electronic monitoring feedback [108], behavioral contracting [109], and a self-medication administration program as a part of discharge planning [107]. The efficacy of these interventions has yet to be formally evaluated. However, of the studies listed here, only four used what can be considered appropriate bias minimizing designs. Of these, three were randomized controlled trials [68, 105, 108]; the fourth was a quasi-experimental (non-randomized) design [106]. These studies are summarized below.

Dew et al. (2004) tested a 4-month multifaceted internet-based intervention program on mental health, quality of life, and medication adherence outcomes using a quasi-experimental design that compared heart transplant patients and their caregivers using the online program (n = 20) with heart transplant patients and their caregivers receiving standard care (n = 40). The intervention consisted of information modules (e.g., a skills workshop on managing post-transplant stress and the medication regimen, a question and answer library, and healthy living tips) and contact modules (e.g., expert advice, recipients' and caregivers' discussion groups) meant to be used at least weekly for four months. Mental health, quality of life and medication adherence were assessed pre- and post-intervention. Mental health scores (i.e., depression, anxiety and anger-hostility, as measured with sub-scales of the Checklist-90 symptom data collection instrument) improved significantly after four months. Pre-intervention assessment revealed that 30% of the intervention group and 44.4% of the control group were non-adherent (p=0.461). These figures had decreased to 25.3% in the intervention group and 33.3% in the control group at 4 months post-intervention (p=0.830). While overall adherence improvement scores did not differ significantly between groups, more frequent use of the web-based intervention was linked with more enhanced intervention, suggesting that frequent use of the modules increased their efficacy [106].

Hardstaff et al. (2003) used a randomized controlled trial to test the effect of electronic monitoring feedback on medication adherence in 48 renal transplant recipients over a 12-

month study period. At the participants' first clinical appointments, members of the intervention group (n=23) received feedback on medication taking, based on electronic monitoring; the control group (n=25) received none. There was no difference between the intervention and control groups regarding medication adherence. Over the first 3-month study period, adherence improved in 26% of intervention patients, worsened in 39%, and remained the same in 35%. In the control group, adherence improved in 20%, worsened in 40% and remained the same in 40%. These findings indicate that a single dose of feedback did not significantly improve adherence, and poorer adherence evolved over time in both groups. The rationale for providing feedback only once over the 12 months of the study remains unclear [108].

In a randomized controlled trial, Chisholm et al. (2001) evaluated the impact of clinical pharmacy services on renal transplant recipients' immunosuppressive drug adherence. In addition to traditional care, the intervention patients received clinical pharmacy services, including medication histories and reviews to optimize medication therapy, and counseling and instructions from the clinical pharmacist on how to take medications properly. The intervention began in the first month post-transplant, and was repeated every month for one year. At the end of one year, the intervention group's (n = 12) mean immunosuppressive drug adherence rate was 96.1% (SD=4.7%) – significantly higher than that of the control group (n = 12), whose mean adherence rate was 81.6% (SD=11.5%) ($p < 0.001$). Additionally, at the end of the study's 12 month period, 75% of the intervention patients remained adherent, compared to 33.3% of the control group, a statistically significant difference ($p<0.05$). The authors concluded that, compared to traditional care, a multidisciplinary team care approach may be beneficial to enhance post-kidney transplantation medication adherence [68].

In a prospective randomized controlled trial, Klein et al. (2006) tested a similar intervention, i.e., the impact of a pharmaceutical care program on liver transplant recipients' (N = 50) adherence to their immunosuppressive regimen for one year post transplantation. The intervention group (n = 24) received a combination of in-hospital and outpatient counseling, addressing immunosuppressive therapy, identification of drug related problems, discussion of vital signs and laboratory tests, adherence enhancing education, and a set of information tools including a diary for documenting vital signs

and laboratory tests. At one year post-transplant, the mean dosing adherence rate was significantly higher in the intervention group than in the control group (p=0.015). Additionally, 92% of the intervention group achieved target immunosuppressive blood levels, compared to 78% in the control group, demonstrating the effectiveness of the intervention [105].

The above examples show some important limitations of the available research regarding the efficacy of immunosuppressive adherence-enhancing interventions. All of these studies can be regarded as methodological weak as assessed by the CONSORT quality criteria [103]. Even among the few studies using bias-minimizing designs, none use theory driven, comprehensive approaches testing multidimensional and multilevel interventions over a sustained period. However, such time-intensive designs may be, as evidence from non-transplant chronic and acute patient populations suggests, effective approaches to enhancing medication adherence - and perhaps other aspects of transplant recipient self-management [110-113].

Chapter 5 is a two-center pilot RCT to test the efficacy of medication adherence enhancing interventions in 18 identified non-adherent renal transplant recipients over a nine- month study period. In addition to their usual care, for the first three months of the study, each intervention group member received theory driven, individualized educational, behavioral, and social support interventions, through a home visit and telephone contacts. The intervention was followed by a six-month follow-up period.

In transplant clinics, which typically follow an acute care model, the prevailing lack of time restricts the support of patient self-management using enhanced human resources. Therefore, innovative systems need to be considered to assist transplant professionals in supporting patient self-management.

1.5. Using information technology and communication systems to support transplant recipients' self-management

E-health, i.e., health care delivery via information technology (Strategic health innovations in [114]), is currently entering the healthcare system, promising dramatic benefits for chronic illness management. Besides facilitating clinical decision making, collection and exchange of clinical information, reduction of medical errors, and further development of clinician – patient interactions, using information technology to help chronically ill patients become active and knowledgeable regarding their illnesses, treatments and self-management activities, is a key element of e-health [12]. For the care of chronically ill patients such as kidney transplant recipients, e-health packages have the potential to complement current care practices, which are characterized by insufficient resources, especially time, to invest in patient self-management programs.

As a segment of e-health technology, computer-assisted or web based patient education refers to interactive computer or web based learning software (CWLS) which helps fulfill the general aims of e-health [115]. CWLS may impact patients' learning both significantly and uniquely: educational science has demonstrated the impact of teacher characteristics, the school or the educational system on learners' achievements, independently of pupil-related variables such as intelligence or motivation [116].

CWLS has several advantages over traditional patient education methods. These include the opportunity for self-directed learning at a self-determined pace, independence from healthcare providers, the consistent provision of information, and the possibility to adapt instructional content to personal needs [115, 117]. Such advantages could be beneficial to assist transplant clinics in supporting transplant recipients self-management. For transplantation clinics, they could help users acquire transplant specific knowledge and technical skills as well as core skills for effective chronic illness self-management (see transplant recipient self-management model).

Based on current evidence, CWLS shows promise as an effective tool to improve patient self-management, and thereby to enhance outcomes in chronic illness populations [38, 118]. Murray et al. (2005) conducted a Cochrane review of 24 randomized clinical trials evaluating the effect of CWLS on knowledge, social support, clinical outcomes,

behavioral outcomes, and perceived self-efficacy, in a total of 3739 chronically ill patients. The project included only studies using computer-based (usually web-based) interactive health communication application packages, combining information with at least one of the following: social support (e.g., online chat rooms), decision support, or support for behavioral change. The meta-analysis showed significantly more improvement in knowledge (SMD 0.46; 95% CI 0.22-0.69; I^2 52.8%), social support (SMD 0.35; 95% CI 0.18-0.52; I^2 0%), and clinical outcomes (SMD 0.18; 95% CI 0.01-0.35; I^2 30.6%) in the intervention groups than in the control groups. Furthermore, patients in the intervention group showed a greater likelihood of positive effects on health behavior and perceived self-efficacy (i.e., the confidence in one's ability to perform a certain task in a certain situation) [118].

The results of this review, along with other findings [38], constitute a first step in building up the empirical evidence that CWLS is effective in supporting self-management and improving health outcomes of chronic illness patients. Effective patient self-management support in chronic illness populations needs to provide not only information but also interactive social support, decision-making support, and support to change counterproductive behavior [37]. One major goal of any such program should be to assist patients to gain or improve skills to manage their conditions in daily life. This emphasizes the need to study and develop CWLS as a health care tool.

1.5.0. The development of patient self-management programs using technological interventions

The development of a CWLS program to meet the demands of an effective intervention is challenging [117, 119-123]. Moreover, the use of a computerized system as an intervention tool implies that such systems need to be easy for patients to operate. This criterion has only recently been articulated and is referred to as system usability: "…the capacity of a system to allow users to carry out their tasks safely, effectively, efficiently, and enjoyably" (p.56) [124].

Recently, research based usability guidelines have been published (REF), and some studies have reported testing the usability of their CWLS programs during the development phase [120, 121, 124-126]. The common finding of these studies was that

involving potential end users during CWLS development allowed the identification of many problems related to its system, including information structuring and user interface issues. These problems were neither anticipated nor identified by the professional development teams who produced them. Thus, the involvement of a group of the CWLS's potential end users helped to improve its operability and efficacy.

Chapter 6 of this research program explores the field of e-health in kidney transplantation by evaluating a computer assisted patient education package from the perspectives of clinicians and patients. The program was developed by a company, and, despite the lack of any previous formal evaluation, has been in use since 2001 at various transplantation clinics worldwide.

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Chapter 2
Aims of this Research Program

Recent large scale analyses of renal transplant registries demonstrate a lack in significant improvements to long-term patient outcomes over the past decades. These findings were initially rather surprising, as previous long-term graft survival assumptions, based on projected half-lives, anticipated major progress, along the path cleared by the tremendous advances in short-term graft survival and immunosuppression, in the direction of long-term outcomes [1, 2]. However, based on Kaplan Meier survival analyses the calculated real half-lives and other hard data now reveal that these expectations have not been realised [1, 2]. Such a pronounced shortfall indicates that major review papers [3-5] have been unable to provide complete strategies for successful long-term management of transplant recipients. Innovative pathways, building upon existing evidence in other patient populations, are therefore highly warranted to improve long-term post-transplant outcomes.

Research on other patient populations shows that using a chronic care model to manage chronic conditions, i.e., conditions that are never completely cured [6], and that require open-ended periods of support to manage the illness itself, coexisting morbidities, treatments, or prevention of further disability [7], results in improved patient outcomes [7, 8].

The chronic illness definition can also be applied to the kidney transplant population. Despite being the treatment of choice for end stage renal disease [9], kidney transplantation requires lifelong medical treatment, including medication taking and regular transplant center follow-ups. Steps are also necessary to prevent or manage risk factors for cardiovascular disease, cancer, coexistent morbidities, or the side effects of immunosuppressive therapy, while patients must self-monitor constantly for signs of rejection and infection [10, 11]. The adoption of a chronic illness model for the management of long-term transplant recipients may therefore be necessary to make progress on long-term graft survival, as it has been shown to be effective in other chronic illness populations [7]. Chronic illness management is characterised by continuity of care, partnership with patients, families, and communities, support for patients in improving

their self-management skills, attention to preventive measures, decision-making support for healthcare providers, and availability of clinical information systems [7, 8, 12, 13]. Of all these management characteristics, improved patient self-management is most closely associated with improved outcomes in chronic patient populations [14, 15].

However, to our knowledge, no comprehensive studies have been conducted on kidney transplant recipient self-management. Therefore, the main purpose of this research program was to undertake the first steps towards developing a kidney transplant recipient self-management program.

To this end, the five objectives of this research program were:

1) to describe the various transplant recipient self-management activities, synthesizing data-based knowledge and using transplant-clinic expertise (Chapter 1);
2) to study transplant recipient medication management (Chapter 3-5), since patient medication management inherits a central role both from observed transplant recipient self-management and from the expertise of the research group which embedded this dissertation; more specifically,
3) to provide an overview of medication adherence in kidney transplantation, as well as a practical approach to improving non-adherence (Chapter 3), in order to enhance our understanding of medication adherence;
4) to study the measurement of medication non-adherence in order to gauge the diagnostic accuracy of state-of-the art measures (Chapter 4);
5) to test theory-based interventions to enhance medication adherence in non-adherent kidney transplant recipients, with the goal of adding to the very limited available information based on randomized controlled trials (Chapter 5), and
6) to evaluate a computer-based patient education program designed to enhance patient self-management after kidney transplantation (Chapter 6), as the importance of e-health technologies and communication innovations in chronic illness management is growing in response to shortages of time and human resources.

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Chapter 3

A practical approach to promoting adherence to immunosuppressive medication after renal transplantation

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Abstract

Renal transplant recipients are expected to adhere to a lifelong therapeutic regimen designed to preserve long-term graft function and to reduce the risk of complications. Adherence to immunosuppression is a critical component of this regimen, but studies using electronic monitoring, the most sensitive tool currently available, have found non-adherence rates of 20-26% in adult patients, whereas a mean prevalence of 32% has been reported among adolescent renal transplant recipients. Non-adherence after renal transplantation is an important clinical problem because even comparatively low rates of non-adherence are associated with increased risks of acute rejection, graft loss, reduced quality of life, and mortality. All members of the transplant team including hospital-based and community nephrologists, surgeons, nurses and therapists, should be aware of the possibility of non-adherence and be prepared to intervene. Promoting adherence is not straightforward, because risk factors for nonadherence are multifactorial and individual to each patient. As a result, intervention is more likely to promote lasting adherence if it is long term and takes place within the context of a chronic-illness management model that integrates behavioral, psychosocial and medical aspects of care appropriate to the unique needs of the individual patient.

Introduction

In the last decades of the 20th century, the challenge for the renal transplant community shifted from preventing acute rejection early after the procedure to ensuring the long-term survival of the patient and graft. As the leading cause of late graft loss in patients who survive to return to dialysis [1], chronic allograft nephropathy has justifiably received much attention from investigators. Non-adherence has been less well studied, although it is a significant problem in clinical practice [2], and it is also a major cause of late graft loss [3].

Renal transplant recipients are expected to adhere to a lifelong therapeutic regimen designed to preserve long-term graft function and to reduce the risk of complications. Adherence to immunosuppression is a critical component of this regimen, and this article outlines the current understanding of non-adherence to these drugs among renal transplant recipients, and discusses how transplant professionals, whether based in the community or in hospital, can promote adherence among their patients.

Understanding non-adherence

Any discussion of non-adherence after renal transplantation is complicated by the varying terminologies, definitions and measurement tools used in studies of the phenomenon. The term “compliance” has been and is still widely used, but as this has negative connotations of patient passivity and professional superiority, the World Health Organization (WHO) has adopted “adherence”, which it defines as: “the extent to which a person’s behavior – taking medications, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider” [4].

The thresholds or cut-offs that differentiate between “good” and “bad” adherence among transplant patients remain unclear, and this is an essential area for future research given the association between minor deviations from the dosing schedule and an increased risk of adverse outcomes as observed in renal [5] and heart transplantation [6], a drug-disease dyad that is similar to the association between adherence and outcomes seen in individuals with HIV/AIDS [7].

The prevalence of non-adherence to immunosuppressive drugs among renal transplant recipients ranges from 2 to 67% depending on the definition, case-finding and measurement methods used by investigators [8]. In particular, self-report, tablet counts, biochemical assay and pharmacy databases are likely to underestimate rates of non-adherence compared with the more sensitive tool of electronic monitoring [4], which uses a pill bottle or a tablet dispenser equipped with a microprocessor that monitors the time and date of each opening. Studies using electronic monitoring found non-adherence rates of 20-26% in adult patients when non-adherence was defined as taking less than 90% of prescribed doses [8]. Non-adherence rates again vary depending on the study among adolescents (aged 11-19 years), but are consistently higher than in younger (aged < 11 years) and adult patients, with a recent review reporting a weighted mean prevalence of 32% [9].

The impact of non-adherence

Although the prevalence of non-adherence among renal transplant recipients is lower than the mean of 50% reported among patients with other long-term conditions [10], it is undoubtedly an important clinical problem because even comparatively low rates of non-adherence are associated with an increased risk of acute rejection, graft loss, reduced quality of life and mortality [11]. One review estimated that non-adherence by renal transplant recipients contributed to 16.3% of graft losses and 19.9% of late acute rejections, but suggested that these percentages are likely to be underestimated because an assessment of non-adherence is rarely routine or standardized in clinical practice [8].

The adverse consequences of non-adherence clearly have important implications for patients in terms of premature death or a return to dialysis, but patients who have lost their grafts primarily as a result of non-adherence are also less likely to be considered for retransplantation by health professionals [12]. Although the loss of a graft in surviving patients has an important impact on society in terms of the increased healthcare costs of dialysis as well as the loss of productivity and personal economic costs to patient and their families, lifetime treatment costs are higher for adherent renal transplant patients because of their greater life expectancy [13].

This utilitarian finding should, however, be set against the 1.108 quality-adjusted life-years gained after transplantation by adherent patients compared with non-adherent patients. As the incremental cost per quality-adjusted life-year of adherence is €35021 [13] - below the benchmark used in healthcare systems that have adopted formal assessment of new technologies [14] – healthcare purchasers are likely to be willing to invest in interventions shown to improve adherence. Transplant clinicians will, of course, be aware of other, equally important factors justifying such an intervention, such as their wish to improve patient outcomes after transplantation and to ensure the optimal use of scarce donor organs.

Correlates of non-adherence

Effective intervention to promote adherence in clinical practice depends on the identification of correlates or risk factors for non-adherence, which WHO categorizes in relation to socioeconomics, the patient, the condition or disease, therapy or treatment, and the healthcare system and the health care team [4]. Under these broad categories, studies have identified a range of risk factors for non-adherence after renal transplantation (Table 1).

Table 1: Risk factors for non-adherence in renal transplant recipients

Socioeconomic	Adolescence
	Cost of medication
	Lack of social support, family instability, social isolation
Patient	Low self-efficacy with medication intake
	High levels of anxiety and hostility
	Perception that the evolution of the disease is a matter of choice
	Beliefs about illness or medication
	Lack of knowledge about the regimen
	Non-adherence before transplantation
Condition or disease	Depression
	Smoking
	Use of illegal substances
Therapy or treatment	Longer time posttransplant
	Complexity of regimen
	Patients' subjective perception of side-effects
	Living-donor graft
Healthcare system/healthcare team	Insurance status and reimbursement of medication costs
	Authoritarian communication style and lack of knowledge of non-adherence by healthcare professionals
	Organizational issues, e.g. time constraints during clinical consultations

Data from Denhaerynck et al, [8].

Socioeconomic variables

Apart from age and social isolation, the evidence is inconsistent that socioeconomic variables contribute to non-adherence after renal transplantation [8].

Patient related variables

The contribution of the patient to non-adherence to immunosuppressive drugs has been well studied, possibly because patients have been seen as primarily responsible, but further investigation is needed to corroborate previous findings and explore other potential influences. The patient's lack of knowledge about the regimen may influence adherence [15], but appears to be less important than the patient's own health beliefs about the illness or the medication regimen; for example, believing that less immunosuppression is needed with a living-donor graft [11]. Studies have also found non-adherence in renal transplant patients to be associated with low self-efficacy with medication intake [15], high levels of anxiety and hostility [16], and an external locus of control [16, 17]; that is, the patient's perception that the evolution of the disease is particularly a matter of chance. One study also found a significant positive correlation between pretransplant and posttransplant non-adherence [18].

Condition-related variables

Depression and other emotional problems increase the risk of non-adherence after renal transplantation [19], possibly by impairing the patient's ability to cope with their condition and its complex management. The absence of symptoms [20] and the presence of substance abuse are also associated with non-adherence [21, 22], but the latter may be difficult to identify, especially if illicit drug use is involved.

Treatment-related variables

There is some evidence that the cost of immunosuppressive drugs influences adherence [23]. Although a small, short-term, non-randomized study reported that patients were more likely to adhere to tacrolimus than cyclosporine when both drugs were supplied free of charge [24], there is little evidence that the particular immunosuppressive drug influences adherence except in patients who experience side-effects with corticosteroids

[8]. The patient's subjective symptom distress associated with side-effects, rather than a particular symptom *per se*, is the main correlate of non-adherence [8, 25]. Health professionals are undoubtedly aware of patients' concern about side-effects, but at present often underestimate their emotional and psychological impact [26].

Health system/health care team

The influence of the healthcare system and transplant professionals themselves remains uncertain, although WHO recognizes that systems have the potential to affect patients' adherence behavior, for example, by controlling health providers' schedules, length of appointments, allocation of resources, fee structures, communication and information systems, and organizational priorities [4]. Similarly, WHO regards the quality of the therapeutic relationship between patient and health-care professional as an important correlate of non-adherence [4]. Insurance status has indeed been shown to influence adherence among black renal transplant recipients in the United States [27], and there are certainly variations in adherence rates between centers and between countries [28, 29]. Further investigation is needed to investigate systemic barriers to adherence and to highlight examples of best practice.

Improving adherence

Consensus, evidence-based guidelines recognize the clinical importance of non-adherence after renal transplantation, and recommend that transplant professionals should intervene to promote adherence [30]. This implies that the long-term monitoring of adherence should be as important after transplantation as monitoring clinical outcomes, but this balance is rarely, if ever, achieved at present. Consequently, centers must invest in training the healthcare team to ensure that all members have the knowledge and skill to promote adherence.

This strategy will be more difficult to implement within an acute-care medical model that envisages transplantation as simply a physiological intervention, in which professionals intervene only when the patient presents with physical symptoms. Whereas quality of life and life expectancy are certainly improved for most patients compared with their

experience of dialysis or chronic kidney disease, they continue to have a chronic condition, in which successful outcomes depend on professional support to promote self-management at a very high level, including adherence to a complex, lifelong therapeutic regimen [31].

In adopting a chronic-disease model of care that integrates behavioral and psychosocial aspects of management, transplant professionals can draw on the experience of clinical colleagues and investigators in other therapeutic disciplines such as diabetes or heart failure, which demonstrates that non-adherence is a complex phenomenon and all contributory factors need to be understood and addressed. All patients should be monitored for correlates or risk factors for non-adherence, which should be targeted with an appropriate intervention that is tailored to the individual patient. Such an approach is more likely to promote lasting adherence if it is: high-dose in that it involves appropriate combinations of educational, affective and behavioral interventions shown to improve adherence; multi-level in that patients, professionals and organizations are targeted; and is applied in the long term [4, 32].

Specific interventions

Most studies among renal transplant patients have investigated interventions designed to promote adherence through education, behavioral interventions, and psychosocial support. It should, however, be borne in mind that to date only one pilot randomized controlled study has sought to evaluate the benefits of a multifaceted program designed to promote adherence among adult renal transplant patients who were identified as non-adherers [33]. A prospective study, however, reported significantly more quality-adjusted treatment-free days among patients receiving an experimental posttransplant care program that was designed to improve kidney transplant recipients' quality of life [34]. There was also significantly better adherence at follow-up among a subgroup of patients using a web-based medical regimen workshop as part of a prospective study that aimed to improve mental health among heart transplant patients and their families [35].

Patient education

Clinical guidelines emphasize the role of specific educational programs to address non-adherence after renal transplantation [30]. Patient education is likely to be most effective if it is consistent and is individualized to each patient, taking into account cognitive, educational, developmental and intellectual capacities. It is also important for transplant professionals to check that the patient has understood the information correctly, and to reinforce educational messages regularly (for example, "refresher courses" for long-term patients).

Whereas many centers provide verbal and written education, it may also be useful to take advantage of specific self-medication education before discharge [36], and computer-based learning tools such as the Organ Transplant Information System™ (Roche Pharmaceuticals, Basel, Switzerland) or the Organ Transplant Visual Med Scheduler™ (Wyeth, Madison, New Jersey, USA), although it should be borne in mind that the efficacy and content validity of such programs has yet to be assessed in prospective studies. Furthermore, education and greater knowledge do not in themselves promote adherence – health professionals are themselves notoriously non-adherent to medication – and behavioral change is strongly influenced by inappropriate health beliefs, such as the perception that immunosuppressive drugs are unnecessary [37].

Behavioral interventions

Interventions that empower patients and enable them to participate in their care are likely to contribute to adherence. Simple suggestions include the use of medication aids such as calendar packs, electronic reminder systems, and advice on how to adapt the regimen to the patient's lifestyle and combine medication taking with routine activities such as mealtimes [38]. Electronic monitoring devices such as pill bottles or dispenser packs not only provide the most accurate measure of adherence [4], but also offer the transplant professional the opportunity to identify the timing of and possible triggers for non-adherence. This knowledge can then be shared with the patient when agreeing on an individualized program to improve adherence and during follow-up provide feedback,

which in positive circumstances can provide the patient with mastery experience thus improving self-efficacy[33] (see Table 2).

Table 2: Case history

After being found to be non-adherent to cyclosporine on electronic monitoring, A.W., a 42-year-old female kidney transplant recipient, was invited and agreed to enter the SMART trial [33]. This prospective randomized study evaluated the benefits of a multifaceted education program in improving adherence among adult renal transplant recipients.
On assessment, risk factors for non-adherence by A.W. were:

- Misconceived health beliefs that "posttransplant drugs last for more than 24 hours in the body" and that "immunosuppressive medication can be so strong that it can cause harm to the body" [20].
- An extremely busy personal schedule without routine except for regular meals.
- A low level of perceived social support in taking her medication.

SMART study interventions consisted of a home visit and three subsequent telephone calls at monthly intervals, designed to support self-efficacy, i.e. the individual's confidence in performing a specific behavior such as medication taking even when in taxing situations. All intervention patients received feedback on their medication intake based on electronic monitoring printouts and a refresher course on their medication management. The intervention nurse also suggested individualized behavioral and social support interventions depending on each patient's risk factors for non-adherence.

A.W. chose to adapt her medication taking to her daily routine, by taking her cyclosporine with her in the morning when leaving for work and by taking the evening dose at dinnertime. Because of her husband's own busy schedule, she decided not to involve him in the management of her medication, and she received counseling about her mistaken health beliefs.

These interventions were applied during the first intervention month, and during the regular telephone calls A.W. received feedback on her adherence based on the results of electronic monitoring. This was designed to support her self-efficacy, verbally reward her improved adherence, and to explore whether she perceived the interventions as helpful.

Based on electronic monitoring, A.W.'s medication taking adherence[a] improved from 87.5% at baseline to 100, 97 and 96.6% after one, 2 and 3 months' intervention, respectively. Her timing adherence[b] improved from 61.4% at baseline to 90.0% at on month, but declined to 69.7% at month 2 and 62.1% at month 3, a result explained by the greater priority given by A.W. to medication taking rather than the timing of the dose.

a (Number of events recorded during the monitored period) / (Number of prescribed doses during the monitored period) x 100.
b (Number of near optimal interdose intervals) / (total amount of observed intervals) x 100.

Affective interventions

Psychosocial support is an essential aspect of chronic disease management designed to reduce the risk of non-adherence associated with depression and other emotional problems [31]. Furthermore, any behavioral change designed to promote adherence depends on a trusting, cooperative relationship between health professionals and patients that takes account of patients' attitudes, intentions and health beliefs [39]. Such a relationship is especially important when managing adolescent transplant recipients. Clinicians should use a non-judgmental, supportive, non-accusatory, information-intensive approach to this age group, and special care should be taken when transferring younger patients from pediatric to adult follow-up. This is because normal developmental issues are the main driver for non-adherence among teenagers (striving for normalcy, issues over autonomy, peer pressure), who characteristically rebel against the advice of authority figures such as parents and health professionals [9].

Increased dosing frequency is associated with non-adherence among renal transplant patients [28], and therefore simplifying the regimen of immunosuppressive and other drugs may improve adherence. It could be hypothesized that immunosuppressive drugs such as sirolimus that have a longer half life are more forgiving in view of non-adherence, however, this needs to be further substantiated by research. Transplant patients should be asked specifically about distressing symptoms related to side-effects because they may be reluctant to bother their hard-pressed transplant professionals about these issues during a short consultation at a busy clinic. Although many patients are prepared to trade off cosmetic side-effects in order to retain their transplant [26], health professionals should reinforce adherence by offering ameliorating treatment or advice (for example, treatment of acne or dental referral to manage gingival hyperplasia).

Immunosuppression should always be tailored to the needs of the individual patient, and switching to another drug in the same class [40] or using a steroid-sparing regimen [41] may also help to reduce side-effects. There should always be a clear rational for adjusting the regimen, however, and it is essential to ensure that the patient continues to receive sufficient immunosuppression to prevent acute rejection. Furthermore, any adjustment to

the regimen should only be implemented after confirming that the side-effect will respond to this approach and after counseling the patient about the possible long-term implications for graft survival. Even then, it may not be practical to change the regimen in well-established patients, for example, some patient may experience intractable symptoms with late corticosteroid withdrawal [42].

Conclusion

Non-adherence is common after renal transplantation and has important clinical consequences. All members of the transplant team – hospital – based and community nephrologists, surgeons, nurses and therapists – should be aware of the possibility of non-adherence and be prepared to intervene. Promoting adherence is not straightforward because there is no single solution that applies to every patient, and centers must be prepared to invest the resources necessary to enable professionals and patients to implement an intensive, multilevel, long-term strategy that systematically promotes adherence as part of a chronic disease model of posttransplant care.

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Chapter 4

Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients

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Abstract

Valid assessment of immunosuppressive therapy non-adherence (NAH) is vital: NAH is associated with negative transplantation outcomes. We studied the diagnostic accuracy of assay, patient self-reports and clinicians' collateral reports and composite adherence scores using electronic monitoring (EM) as a reference standard.

This cross-sectional study included a convenience sample of 249 adult kidney transplant recipients (Ktx) (female: 43.4%; mean age 53.6 (SD: 12.7), median 7 years (IQR: 9 years)) post-Ktx. NAH was assessed using EM over 3 months (i.e., reference standard), assays of cyclosporine, tacrolimus, mycophenolat-mofetil, patients' self-reports, and clinicians' collateral reports. The constructed composite adherence score included assay, self-reports, and collateral reports.

NAH's prevalence across the measurement methods was: EM: 17.3%; assay: 33% (cyclosporine: 25.8%; tacrolimus: 35.1%; mycophenolat-mofetil: 40.2%;); self-report: 12.4%; collateral reports: 23.9%, and composite adherence score: 38.9%, respectively. The composite adherence score and collateral reports showed the highest and lowest sensitivities to NAH (72.1% and 15.8% respectively). Specificity was highest for collateral reports of at least three clinicians (93.1%). Likelihood ratio of a positive test was 2.74 for composite adherence score.

No measures showed high sensitivity alongside high specificity. Combining measures increased diagnostic accuracy, indicating the relevance of combined measures for clinical and research purposes.

Introduction

Favorable kidney transplantation (Ktx) outcomes depend on strict adherence to immunosuppressive medication (IS) regimens [1-4]. However, empirical evidence shows an average non-adherence prevalence of 28% (range: 8-65%) among adult recipients [1], accounting for 20% (range: 2.5-80%) of late acute rejections, and 16% (range: 10-64%) of all graft losses [1]. NAH is also associated with poor economic outcomes [5].

Non-adherence measurement

The wide range of NAH prevalences results partly from differences in methods of case definition and measurement. Assessment methods can be direct or indirect, and offer varying levels of sensitivity [6].

Direct measures include observation of medication intake and biological assay of drug levels or drug metabolites in the blood or urine [6]. Observation verifies adherence, yet necessitates direct patient–clinician encounters, and does not elucidate medication intake dynamics [7], which is also true for biological assay [8]. Although drug monitoring depicts the patient's state of immunosuppression, results are influenced by the drug's half-life, metabolic rates, drug-drug interactions, and white coat adherence (i.e., greater adherence before a clinical visit) [9-11]. In the Tx literature, few studies [12-14] have included direct measures, such as IS assays, to measure NAH.

Indirect measures include patient self-reporting, collateral reports from family members or clinicians, prescription fills, pill counts, and electronic monitoring [6]. Self- and collateral reporting are uncomplicated, inexpensive, and feasible in most clinical settings, but are prone to recall and social desirability response bias. Collateral reporting depends on the reporter's familiarity with the patient [8, 10]. The fill frequency of prescriptions requires complete pharmacy records – problematic when patients use a number of non-networked pharmacies [7, 8, 15]; and pill counts (i.e., pills dispensed, remaining, and prescribed) are invalidated when patients hoard or discard drugs [8, 10]. In summary, *state-of-the-art measures* such as self-reporting, collateral reporting, prescription refills, and pill count usually under-represent non-adherence, while providing little information about individual medication-related behavior [7, 10].

In Tx, for over a decade, most studies have relied on patient self-reporting (e.g., surveys, questionnaires, interviews) [3, 16-28] to measure NAH, whereas collateral reporting [13], pharmacy refill records [29, 30], and pill counts [31] have rarely been used.

Reference standards allow superior validity. Electronic monitoring (EM) provides detailed information on individual medication use [32], and is therefore recommended as the reference standard for medication non-adherence [33]. EM involves fitting a pill bottle with a timer/counter, which continuously records every cap opening date and time. Data can be uploaded to a computer to chart individual medication use dynamics [8, 32]. However, EM can 1) be used incorrectly [34], 2) negatively impact established adherence routines [35], or 3) improve normal adherence through an intervention effect [36]. If applicable, these factors affect the validity of EM. Nevertheless, EM's superiority in assessing non-adherence makes it a logical reference standard. Recently, a growing number of studies in Tx [13, 37-42] shifted to EM to assess NAH.

Diagnostic values of state-of-the-art measures

To our knowledge, only one study has assessed diagnostic values of Tx NAH measures using an EM (of prednisolone intake) reference standard [13]. A confidential interview by the researcher focusing on late medication use showed the highest sensitivity (85.7%) and specificity (72.5%). Self-report questionnaires (i.e., Morisky scale and medication adherence rating scale (MARS)), collateral reporting by nephrologists and by the researcher, and cyclosporine levels showed sensitivity ranging from 42.9% to 100% [13] (the cut-off point necessary for 100% sensitivity misclassified half of the sample). Specificities were below 69% [13]. These findings match those regarding other chronically ill patient populations using EM reference standards [43-47].

Given the clinical relevance of IS non-adherence, this study aimed to assess the diagnostic accuracy of assay, self-reporting, collateral reporting, and composite adherence scores as compared to EM in adult Ktx recipients.

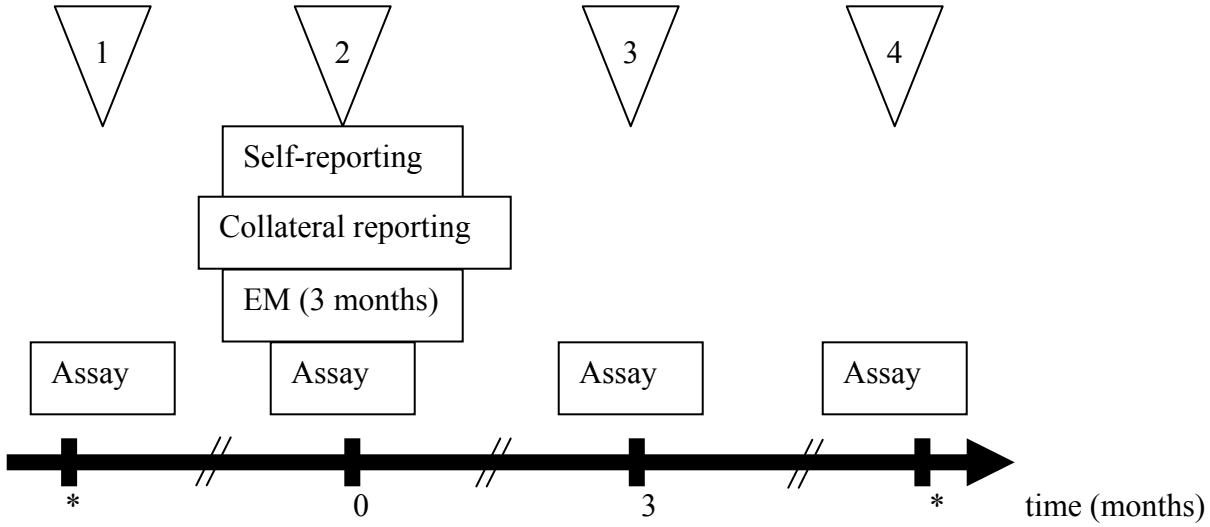
Materials and Methods

This report complies with the Standard of Reporting Diagnostic Study (STARDS) criteria [48].

Design, sample and setting

This study was a sub-analysis of the SMART (Supporting Medication Adherence in Renal Transplantation) study [49]. Figure 1 shows the various adherence measures as assessed over several data collection time points to determine point and period prevalence of non-adherence to IS.

Figure 1: Design of the study



Measurement points are shown as triangles, the various adherence measures as squares.
Measurement point 2 = inclusion into study
EM = electronic monitoring
* We collected the first assay result before inclusion into the study, and the last after finishing the 3-months study period.

The convenience sample of the study included adult Ktx recipients, all more than one year post Ktx, taking IS, having given written informed consent (see Denhaerynck, et al. [37] for a complete description of inclusion and exclusion criteria), and having a valid EM dataset for analysis (procedure described elsewhere [37]). The valid EM data criteria allowed the exclusion of patients who had failed to use EM correctly for their daily IS use. No significant differences existed between self-reported adherence of included and excluded patients. The study was performed at two Swiss outpatient teaching hospital clinics. See Denhaerynck et al. [37] for study setting details.

Variables and measurement

Demographic and clinical variables are reported elsewhere [37].

Non-adherence measures. We used the MEMS®-V TrackCap electronic monitoring (EM) system (Aardex, Ltd., Zug, Switzerland) as our reference standard to assess NAH to IS taken twice daily, consisting of the smallest pill size (for easier storage). We defined EM period prevalences (three

month study period) as: taking adherence (the percentage of prescribed doses taken), dosing adherence (the percentage of days with correct dosing), timing adherence (the percentage of inter-dose intervals within 25% of the prescribed interval) and drug holidays (the number of periods without drug intake exceeding 60h or 36h for a once and twice daily regimen, respectively, standardized over 100 days) [37]. Because evidence suggested statistically significantly higher adherence at the start of the study [50], we excluded the first 35 days of EM monitoring. We defined the following cut-off (i.e., EM algorithm) to assign Ktx recipients to the non-adherent subgroup: < 98% taking adherence and/or at least one drug holiday. Evidence from previous research, showing that minimal deviations from the dosing schedule were associated with increased risk of late acute rejection episodes in adult heart [42] and renal [2] transplant recipients, supports this stringent cut-off.

Assay: Trough blood levels for the drugs monitored by EM (i.e., cyclosporine (CsA), tacrolimus (FK), mycophenolat-mofetil (MMF) and sirolimus (Rapa)) were performed using Fluorescence Polarization Immunoassay, High Performance Liquid Chromatography or Microparticle Enzyme Immunoassay technology at four time points (see figure 1). No assay for Azathioprin (Aza) and Prednisone (Pred) is available, therefore recipients regarding whom these drugs were monitored were not included in this part of the analysis. We specified a therapeutic range for each drug based on clinical guidelines used at the renal transplant program of the Basel University Hospital. Independently of the medication regimens, which included multi-drug combinations (dosage adjusted to compensate for interactions between calcineurin inhibitors and MMF), measured therapeutic ranges were 100-150ng/ml for CsA, 2-4ng/ml for MMF, and 5-10ng/ml for FK and Rapa. To determine therapeutic ranges, we also considered individual target trough blood levels (e.g., as in response to clinical issues such as rejection and toxicity status) as noted in the medical records. To combine several trough blood level results we assessed the non-therapeutic blood assay *variability* of CsA, MMF, and FK using the following approach (adapted from [51]). The percentage of sub-therapeutic CsA assay variability was calculated by dividing the number of sub-therapeutic CsA (< 100ng/ml, or lower than individual target) blood assay levels through the total number of CsA levels analyzed per patient. The percentage of supra-therapeutic CsA variability was determined by dividing the number of supra-therapeutic (> 150 ng/ml or higher than individual target) blood assay levels by the total number of CsA levels analyzed per patient. The percentage of sub- and supra-therapeutic CsA blood assay variability was a combination of

both. Accordingly, non-therapeutic blood assay variability for MMF and FK was determined using MMF and FK specific values indicated in the clinical guidelines (see above).

Self-report: At inclusion, we measured self-reported non-adherence to IS with the Siegal scale [52] by asking recipients in a non-accusatory, information-seeking way [13, 53] about how often, over the preceding four weeks, they 1) had not taken their IS, 2) had forgotten to take there IS, 3) had not taken their IS because they believed that they did not need them, and 4) had reduced the prescribed amount of IS. A 7-point scale assessed their answers, ranging from 0 (never) to 6 (on a daily basis). No validity data have been reported; however, this instrument has been used in previous studies [52, 54, 55]. Any reported non-adherence on any of the four items served as a cut-off criterion [52, 54] to split the sample into an adherent and a non-adherent group.

Collateral report: Non-adherence was also assessed using collateral reports by transplant clinicians. During the first study month, we asked 7 physicians, 4 nurses, and 2 medical assistants involved in the follow-up care of Ktx recipients to score recipients' adherence in one of three categories: good, fair, or poor. We developed the following algorithm to combine responses of different clinicians per recipient. A recipient received a score of 0 if all clinicians estimated his/her adherence as good. A recipient received a score of 1, 2, 3, or 4 according to the number of clinicians (i.e., one to four clinician/s) estimating his/her adherence as fair. A recipient received a score of 5 if even one clinician estimated his adherence as poor, independently of the estimations given by other clinicians. Thus, perfect adherence corresponded to a total score of 0, increasing uncertainty with regard to adherence to a score of 1 to 4, and non-adherence to a score of 5.

Composite adherence score. We developed two composite adherence scores combining various methods of non-adherence assessment. Composite adherence score 1 (CAS 1) consisted of self-reported non-adherence and/or collateral-reports (scores 1 to 5). Composite adherence score 2 (CAS 2) used self-reported non-adherence and/or collateral-reported non-adherence (score 1 to 5) and/or non-therapeutic blood assay variability.

Data collection

Data collection took place between June 2001 and January 2004. One of four research assistants, none of whom belonged to the therapeutic team, approached each recipient who met the inclusion criteria during their regular yearly check-up visits to the outpatient clinic serving the two study centers. The research assistant informed prospective subjects about the purpose of the study, explained the use of the EM system, disclosed that the cap would monitor medication taking behavior, obtained written informed consent, and gathered demographic data and self-reported

adherence via a structured interview. Participants received a stamped, addressed envelope with which to return the EM cap after 3 months of monitoring. If necessary, they were reminded by mail to return the EM device. We used Powerview® (Aardex Ltd.) hardware and software to upload the EM data from the device. A research assistant approached the clinicians individually to assess collateral reports of IS non-adherence for each patient. These face-to-face and oral interviews were performed within one month after the start of the data collection. Self-reports and collateral reports were collected before results of EM were available. Data collectors, blinded to the results of other NAH measurement methods, retrieved assay values and selected clinical data from the medical records.

Ethical considerations

In addition to the regional ethical committees of "Beider Basel" and Aarau, the Swiss federal ethics committee approved this study in 2001.

Data analysis

Correlation analysis (Spearman's rho) assessed the associations between the different measurement methods. We performed receiver operating characteristic (ROC) analysis for two purposes: 1) to dichotomize ordinal (i.e., collateral reports) and interval scaled variables (i.e., assay) in relation to sensitivity and specificity, in order to develop a 2x2 table for calculating diagnostic values; and 2) to calculate the area under the curves (AUC) as a measure of discriminant power. For information on dichotomizing other variables (i.e., EM and self-reports) see "Variables and measurement". Diagnostic values of assays, self-reports, collateral reports, and composite adherence scores using EM as the reference standard were determined using sensitivity, specificity, accuracy, positive and negative predictive value, and likelihood ratios of positive and negative tests.

All calculations were performed using the SPSS® version 14.0 statistical software package (SPSS® Inc. Headquarters, Chicago, Illinois, USA). We considered a p value < 0.05 as statistically significant.

Results

Sample

The SMART study [37] invited 413 eligible Ktx recipients to participate. Of the 356 (86%) who accepted, 291 (82%) agreed to electronic monitoring, while 65 (18%) choose to fill in questionnaires only. Of the 291 EM consenting recipients, seven (2%) dropped out (3 never started; 3 did not return the monitor; 1 died). Of the remaining 284, 35 (12%) did not follow EM guidelines. Thus, 249 Ktx recipients met the inclusion criteria and provided usable EM data for this study (see Figure 1: sample profile in [37]). Table 1 lists selected demographic and clinical sample characteristics.

Table 1: Demographic and clinical sample characteristics (N=249)

	Mean (SD) Median [iqr] Frequency (%)	Range
Sex		
Women	43.4	
Men	56.6	
Age (in years)	53.6 (12.7)	25-81
Caucasian (n=245)	96.4	
Nationality		
Switzerland	83.5	
Other European countries	14.0	
Other Countries	2.5	
Education (in years)		
Primary school (6/7 years of school)	13.3	
Secondary school (8/9 years of school)	47.0	
Additional schools	39.7	
Marital status		
Single/Divorced/Widowed	17.7/9.6/5.2	
Married/Living with partner	67.5	
Not enough resources to pay for medications	19.5	
Graft type		
Deceased donor	60.6	
Living related	26.9	
Living unrelated	12.0	
Time post transplantation (in years)	7 [9]	0.92-34
Dosage of immunosuppressive drugs (mg/day)		
Cyclosporine (n=166)	200 [75]	75-450
Mycophenolat-Mofetil (n=117)	1500 [1000]	500-3000
Tacrolimus (n=42)	5 [3]	1-8
Sirolimus (n=15)	2.5 [2.8]	1-8
Azathioprin (n=76)	100 [50]	25-200
Prednisone (n=62)	7.5 [2.5]	2.5-20
Frequency of immunosuppressive drug (IS) intake per day	2 [0]	1-4
Number of medication to take (other than IS)	4 [4]	0-12

Prevalences of non-adherence

Electronic monitoring. A total of 22,535 subject days were electronically monitored, with a mean monitored time of 91 days (SD = 8.9, range 43-127). Mycophenolat-Mofetil (40.9%) was monitored most often, followed by Cyclosporine (36.0%), Tacrolimus (14.6%), combined Azathioprin and Prednisone (7.3%), Sirolimus (0.8%), and Prednisone alone (0.4%) respectively. The mean three-month prevalence of EM adherence parameters were: taking adherence 98.4% (SD = 5.07), dosing adherence 96.2% (SD = 8.7), timing adherence 91.9% (SD = 15.1), and drug holidays 0.2 days (SD = 1.7). The EM algorithm yielded a non-adherence prevalence of 17.3%.

Assay. We collected a median of 4 (range: 1-17) blood samples per recipient (n = 230), with a total of 940 samples of the monitored CsA, MMF, FK, and Rapa. Table 2 shows the three-month prevalence of blood assay variability for the monitored drugs. The prevalence of non-adherence, as reflected by all immunosuppressive blood levels (cut-off > 52%), non-therapeutic FK blood levels (cut-off > 29%), supra-therapeutic MMF blood levels (cut-off > 29%), and non-therapeutic CsA blood levels (cut-off > 70%), were 33%, 35.1%, 40.2%, and 25.8%, respectively.

Table 2: Assay result variability (in %)*

	Sub-therapeutic blood levels Median (Q1, Q3), Range	Supra-therapeutic blood levels Median (Q1, Q3), Range	Non-therapeutic blood levels Median (Q1, Q3), Range
All immunosuppressive drugs (n = 230)	20.0 (0.0, 50.0), 0.0-100.0	0.0 (0.0, 33.3), 0.0-100.0	45.0 (25.0, 66.7), 0.0-100.0
Cyclosporine (n = 89)	25.0 (0.0, 63.3), 0.0-100.0	0.0 (0.0, 25.0), 0.0-100.0	40.0 (25.0, 75.0), 0.0-100.0
Mycophenolat-Mofetil (n = 102)	20.0 (0.0, 42.5), 0.0-100.0	17.8 (0.0, 50.0), 0-100	50.0 (32.1, 67.9), 0.0-100.0
Tacrolimus (n = 37)	12.5 (0.0, 25.0), 0.0-80.0	0.0 (0.0, 22.5), 0.0-87.5	25.0 (0.0, 43.1), 0.0-87.5

* see variables and methods section for definitions
Note: Sirolimus accounted for too few cases (n = 2) and was therefore not separately explored.

Self-report. Table 3 lists the prevalence of self-reported non-adherence at inclusion into the study, assessed via the Siegal Scale. The prevalence of reported non-adherence on any of the four items was 12.4%.

Table 3: Self reported non-adherence (Siegal scale *) (N=249)

	Once a month	Every 2 weeks
Item 1 In the last four weeks, how often have you **not taken** your immunosuppressive medications?	7.4%	3.7%
Item 2 In the last four weeks, how often have you not taken your immunosuppressive drugs because you **forgot** them?	7.3%	2.0%
Item 3 In the last four weeks, have you ever not taken your immunosuppressive drugs because you believed you did **not need** them?	-	0.4%
Item 4 In the last four weeks have you ever reduced the amount of your immunosuppressive drugs because you believed you did **not need as much of them** as your doctors thought?	-	0.4%
Any self-reported non-adherence: 12.4%		

* Participants could answer the items with never (corresponds to being adherent), once a month, every 2 weeks, every week, every 3 to 4 days, every other day; every day

Collateral reports. For a total of 213 patients at the two centers, seven physicians, 4 nurses, and 2 medical assistants provided 1278 estimates. Of these, 72% were rated as "good", 13.4% as "fair", 0.3% as "poor", and 14.3% as "missing values". Non-adherence as assessed by clinicians' collateral reports from two centers ranged from 0.9% to 23.9% (see table 4).

The prevalences of collaterally reported non-adherence were 45.1% (cut-off ≥ 1 clinicians' responses of fair or lower adherence), 21.1% (cut-off ≥ 2 clinicians' responses of fair or lower adherence), and 8.5% (cut-off ≥ 3 clinicians' responses of fair or lower adherence).

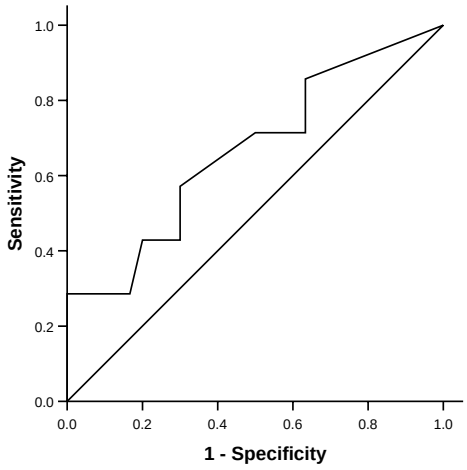
Table 4: Non-adherence as assessed by clinicians' collateral reports from two centers (n = 213)

Participants with	Frequency
1 clinician's response of fair adherence	23.9%
2 clinicians' responses of fair adherence	12.7%
3 clinicians' responses of fair adherence	5.2%
4 clinicians' responses of fair adherence	2.3%
1 clinician's response of poor adherence	0.9%

ROC analysis

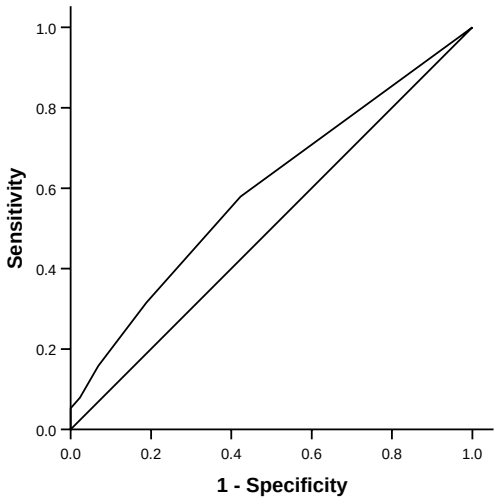
Area under the curves (AUC). The largest AUC's for drug assay variability ranged from .554 for non-therapeutic CSA assay variability, to .567 for supra-therapeutic MMF, and to .667 for non-therapeutic FK (only FK shown, see figure 2). Other blood assay variability revealed no discriminating power (e.g., AUC of sub-therapeutic MMF = .436, figure not shown). Area under the curve for clinicians' collateral reports was .596 (see figure 3). More specifically, AUC's of individual clinicians' collateral reports ranged from .457 to .625 (figures not shown).

Figure 2: Receiver operating characteristic of non-therapeutic blood variability of tacrolimus (n = 37)



Area under the curve = .667 (95% CI = .432 - .902)

Figure 3: Receiver operating characteristic of clinicians' collateral reports (N = 213)

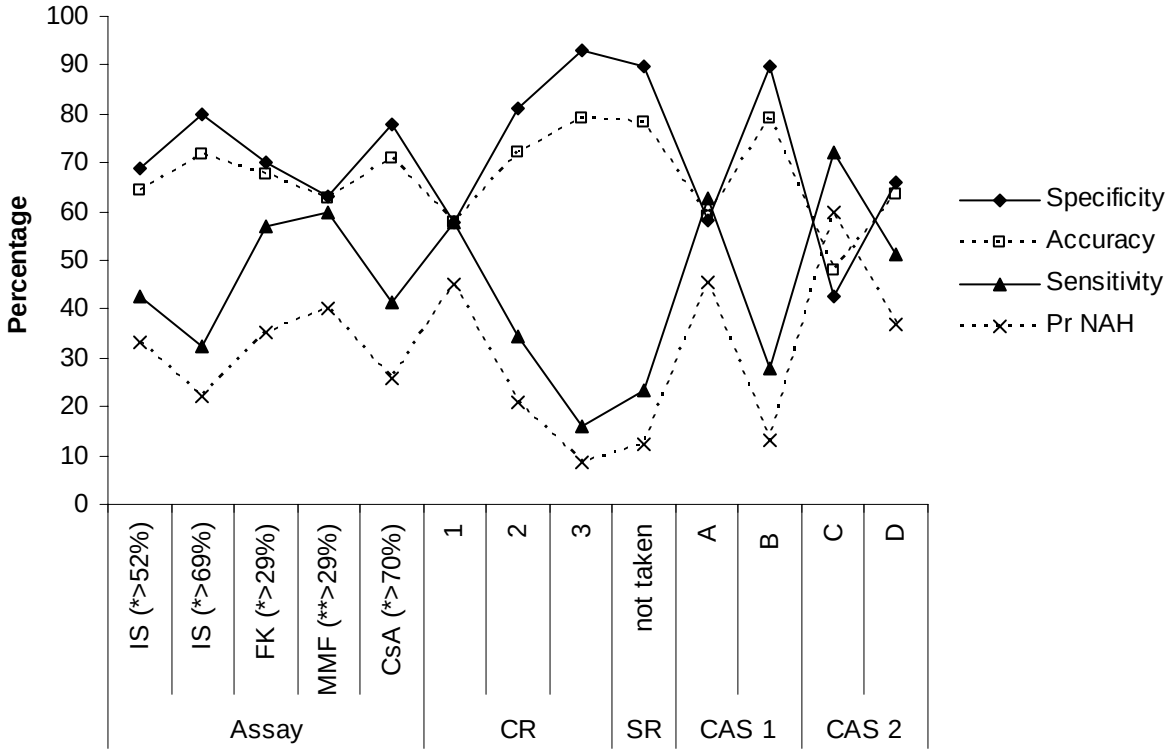


Area under the curve = .596 (95% CI = .492 - .699)

Diagnostic values

Figure 4a-b shows the diagnostic values of assays, self-reports, clinicians' collateral reports, and the composite adherence scores as compared to the EM algorithm.

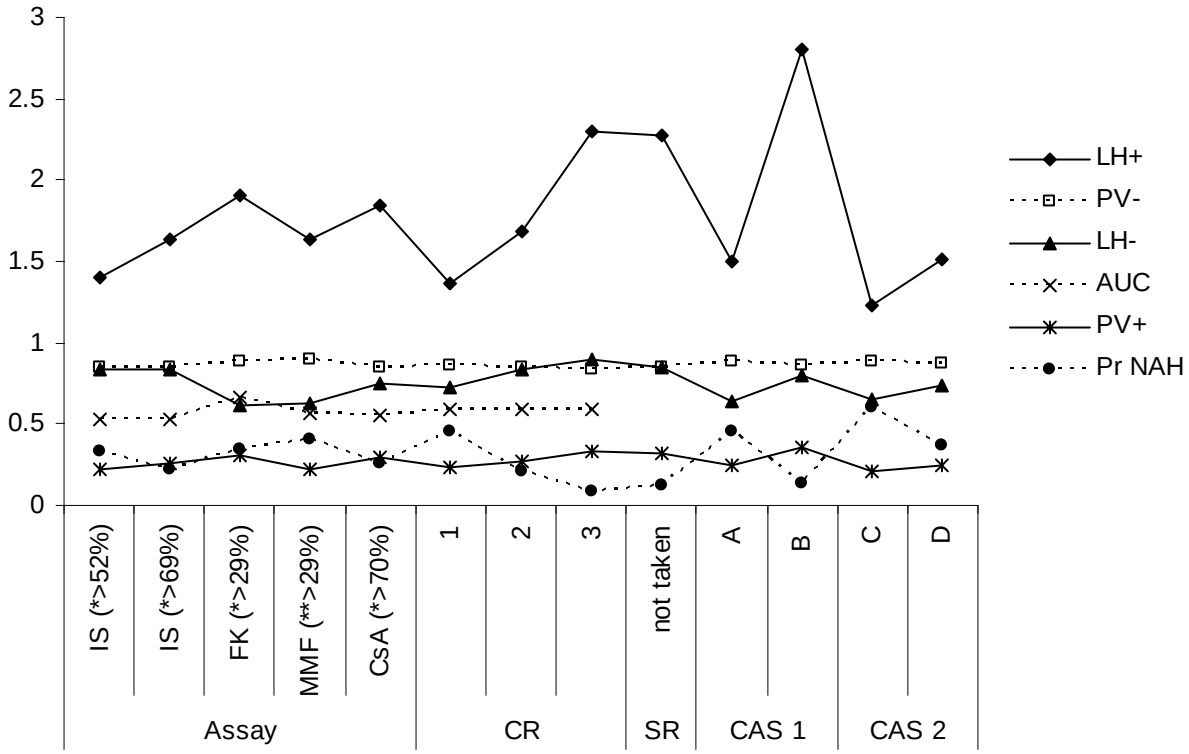
Figure 4a: Selected diagnostic values of assays, self-reports, clinicians' collateral reports, and composite adherence scores as compared to EM algorithm.



EM (electronic monitoring) algorithm (i.e., reference standard) = taking adherence < 98% and/or at least 1 drug holiday
IS = immunosuppressive drugs; CsA = cyclosporine; MMF = mycophenolat-mofetil; FK = tacrolimus
SR = patient self-reports; CR = clinicians' collateral reports; CAS 1, CAS 2 = composite adherence scores
Pr NAH = prevalence of non-adherence
* non-therapeutic blood assay variability; ** supra-therapeutic blood assay variability
1 = Patients were classified as non-adherent if they had at least 1 clinician's response of fair or lower adherence.
2 = Patients were classified as non-adherent if they had at least 2 clinicians' responses of fair or lower adherence.
3 = Patients were classified as non-adherent if they had at least 3 clinicians' responses of fair or lower adherence.
A = Patients were classified as non-adherent if they self-reported non-adherence and/or had at least 1 clinician's response of fair or lower adherence.
B = Patients were classified as non-adherent if they self-reported non-adherence and/or had at least 4 clinicians' responses of fair or lower adherence.

C = Patients were classified as non-adherent if they self-reported non-adherence and/or had at least 1 clinician's response of fair or lower adherence and/or had non-therapeutic blood assay variability (cut-off > 69%).
D = Patients were classified as non-adherent if they self-reported non-adherence and/or had at least 4 clinicians' responses of fair or lower adherence and/or had non-therapeutic blood assay variability (cut-off > 69%).

Figure 4b: Selected diagnostic values of assays, self-reports, clinicians' collateral reports, and composite adherence scores as compared to EM algorithm



LH+ = likelihood ratio of a positive test result; PV- = negative predictive value; LH- = likelihood ratio of a negative test result; AUC = area under the curve; PV+ = positive predictive value; Pr NAH = prevalence of non-adherence
Further abbreviations, see legend figure 4a

Sensitivity. Composite adherence score 2 resulted in the highest sensitivity (72.1%) followed by composite adherence score 1 (62.8%), collateral reports (57.9%), and supra-therapeutic MMF

assay variability (60.0%) Table 5a presents a cross tabulation of the results of the CAS 2 alongside the results of the EM algorithm.

Table5a: Cross tabulation: composite adherence score 2 using EM algorithm

		EM algorithm
CAS 2	Non-adherent patients	Adherent patients
Non-adherent patients	31	118
Adherent patients	12	88

CAS 2 = composite adherence score 2 (cut-off = self-reported non-adherence and/or at least 1 clinician's response of "fair" or lower adherence and/or non-therapeutic assay variability)
EM = electronic monitoring
EM algorithm = taking adherence < 98.0% and/or at least 1 drug holiday
Sensitivity = 31/43 x 100%= 72.0%

Specificity. Collateral reports of three clinicians' responses of fair adherence showed 93.1% specificity, followed by self-reports and composite adherence score 1 (cut-off = self-reported non-adherence and/or at least 4 clinicians' responses of fair or lower adherence) which gave equal values of 89.8%, followed in turn by collateral reports of at least 2 clinicians' responses of fair or lower adherence (81.1%). Table 5b presents a cross tabulation of the results of the CR alongside the results of the EM algorithm.

Table 5b: Cross tabulation: collateral reports using EM algorithm

		EM algorithm
CR	Non-adherent patients	Adherent patients
Non-adherent patients	6	12
Adherent patients	32	163

CR = collateral reports (cut-off = at least 3 clinicians' responses of "fair" or lower adherence)
EM = electronic monitoring
EM algorithm = taking adherence < 98.0% and/or at least 1 drug holiday
Specificity = 163/175 x 100%= 93.1%

Likelihood ratios of positive tests. Composite adherence score 1 (cut-off = self-reported non-adherence and/or at least 4 clinicians' responses of fair or lower adherence) resulted in a 2.74 likelihood ratio of a positive test (LH+), indicating that a patient whose test results indicated non-adherence was almost three times more likely to actually be non-adherent than a patient with no such findings. LH+ results of at least three clinicians' collateral reports, self-reported non-adherence and non-therapeutic FK assay variability (cut-off > 29%) ranged from 2.3 to 1.9. Table 5c presents a cross tabulation of the results of the CAS 1 with the results of the EM algorithm.

Table 5c: Cross tabulation: composite adherence score 1 using EM algorithm

		EM algorithm
CAS 1	Non-adherent patients	Adherent patients
Non-adherent patients	12	21
Adherent patients	31	185

CAS 1 = composite adherence score 1 (cut-off = self-reported non-adherence and/or at least 4 clinicians' responses of "fair" or lower adherence)
EM = electronic monitoring
EM algorithm = taking adherence < 98.0% and/or at least 1 drug holiday
Likelihood ratio of a positive test (LH+) = Sensitivity / (1 - Specificity) = (12/43) / (1-(185/206)) = 2.74

Validation of the different methods

Table 6 shows the correlations (spearman's rho, two-tailed) between the different methods.

Table 6: Spearman's rho correlation table of all measurement methods

	Sb	Sp	Nt	SR	EM A	TA	DA	TiA	DH /100d	CR	CAS1	CAS2
Sub-therapeutic blood levels (Sb)	1.000	-.447**	.527**	-.046	-.021	-.041	-.017	-.004	.019	.109	-.078	-.325*
Supra-therapeutic blood levels (Sp)		1.000	.379**	-.122	.026	-.045	-.076	-.118	-.003	-.023	-.097	-.218**
Non-therapeutic blood levels (Nt)			1.000	-.140*	-.041	-.101	-.073	-.084	.042	.063	-.155*	-.657**
Self report (SR)				1.000	.150*	.099	.091	.331*	-.133*	-.075	.965**	.493**
EM algorithm (EM A)					1.000	.683**	.645**	.481**	-.513**	-.140*	.197*	.135*
Taking adherence (TA)						1.000	.706**	.438**	-.348**	-.166*	.129*	.168**
Dosing adherence (DA)							1.000	.667**	-.340**	-.146*	.119	.155*
Timing adherence (TiA)								1.000	-.262**	-.093	.333**	.289**
Drug holiday / 100 days (DH/100d)									1.000	.049	-.122	-.148*
Clinicians collateral report (CR)										1.000	-.121	-.036
Composite adherence score 1[†]											1.000	.511**
Composite adherence score 2[††]												1.000

* Correlation is significant at the .05 level (2-tailed)

** Correlation is significant at the .01 level (2-tailed)

[†] Composite adherence score 1 = self-reported non-adherence and/or clinicians' responses of fair or lower adherence (CAS1 B, see legend figure 4 for details)

[††] Composite adherence score 2 = self-reported non-adherence and/or clinicians' responses of fair or lower adherence and/or non-therapeutic blood assay variability (CAS2 D, see legend figure 4 for details)

Assays. Significant correlations were found between non-therapeutic assay variability and self-reported non-adherence $r_{rho} = -.140$ ($p < .05$).

Self-reports. Self-reported non-adherence significantly correlated with EM drug holidays, the EM algorithm, and EM timing adherence, ranging from $r_{rho} = -.133$ ($p < .05$) to $r_{rho} = .331$ ($p < .05$).

Clinicians' collateral reports. Clinicians collateral reports correlated significantly with the EM algorithm $r_{rho} = -.140$ ($p < .05$), EM dosing adherence $r_{rho} = -.146$ ($p < .05$), and EM taking adherence $r_{rho} = -.166$ ($p < .05$).

Composite adherence scores. Composite adherence score 1 correlated significantly with EM taking adherence, non-therapeutic blood levels, the EM algorithm, and EM timing adherence (ranging from $r_{rho} = .129$ ($p < .05$) to $r_{rho} = .333$ ($p < .01$)). Composite adherence score 2 correlated significantly with the EM algorithm, EM drug holidays/100d, EM dosing adherence, EM taking adherence, and EM timing adherence (ranging from $r_{rho} = .135$ ($p < .05$) to $r_{rho} = .289$ ($p < .01$)).

Discussion

This study is one of the few studies assessing the diagnostic accuracy of state-of-the-art measures of non-adherence to immunosuppressive regimens (assays, self-reports, clinicians' collateral reports, and composite adherence scores) as compared to electronic monitoring. The prevalences of non-adherence in our sample match those reported in other studies [1]. Furthermore, the data of this study reflect the wide variation of prevalences of non-adherence with respect to various measurement methods and specific cut-off points.

The study findings suggest that the most valuable measurement approach in view of detecting the highest rate of non-adherent patients (i.e., high sensitivity) was the use of a composite adherence score, drawing non-adherence information from patient self-reports, nurses' or physicians' collateral reports and non-therapeutic assay results. However, this measure concurrently showed low specificity, indicating its value for "screening" (i.e., a first step) rather than diagnosis. Other work with HIV infected patients also showed that a composite adherence score achieved the highest sensitivity [56]. As in other studies investigating diverse patient populations [44-47], our study found low sensitivity to non-adherence when only one state-of-the-art measure was used to indicate non-adherence. Poor sensitivity of individual measures means that they failed to identify many truly non-adherent patients.

Our data suggest that high specificity can best be achieved by combining several clinicians' reports of "fair" adherence, by combining several methods, or by assessing patients' self-reports. The combined value of several clinicians' reports regarding uncertain adherence to medications is noteworthy: thus far, collateral reporting by a single clinician has been regarded an invalid method of assessing medication non-adherence [7, 45, 57].

Although non-therapeutic FK assay variability, non-therapeutic CsA assay variability and supra-therapeutic MMF assay variability provided useful levels either of specificity or of sensitivity, nowhere did we find consistency regarding both, nor could consistent cut-off values, sub-therapeutic, non-therapeutic or supra-therapeutic assay values be determined across the various immunosuppressive regimens, even after multiple sensitivity analyses (data not presented). We therefore emphasize that this study's blood assay findings should be treated with caution when used to infer information about patients' non-adherence status.

The study revealed unexpectedly low inter-method correlations. When methods were combined, however, correlations improved. These findings suggest that, while the applied methods did not overlap strongly in measuring medication non-adherence as a whole, each method still functioned as a partial indicator. For maximum validity, then, EM should be combined with other methods, rather than used as a reference standard to evaluate them.

Limitations

First, this study did not clinically validate the EM algorithm, which was used as the reference standard, because of the lack of prospective clinical outcomes. However, we performed sensitivity analysis with various EM cut-offs which resulted in stable diagnostic values (data not presented), which supports the accuracy and robustness of the presented results. Furthermore, in a previous study investigating a sample of heart transplanted recipients more than one year after Tx on a CsA regimen [54], this EM algorithm showed discriminative power concerning partly prospective data of late acute rejection episodes.

Second, it is possible that participant selection bias occurred in the following ways: 1) non-adherent recipients may have been more likely to refuse EM monitoring, although we found no evidence of this (i.e., no differences in non-adherence state-of-the-art measures between EM participants and eligible EM non-participants [37]); and 2) due to recent changes in Swiss law, it is not possible to determine whether the sample was representative of the kidney-transplanted population of the two centers. The law requires informed consent – which was not available in

this study – to collect demographic and clinical data on patients who refuse to participate. Therefore, the findings of this study can not be generalized.

Third, it is possible that the study suffered from a bias of survivor selection by including only recipients more than one year post-transplantation. Recipients with severe non-adherence may already have been ineligible for this study due to a nonfunctioning graft.

Fourth, the results of the state-of-the-art measurement methods and reference standard were not read blinded. However, the criteria used to classify participants as non-adherent were not prone to subjective interpretation but based on a predefined algorithm (reference standard) and ROC. Therefore, it is unlikely that the lack of blinding influenced the reading of the results of either the state-of-the-art measures or the reference standard.

Fifth, in our study, while EM measured a three-month period, assay ranged beyond this period, and self- and collateral reporting dealt with non-adherence prior to the start of EM. However, we did not consider these non-identical measurement times as problematic: previous work suggested that, barring the occurrence of a major event, adherence to medication should be a stable behavior [58].

Finally, this study assessed patients' adherence to only one immunosuppressive drug. Therefore, the findings might not reflect adherence to the full immunosuppressive regimen. However, empirical evidence suggests that non-adherence should be comparable between several medications [59], yet research should substantiate this in Tx.

To conclude, our findings add to the limited evidence concerning the diagnostic accuracy of adherence measurement with immunosuppressive regimens using EM as a reference standard. Using EM as a reference standard depends on two conditions: 1) an assumption that the patient is not systematically deceiving the monitoring process; and 2) the use of measures to address validity threats to EM [34], (e.g., differentiation between adherence to medication taking and adherence to EM guidelines). This study showed that none of the state-of-the-art measures resulted in both high sensitivity and high specificity, when compared to EM. Despite the clear shortcomings of using any single measure, the most valid measure to correctly identify NAH was to combine the results of several tests, each of which included consistent known limitations. This implies that, for clinical practice any information suggesting non-adherence, regardless of its source, should be taken seriously as a possible non-adherence indicator, and should lead to a non-accusatory and non-threatening non-adherence assessment, followed, if applicable, by offering

appropriate interventions. In individual patients with non-adherence indications, EM may then be used to monitor medication taking behavior, because it provides data that are helpful for both problem detection and encouraging mastery experience in medication taking [50]. In the absence of a perfect method, further research is clearly warranted, however, to focus specifically on combined measurement methods, which have considerable potential to enhance our understanding of medication non-adherence detection and measurement.

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Chapter 5

Supporting medication adherence in renal transplantation (SMART): a pilot RCT to improve adherence to immunosuppressive regimens

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Abstract

Background. Although non-adherence to an immunosuppressive regimen (NAH) is a major risk factor for poor outcome after renal transplantation (RTx), very few studies have examined non-adherence intervention in this context. This pilot randomized controlled trial (RCT) tested the efficacy of an educational-behavioral intervention to increase adherence in non-adherent RTx patients. We also assessed how NAH evolves over time.

Methods. Eighteen RTx non-adherent patients (age: 45.6±1.2 yr; 78.6% male) were randomly assigned to either an intervention group (IG) (N=6) or an enhanced usual care group (EUCG) (N=12), the latter receiving the usual clinical care. The IG received one home visit and three telephone interviews. We assessed NAH through electronic monitoring (EM) of medication intake during a nine-month period (three months intervention, six months follow-up).

Results. Five of 18 patients withdrew. Inclusion in the study resulted in a remarkable decrease in NAH in both groups over the first three months (IG χ^2 =3.97, df=1, p=.04; EUCG χ^2=3.40, df=1, p=.06). The IG showed the greatest decrease in NAH after three months, although this did not reach statistical significance (at 90 d, χ^2=1.05, df=1, p=.31). Thereafter, NAH increased gradually in both groups, reaching comparable levels at the end of the six-month follow-up (i.e., at nine months).

Conclusion. Our findings suggest an *inclusion effect*. Although the intervention in this pilot RCT appeared to add further benefit in medication compliance, a lack of statistical power prevented us from making a strong statistical statement.

Introduction

A recent systematic review of the literature showed that 28% of adult renal transplant recipients report that they do not adhere to their immunosuppressive regimen [1]. Several studies have shown that patient non-adherence to immunosuppressive drugs detrimentally affects the short- and long-term outcomes of renal transplantation [2-4]. Twenty percent of late acute rejections and 16% of graft losses have been associated with non-adherence to the immunosuppressive regimen (NAH) [1]. This evidence highlights the importance of adherence-enhancing intervention as a possible pathway to improve the clinical outcome of renal transplantation. The value of this pathway is not well recognized in the medical literature. Indeed, a recent review of strategies aimed at enhancing long-term outcome after renal transplantation did not consider the potential value of adherence enhancing interventions [5].

Scarce evidence exists on interventions that promote medication adherence in populations receiving solid organ transplants. Several possible interventions have been described: educational approaches [6], behavioral contracting [7], financial support programs for drugs [8], feedback on medication intake via electronic monitoring [9], and self-medication administration program as part of discharge planning [10]. The efficacy of these interventions is yet to be formally tested. To date, the only study to assess the efficacy of a non-adherence intervention was that of Dew et al. [11]. This study used a non-equivalent comparative design to test the efficacy of a multifaceted web-based intervention program in improving mental health, quality of life, and adherence. Although Dew et al. found no improvement in overall adherence scores, they did find that patients using the web-based intervention more often had high adherence scores, suggesting that increased participation in the intervention resulted in increased adherence. To our knowledge, no randomized controlled trials (RCT) have been carried out with the aim of testing the efficacy of adherence-enhancing interventions for medication regimens following solid organ transplantation.

Two meta-analyses [12, 13] and two structured literature reviews [14, 15] have described the efficacy of adherence-enhancing interventions for medication regimens in non-transplant, chronic- and acute-care populations. The most effective approaches are multilevel, targeting more than one risk factor over a sustained time. Multilevel interventions are integrated not only at the patient-provider level but also at organizational and health-care system levels. Targeting risk factors of non-adherence includes approaches that use a combination of educational, cognitive behavioral, and social support interventions to change modifiable socioeconomic, patient-,

treatment-, condition-, and health-care team-related factors that are linked to non-adherence [16]. For instance, a knowledge deficit can be remedied by educational interventions. Patient education alone, however, is not an effective adherence-enhancing strategy [12-15]. A major determinant of NAH in transplant populations is low self-efficacy [17, 18]. This refers to a person's confidence in successfully performing a specific behavior (e.g., medication taking), even in taxing situations [19]. Self-efficacy can be targeted by specific interventions such as having the patient experience mastery experiences, role modelling, verbal persuasion, and decreasing physiological arousal [20]. Because non-adherent patients are three times higher at risk for depression [21], depression should be treated as part of the adherence-enhancing intervention. In summary, it is the combination of interventions over a sustained time that seems to be most effective in preventing non-adherence [22].

Scant evidence exists concerning the effectiveness of adherence-enhancing interventions in solid organ transplant populations. Given this, and the evidence that non-adherence is a major risk factor for poor outcome after transplantation, the purpose of this pilot RCT was to test the efficacy of a three-month adherence-enhancing intervention in non-adherent renal transplant recipients. Adherence was assessed at the end of the intervention and at the end of a six-month follow-up (i.e., nine months after initiation of the intervention).

The *alternative hypotheses* guiding this study were following:

- Patients in the intervention group will show a lower chance of being non-adherent compared to the enhanced usual care group at the end of the intervention period (three months) and at the end of the six months follow-up (i.e. nine months), respectively.
- The chance of being non-adherent will increase in patients in the intervention group after the end of the intervention (i.e. between three months and nine months follow-up)

Patients and Methods

Design

This study was a RCT. Three months of intervention treatment took place followed by six months of follow-up.

Sample and Setting

Inclusion and exclusion criteria

To be included in the present study, the patient had to be non-adherent to their immunosuppressive regimen (see below), at least 18 yr old; to be in follow-up at the University Hospital Basel, Switzerland, or at the Cantonal Hospital, Aarau, Switzerland; to speak German or French; to be literate; to have undergone kidney transplant surgery at least one year prior to the study; to be able to self-administer immunosuppressive drugs; to reside within a 180-km radius of Basel; and to provide written informed consent to participate in the RCT.

Patients included in this study were previously identified as being non-adherent to their immunosuppressive regimen in a previous study based on the three months of EM [17]. Period prevalences of non-adherence were calculated and eligibility status for the present study was determined by predefined algorithm (Table 1). The algorithm's stringent cut-off for non-adherence was based on previous research showing that minimal deviations from dosing schedule of the immunosuppressive regimen were associated with an increased risk for poor clinical outcome [2, 23].

Table 1: Non-adherence algorithm

< 98% taking adherence and / or one or more drug holidays	
EM [a] parameters	**Operationalization**
Taking adherence	Number of events recorded during the monitoring period / Number of prescribed doses during the monitoring period x 100
Drug holiday	No medication intake ➢ 36 hours for a twice daily dosing regimen (Cyclosporine, Mycophenolat-Mofetil, Tacrolimus, Sirolimus), or ➢ > 60 hours for a once daily dosing regimen (Azathioprin/Prednison®)
Timing adherence	Number of near optimal inter-dose intervals[a] / Total number of observed intervals x 100

[a] The near optimal inter-administration interval was calculated as the time interval between events (pill-bottle-cap openings) within 24 ± 6 hours of the previous event for a once-daily dosing regimen, within 12 ± 3 hours for a twice-daily dosing regimen, and within 8 ± 2 hours for a three-times-a-day dosing regimen (thus accounting for 25% of the optimal dosing interval).
EM, electronic monitoring

Patients were excluded if they lacked mental clarity based on clinician's appraisal, could not read forms or EM printouts with at least corrective lens, or had no telephone service at home.

Setting

This study was carried out in Switzerland, which has a compulsory health insurance system. The standard health-care package covers transplantation, the majority of costs for follow-up care, and immunosuppressive medications. However, patients pay premiums, franchise, and 10% of out-of-pocket costs for hospital and outpatient care and for prescribed drugs. Most patients resided in Switzerland, a country about half the area of Maine (USA), thus minimizing the travel distance to the transplant center.

Randomization procedures

Patients were randomly assigned to an enhanced usual care group (EUCG) or an intervention group (IG), stratified by site, using a 2:1 randomization scheme in favor of the enhanced usual care group (23). A person independent of the research team performed the assignments using random number tables. Group assignment was sealed in envelopes until the end of the study.

Variables and measurement

Demographic and clinical data

We used demographic and clinical data that were part of the baseline measurements from our previous descriptive study [17]; these data were acquired from the patients' original medical files.

Adherence to immunosuppressive regimen

We measured adherence to the immunosuppressive regimen by EM throughout the nine-month study (i.e., three months intervention and six months follow-up). EM consisted of gathering digital data about a patient's medicine-taking habits. A microelectronic circuit contained in the bottle cap of the patient's pill bottle registered the date and time of each bottle opening. Data were downloaded to a computer, which in turn generated lists and graphics of medication-taking habits [24]. Although an indirect method, EM is more sensitive in measuring non-adherence compared to other tools, such as self-reporting, blood testing, or pill counts [25-28]. Moreover, because it measures both if and when the patient took their medication, "drug holidays" (i.e., no medication intake for more than 36 or 60 hours, depending on dosing regimen and drugs) were easily detected. Immunosuppressive drugs for the present study were repackaged into individual EM containers labeled with each patient's regimen, according to current GMP and GCP guidelines. To guarantee the chemical stability of the medication, we left the pills in their drug blisters.

Consistent with ethical guidelines, we informed patients that the EM measured medication intake. We also gave oral and written instructions on how to use the bottle correctly. Because using the EM can be challenging in daily life, patients were allowed to note deviations from EM guidelines on a custom form. An example deviation would be removing a dose from the EM bottle before leaving the house and ingesting the medication at a later time. At the end of the nine months, we assessed reliability and validity of EM data by interviewing patients over the telephone using

structured questions based on previously developed methodology [23]. We also asked patients about practical problems with using EM in daily life and adherence with EM guidelines [23].

A research associate aware of the group assignments downloaded the EM data using Powerview® software (Aardex Ltd., Zug, Switzerland). We made adjustments to each patient's data based on entries on the patient's note form (see above), and then we calculated EM parameters (see below).

Enhanced usual care

Patients in the EUCG received the usual kind of care that outpatients receive during post-transplant follow-up care. The ethics committee overseeing the study (see below) requested that we inform the treating physicians if their patients were identified as being non-adherent. They also asked us to inform the treating physicians if their patients' scores on the Beck Depression Inventory (BDI; score of >15 on BDI), completed during the previous study, suggested moderate or severe depression or suicidal ideation [29]. We asked the treating physicians to note the intervention(s) they performed after learning of their patients' non-adherence.

Intervention

Patients in the IG received enhanced usual care plus one home visit after inclusion in the study, followed by three follow-up calls, one at the end of the month for three consecutive months. Table 2 summarizes the different parts of the intervention.

Table 2: Elements of the Intervention

Type of intervention	**Elements**
Behavioral: self-efficacy	Initiating mastery experience using EM printouts Verbal persuasion: motivation & empowerment Role modeling using EM printouts of adherent patients Decreasing physiological arousal especially in view of symptom distress
Other behavioral interventions	Cues: Linking medication taking with a routine behavior Reminders: e.g. alarm signal (watch, mobile phone) Reducing complexity of medication regimen Referral to psychiatrist: BDI scores of >15
Educational: tailored + individualized	Refreshment course: -Assessment of knowledge status; -Discuss purpose, intake and monitoring of medication Problem solving strategies: Address possible coping strategies with specific issues related to medication taking
Social support	Involvement of significant others in: -Preparation and reminding of medication administration -Filling prescriptions -Assisting in deciding to contact a HCW when problems occur

EM, electronic monitoring; BDI, Beck Depression Inventory; HCW, health-care workers.

The core of the intervention was aimed at increasing patients' self-efficacy in taking their medication consistently. To accomplish this, we used EM printouts for problem detection, proxy goal setting (i.e., definition of short-term goals), and regular targeted feedback [20]. EM printouts tabulated and graphed each patient's daily adherence dynamics (intake and regularity of medication taking). We implemented additional educational, behavioral, and/or social support interventions during the home visit (see below) that were based on an individualized assessment of reasons for non-adherence and/or information on determinants of non-adherence gathered during the previous study [17] and new information gathered during the home visit.

Home Visit

The patient, and if applicable a family member, participated in the home visit. First, we assessed daily medication management by observing where medications were located and how the patient or family member handled the medications, and by questioning. This was followed by a discussion of non-adherence issues we detected in the EM data from the previous study. We discussed possible factors associated with non-adherence (e.g., knowledge of adherence status, problematic illness representations, and side-effects from the immunosuppressive therapy). We made a special effort to respect the patients' perspective, acknowledging that they are in charge of their own self-management.

Next, the intervention nurse, patient, and family members together discussed possible adherence-enhancing interventions the patient and family perceived to be feasible and acceptable. All patients received self-efficacy interventions consisting of four elements: 1) developing mastery experiences in taking medications correctly (e.g., setting and successfully meeting proxy goals for the next month that were feasible for implementing a specific behavior —see Telephone Follow-up below); 2) participating in role modeling (e.g., using EM printouts of comparable RTx patients showing the targeted behavior); 3) verbally persuading by the intervention nurse; and 4) addressing negative effects of physiological arousal, if applicable (e.g., discussing strategies to cope with the side effects of immunosuppressive drugs).

In addition to self-efficacy interventions, the intervention nurse applied individualized intervention strategies that were derived from specific non-adherence–related dynamics. These included a refreshment course on 1) purpose of the medication; 2) taking of the medication; 3) monitoring of the medication; 4) assessment of side effects and symptom experience; and 5) individualized problem-solving strategies for managing immunosuppressive drugs in daily life based on the patients' specific needs. Possible behavioral interventions included cueing (e.g., placing pill bottle next to patient's purse as a reminder to bring the medication on trips, or taking medications with meals or at bedtime); explicit reminders (e.g., alarm using a watch or mobile telephone to signal time to take the medication); and reducing the complexity of medication regimen, if possible. Social support interventions included family members, friends, or colleagues involved in medication management (e.g., preparing patients' medication for administration, reminding patients to be punctual about taking their medications, filling

prescriptions, and assisting in contacting a health-care worker when problems arise). The protocol stipulated that patients with moderate and severe depressive symptoms (BDI score > 15) would be referred to a psychiatrist for further evaluation.

The intervention nurse, patient, and family defined proxy goals aimed at increasing adherence for the next month. Before leaving the patient's home, a telephone connected interface (Homelink) was installed, allowing the patient to send their monthly EM data to the research team.

Telephone follow-up

After the home visit, we contacted the patients by telephone three times, once at the end of the month for three consecutive months. Before each telephone follow-up session, we sent EM printouts to each patient by fax, mail, or email so that the patient could review them and refer to them during the telephone follow-up interview. The researcher began each session by briefly assessing the patient's current health status (e.g., infections, hospital admission) and/or by asking the patient about any recent special events (e.g., holidays, work, and family situation). Next, the researcher discussed the EM printout with the patient. Improvement in the patient's adherence was rewarded by positive comments to promote in the patient mastery experiences. Non-adherence was addressed in a supportive, non-accusatory manner, with the aim of determining the patient's reasoning for failing to take the medication. The researcher and patient discussed the efficacy of adherence strategies the patient used that month. If the patient's strategies were ineffective, the researcher suggested alternative strategies for the upcoming month. The nurse attempted to engage the patient in role modeling, if deemed appropriate. The telephone call concluded by setting proxy goals to increase adherence for the next month. The home visits and telephone contacts were tape-recorded to maintain data integrity and for qualitative data analysis. At the end of the intervention period, the researcher asked the patients which intervention(s) they remembered and perceived as being most helpful.

Data collection procedures

A Master's degree-level nurse, not part of the transplant team, recruited patients by telephone. The nurse explained the goals of the study and obtained oral informed consent for participation. We also obtained written informed consent through follow-up mail. After randomly assigning patients to the IG or the EHCG, we informed them by telephone to which group they were

assigned. We also verbally verified their actual immunosuppressive regimen, so that the hospital pharmacy could prepare the EM bottles accordingly. For the EUCG, we mailed the EM pill bottles, and for the IG, we hand delivered the bottles to the patients' homes.

After we obtained written informed consent from each patient, we notified the treating physicians by letter about the non-adherence status of their patients (see above). Patients received a new supply of immunosuppressive drugs by mail every 3 months during the 9 months of EM monitoring. At the completion of the study, we interviewed the patients to assess the validity and reliability of the EM monitoring.

Data analysis

Daily EM events were used as the unit of analysis for descriptive and inferential statistics. These data were binary (i.e., dose was taken or not taken).

Descriptive statistics

Demographic and clinical variables were expressed, as appropriate, in frequencies, mean and standard deviations (normally distributed and interval scaled variables), and median and interquartiles ranges (not normal distributed and ordinal scaled variables). We used the Statistical Software Package of Social Science (SPSS®, Chicago, IL, USA) version 11.1.

Inferential statistics

We used Intention-to-Treat principles for analysis. To test whether adherence levels differed between the study groups at three months and nine months, we designated a binary variable to each patient's daily adherence and modeled the probability of non-adherence using a corrected logistic regression analysis (Generalized Estimating Equations) [30]. We tested for a possible difference in temporal evolution of non-adherence from baseline in both study groups by specifying an interaction term between study group and time. Modelling was done with the GENMOD procedure in SAS 8.1 statistical software.

Statistical significance was set at $p < 0.05$. For exploratory purposes, we also fit a generalized additive model with a logit link function, because this technique enabled us to visually detect possible nonlinear trajectories of the predicted logarithmized odds (log odds) on non-adherence in both study groups. Log odds are algebraically transformed probabilities that enable the use of linear functions in logistic regression analysis. Generalized additive models allow one to explore how the chances on non-adherence evolve nonlinearly over time, which in turn allows one to test whether the assumption of linearity underlying logistic regression analysis corresponds with reality. We calculated the sample size required to achieve 80% statistical power using the SAS "UnifyPow" macro. This was done post hoc and was based on the χ^2.

Qualitative assessment of intervention effect

We either noted responses to the open-ended question at the end of the intervention, or tape recorded and transcribed them. We used content analysis techniques [31] to do a preliminary analysis of these data.

Human subjects' consideration

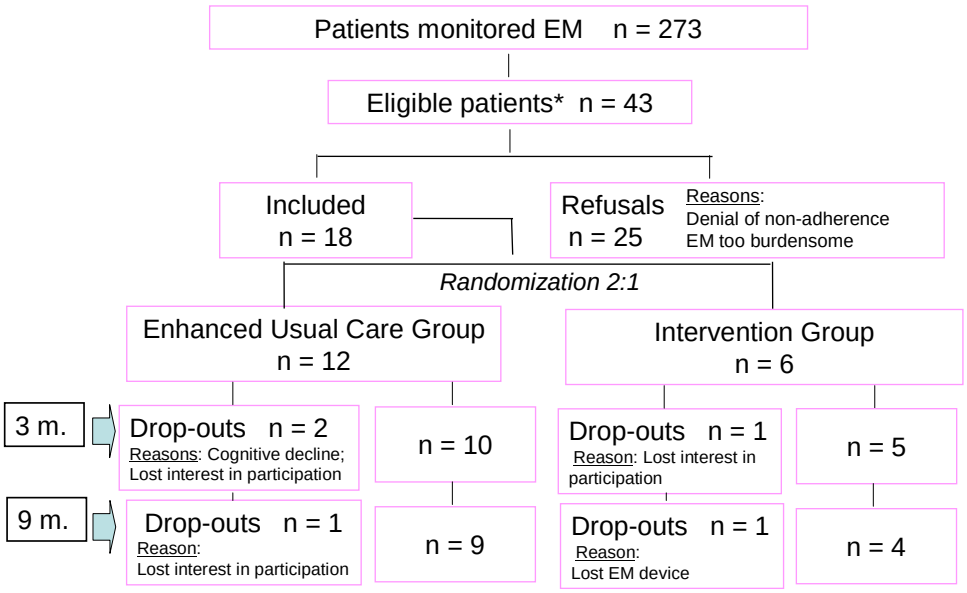
The study was approved by the ethics committees of the University Hospital Basel and the Cantonal Hospital of Aarau, as well as by the Federal Ethics Committee of Switzerland. Besides giving oral and written informed consent for participation, IG patients gave additional oral informed consent to tape-record during the home visits and telephone interviews. We informed the treating physicians of the subjects' non-adherence and depression status, as required by the ethics committee.

Results

Of 273 renal transplant recipients participating in the previous descriptive study [17], 43 patients were categorized as being non-adherent (Table 1), all of whom were invited to participate in the present study (see CONSORT flow diagram: Figure 1). Eighteen patients (37%) agreed to participate. Of these, six were assigned to the intervention group (IG), and 12 were assigned to the EUCG. Self-exclusion reasons ranged from the patients' denial of a non-adherence problem to the patients' perception that EM was too burdensome to use daily. Participants (n=18) and those declining to participate (n=25) were similar in age ($t = 1.254$, $df = 41$, $p = 0.217$); gender ($\chi^2=2.185$, $df=1$, $p = 0.139$); time since transplantation ($t = -.378$, $df = 41$, $p = 0.707$); medication taking adherence (U=207.5 [25/18], $p = 0.667$); and dosing adherence (U=213.5 [25/18], $p = 0.777$). They differed significantly in timing adherence and drug holidays, with participants showing less adherence in taking their medication at the correct time (median: 67.4% vs 82.6%; U=130.5 [25/18], $p = 0.02$), and fewer drug holidays per 100 d of monitoring (median: 0 vs. 1; U = 134 [25/18], $p = 0.017$). Patients in the intervention group and enhanced usual care group were comparable in view of age, time post-transplantation and baseline adherence levels.

Five patients dropped out during the study (three EUCG and two IG). One EUCG patient eventually failed to independently manage his medication because of cognitive decline, and two lost interest in participating. One IG patient decided to withdraw before the start of the home visit, one lost the EM device at the end of the study. Thus, complete data were available for 10 EUCG and five IG patients at three months follow-up (end of intervention period, and for nine EUCG and four IG at nine months follow-up, respectively (see CONSORT flow diagram: Figure 1).

Figure 1: Consort diagram

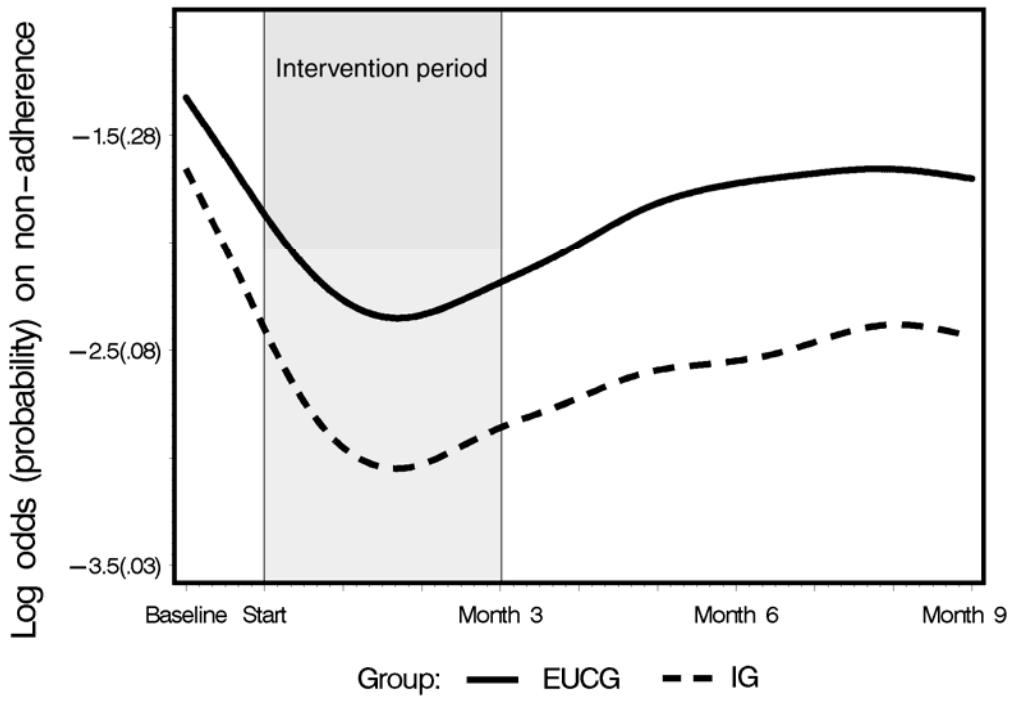


* Eligibility based on algorithm (see Table 1)

Evolution of non-adherence *within* the IG and EUCG

To understand the evolution of non-adherence over the course of the study, we calculated a smoothed plot of the nonlinear trajectories of the predicted chance of non-adherence (Figure 2).

Figure 2: Nonlinear regression lines, modeling the temporal evolution of non-adherence during the baseline measurement, the three-month intervention, and the six-month follow-up. The probability of being adherent versus being non-adherent (averaged over patients within a group) is plotted. Only the IG patients received a specific intervention (see text).



Non-adherence declined remarkably in both groups during the first three months of the study (IG χ^2=3.97, df=1, p=.04; EUCG χ^2=3.40, df=1, p=.06). Although the chance of non-adherence gradually increased after this initial decline, by the end of the nine-month study, non-adherence had leveled off to a probability that was lower than that calculated at the start of the study, especially for the IG patients. This gradual increase in non-adherence for the IG patients after the three-month intervention suggests, however, that in order for the full effects to persist, intervention procedures must continue for longer than three months.

Evolution of non-adherence *between* IG and EUCG

Although the IG patients' chance of being non-adherent during the first 3 months decreased more than the EUCG patients' chance, as shown by the smoothed plot of Figure 2, this group difference did not reach statistical significance (χ^2=1.05, df=1, p=0.31). This was also the case at nine months (χ^2=0.3, df=1, p=0.58).

Qualitative assessment of intervention effect

The answer to the open-ended question posed to IG patients at the end of the intervention period indicated that they perceived the procedures to be beneficial. IG patients felt that the most helpful part of the intervention involved using EM printouts for detecting problems, providing feedback, and defining proxy goals. Specifically, one patient appreciated that we cared about her medication management. She felt that the repeated discussions helped in reminding her to take the medications correctly.

Discussion

Our study is among the first to test an adherence-enhancing intervention in identified non-adherent renal transplant recipients, showing that NAH can be modified in this patient population. The most important finding of our study is that mere inclusion resulted in a significant decline of NAH in both the IG and EUCG. The IG appeared to have also benefited further from the multidimensional intervention procedures we employed, although this effect failed to reach statistical significance. This study adds to the limited evidence on the effectiveness of adherence-enhancing interventions for medication regimens in other chronic patient populations. A methodological strength of our design was the use of EM, the most sensitive way to assess medication adherence [25-28]. The collection of sequences of binary EM data [30] allowed us to analyze in detail the time-component of medication non-adherence and to perform multiple modeling runs.

Our observation of an *inclusion effect* merits further comment. When patients were invited to participate, they were informed that they had been identified as non-adherers in the previous EM study of post-transplantation medication compliance. This fact might have elevated awareness in patients, and thus could underlie the initial decrease in non-adherence observed in the two groups. If this hypothesized mechanism were in operation, our findings suggest that it would make sense to monitor patients for non-adherence and to provide feedback if it occurs. Indeed, it

should be imperative to include non-adherence as an important clinical parameter to be monitored in post-transplantation follow-up, given the major negative impact of non-adherence on outcome [1, 2, 32]. Measurement of non-adherence in daily clinical practice using EM, however, is not feasible. While EM is the gold standard for assessing non-adherence, we found previously that *combining* non-adherence information derived from various sources (i.e., self-report, collateral report, assay) is much more sensitive compared to single-measurement methods. More specifically, sensitivity of a composite adherence score shows 80% sensitivity in identifying non-adherent RTx patients [33]. Patients' self-report, despite its limitations of underreporting and recall bias [34], shows high specificity when questions are stated in a non-accusatory, information-intensive, and supportive manner [33, 35]. For instance, patients can be asked: "We know that taking medications after transplantation can be challenging. Some patients have difficulty in taking their prescribed drugs daily. How about you? Do you sometimes forget to take a dose? How often has this happened in the past week or month?"

Our results suggest that the three-month intervention had an additional benefit on decreasing non-adherence beyond the inclusion effect (Fig.2). However, the data lacked statistical power; thus, we were unable to make reliable statistical inferences on this point. Post hoc power analysis revealed that, in order to detect a significant difference in non-adherence between the study groups after 3 months, we would require a sample of 113 patients. This is with alpha set at 0.05 and a power of 0.80 based on the χ^2 effect size of 1.05. Our post-intervention questioning suggests, however, that the intervention effect may be reliable and that a larger study may be able to make a statistical statement about additional benefit derived from the kind of intervention procedures we used.

The core strategy we used in the multidimensional, "high-dose" intervention was self-efficacy intervention. EM printouts were used as a tool for problem detection, feedback, and proxy goal setting. These allowed us to encourage mastery experiences and to initiate role modeling and verbal persuasion, known to be effective self-efficacy enhancing interventions. We employed additional individualized educational, behavioral, and social support interventions when appropriate. Since no patients in the intervention group was found to show depressive symptomatology (BDI>15) none of these patients were referred for further psychiatric evaluation or screening. Although our study design did not allow us to disentangle each discrete effect of these interventions, the interview at the end of the intervention period revealed that patients perceived the use of EM printouts and the associated self-efficacy interventions as most helpful

in increasing their medication adherence. This is in line with objective evidence, showing the effectiveness of self-efficacy interventions in improving adherence with smoking cessation [36] and maintaining exercise routines [37]. Improving self-efficacy is a behavioral intervention. Meta analyses comparing the effect sizes of different kinds of adherence-enhancing interventions with medication regimens confirm the superiority of behavioral interventions over other interventions (effect sizes: behavioral = 0.22; behavioral + educational = 0.35; affective = 0.20; educational = 0.20) [12],[13].

Admittedly, the intervention we used was complex, very intense, and time consuming, which limits its use in routine clinical settings. Nevertheless, the basic principles and interventions applied in this study could be learned by members of the transplant team, allowing them to deal more effectively with non-adherent patients during routine hospital visits. A major obstacle to overcome is the prevalence of the acute-care model employed in most transplant follow-up care, meaning that no room is left for integrating adherence interventions into clinical practice. This is typically due to time constraints. An alternative might be to employ a chronic disease-management model [16], [38, 39], in which not only medical but also psychosocial and behavioral dimensions of transplant management are optimally integrated into follow-up care. This would be more appropriate, given the increasing evidence that behavioral and psychosocial risk factors independently have a negative impact on clinical outcome in solid organ transplant populations. Chronic disease management also implies continuity of care, a strong emphasis on patients being an active partner in the clinical care, as well as the importance of adequate patient self-management [16], [38, 39].

In generalizing our results to other patient populations, we should emphasize that the definition of non-adherence to immunosuppressive therapy we employed in the present study (see Table 1) is more stringent compared to the definition used with other medication regimens. For instance, with antihypertensive treatment, it is common to define medication non-adherence as adherence of less then 80%. Indeed, to guarantee favorable therapeutic outcomes in transplantation, nearly perfect adherence should be the goal, because minimal deviations from a dosing schedule are associated with negative outcome [2, 40]. The improvement in adherence levels in our renal transplant sample showed the feasibility of increasing adherence, even when baseline adherence levels were fairly high. This is especially important for medication regimens with limited forgiveness referring to narrow therapeutic windows such as regimens required for renal and heart transplant patients [40], [2] and HIV/AIDS patients on antiretroviral therapy [41], [42].

Limitations of the study

The main limitation of this study was the self-exclusion rate, which resulted in a small sample size. The power of the study, therefore, was not sufficient to make reliable statistical inferences about the efficacy of the main intervention. It surprised us that many of the patients declined to participate in the present study. We were especially surprised that many were unaware of being non-adherent in the previous study. This suggests that we should routinely use EM printouts before including patients in any research study in order to provide them with feedback on non-adherence, which may in turn encourage them to participate in this kind of research.

Conclusion

Overcoming non-adherence in solid organ transplant populations could be a major pathway for improving clinical outcome. This study provides a first indication that behavioral intervention, especially self-efficacy intervention using EM methodology, is a feasible strategy for improving adherence in one class of identified immunosuppressive-regimen non-adherers. Our study has shown that this strategy can be incorporated into routine clinical care for RTx non-adherent patients. Additional large-scale studies are needed to test adherence-enhancing interventions in routine clinical care and to assess the impact of interventions on clinical outcome.

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Chapter 6

Computerized patient education in kidney transplantation: Testing the content validity and usability of the Organ Transplant Information System (OTIS™)

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Abstract

Objective: To test content validity and usability of the Organ Transplant Information System (OTIS™).

Methods: This study used qualitative methods. The purposive sample consisted of 8 clinicians and 14 patients. Clinicians rated the content's congruence with current medical practice. We used the clinicians' evaluations to revise the OTIS™ content; then each patient evaluated the revised OTIS™ modules using the thinking-aloud method and via structured interviews. Descriptive statistics were applied for demographic and clinical data, and for the clinicians' ratings. Content data usability and validity were analyzed using Content Analysis.

Results: Clinicians identified deviations from current medical practice regarding content, language, and information structure of OTIS™. Seven rated OTIS™ as non-relevant for implementation into clinical practice. Five rated the program's content – with the stipulated adaptations – as important for patients. All patients encountered usability problems, mostly regarding the program's interface. Emerging categories from the patients' perspectives vis à vis content were knowledge acquisition, illness management, and partnership forming.

Conclusion: Problems arose regarding OTIS's™ initial content validity and usability, demonstrating the need to establish the presented material's content validity and usability by involving clinicians and patients before its clinical implementation.

Practice Implications: High quality computer-learning-software is needed to enhance patient self-management.

Introduction

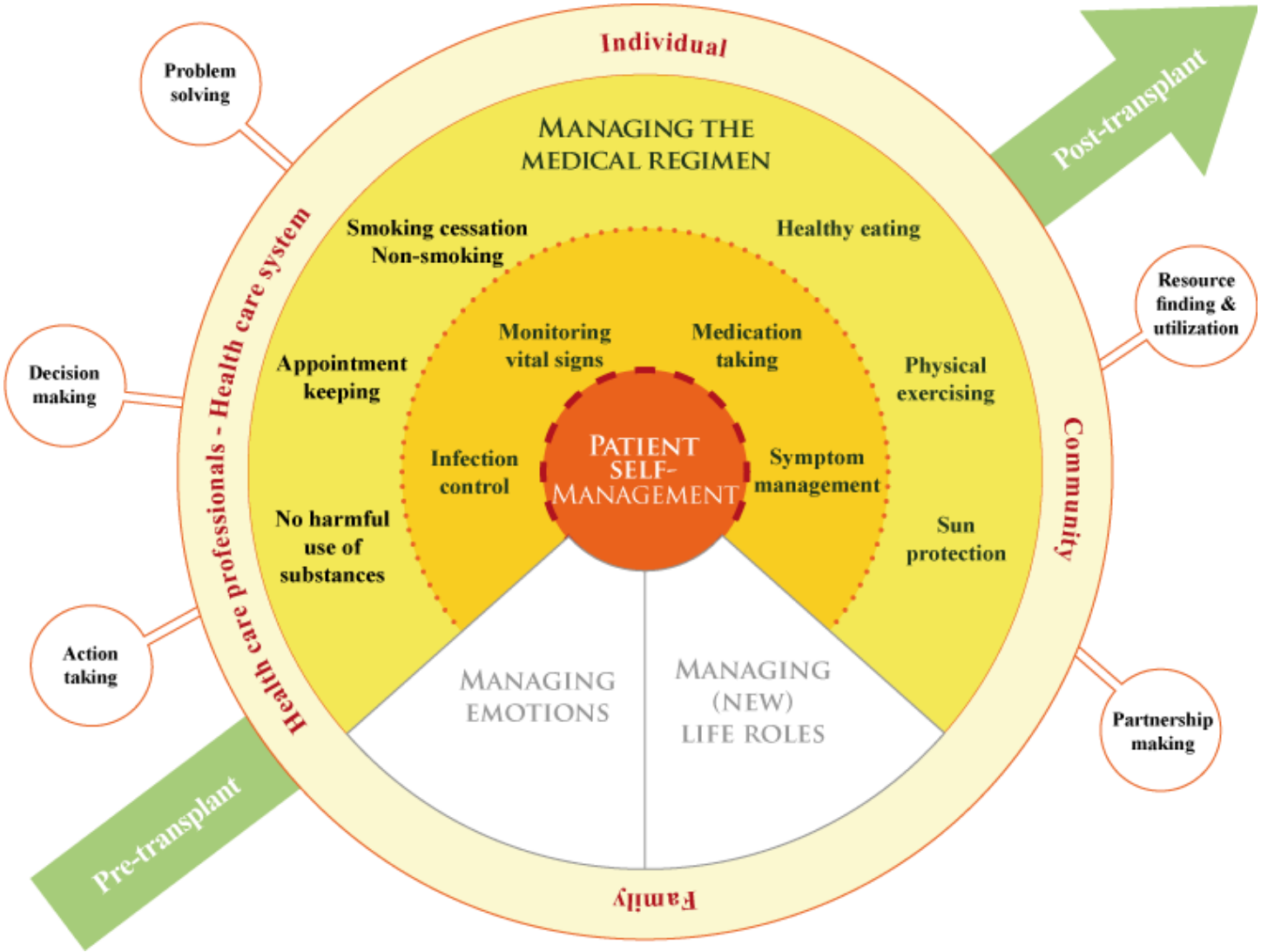
For chronic illness populations, "patient self-management" means continuous active involvement in their own care [1]. Gradually, patients develop expertise at managing their illness, thereby nurturing and influencing their daily decisions [1]. While the significance of such self-management to health outcomes is widely acknowledged [1-3], however, patient self-management is usually under-supported in clinical care, possibly due to time constraints in acute care settings. Therefore, effective interactive health communication applications [4-6] may offer valuable support.

One such application, in use since 2001 at various transplantation clinics worldwide, is the Organ Transplant Information System (OTIS™) [7, 8], a computer assisted patient education package developed by Biocom Ltd, Zurich, Switzerland (see section 1.3.). Until this study, however, the program had never been systematically evaluated and validated. The purpose of this study was therefore to examine OTIS's™ content and structure, particularly with regard to usability issues involving a group of potential end users.

Transplant recipient self-management

Kidney transplantation requires long-term treatment and follow-up care. Outcomes depend largely on effective recipient self-management, which requires support regarding knowledge, skills, and motivation. To guide both researchers and clinicians when aiming to enhance and support self-management using a comprehensive approach, we suggest a conceptual model derived from earlier research-based evidence in other chronic patient populations [9, 10]. In this paper, we focus on the "managing the medical regimen" segment, on which topic transplant research based evidence is available (see below).

Figure 1: Conceptual model of the (renal) transplant recipient's self-management



As figure 1 shows, kidney transplant recipient self-management includes managing a medical regimen, emotions, and (new) life roles [9]. It may affect the patient's family and/or community and should significantly influence interaction with healthcare professionals (outer circle). This may begin pre-transplantation (see arrow), with specific aspects assuming varying levels of importance at each stage. Finally, core skills [10] deemed reasonable for kidney recipients to have or acquire are specified in the small circles.

All self-management practices of the (kidney) transplant population can be regarded as understudied except with regard to *adherence to managing medical regimens*, which has been found deficient, potentially leading to poor health outcomes. Non-adherence to immunosuppressive therapy occurs in an average of 28% of adult kidney transplant recipients (range 8-65%) accounting for 20% (range 2.5%-80%) of late acute rejections and 16% (range 10%-64%) of all graft losses [11]. Suboptimal self-management is also prevalent in other aspects of the medical regimen, including inadequate sun protection [12-15], smoking, overweight [16, 17], sedentary lifestyle [3, 18], and failure to monitor relevant signs and symptoms [19, 20]. Among kidney transplant recipients, adherence self-management gaps suggest a need to integrate systematic patient self-management support into clinical transplant management applying state-of-the-art knowledge [3, 21]. While a small number of studies have evaluated attempts to enhance transplant medication adherence [22-24], related research suggests that improvements require frequent, time-intensive interventions combining educational, behavioral and social support [25-28]. However, in clinical settings, time constraints demand innovative uses of technology to help transplant recipients become active, knowledgeable partners in managing their therapy.

The development of interactive health communication applications (IHCAs)

The development of a technological intervention should include usability testing [29], to assure that the intervention allows users "to carry out their tasks safely, effectively, efficiently, and enjoyably" (p.56) [30]. Research on the usability of studied IHCAs programs during development showed that involving potential end users allowed the identification of otherwise unforeseeable usability issues [30-34]. Thus, IHCAs programs should be carefully evaluated with regard to both *content* and *usability.*

The Organ Transplant Information System™

Since 2000, in collaboration with transplant hospitals in the US, Germany and the UK (K. Youngstein [youngstein@biocom-ltd.com], e-mail, December, 30, 2007), Biocom Ltd. of Zurich, Switzerland, has been developing the Organ Transplant Information System (OTIS),™ a computer-based training and assessment program for transplant recipients [7, 8]. Intended to assist transplantation teams in enhancing patients' self-management, OTIS™ consists of two applications: OTIS Education™ for patients and OTIS Editor™ for transplantation center staff. OTIS Education™ consists of six modules: 1) "pre-transplantation"; 2) "your transplantation"; 3) "transplantation medicines"; 4) "your transplantation medicines"; 5) "rejection and infection"; and 6) "discharge from hospital". The program contains texts and multimedia components such as simulations, graphics, and video recordings. OTIS Editor™ allows customization of medication-specific content. Since completion of an international OTIS™ prototype in 2003, adaptations have been made based on user feedback. However, while OTIS™ is available internationally, the program has not previously been evaluated formally regarding usability, content validity and efficacy concerning patient outcomes.

This study's aims were: 1) to evaluate OTIS's™ content validity (i.e., the content's congruity concerning both current medical practice and its intended use setting) from the perspectives of clinicians and patients; and 2) to test the application's usability by target patients.

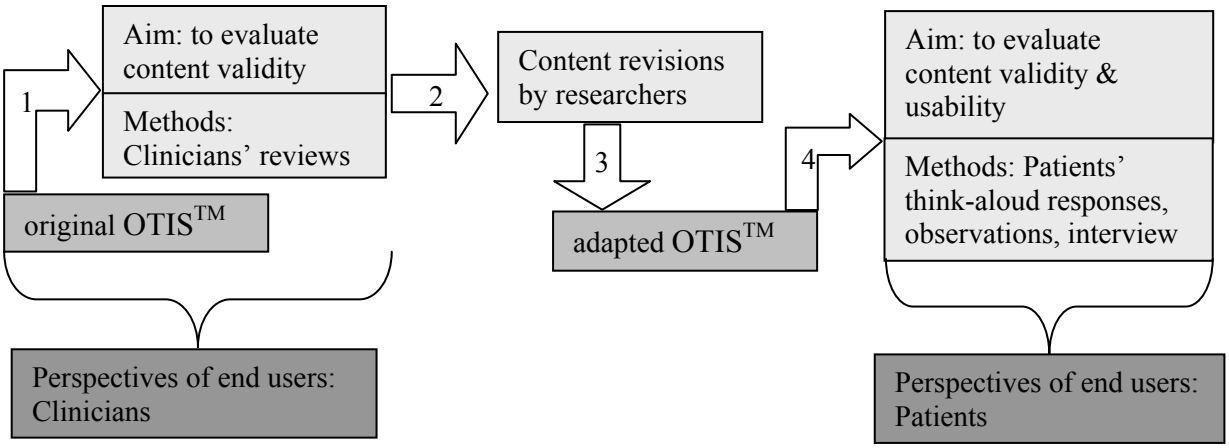
Methods

This study employed usability engineering [35] to test the degree to which OTIS™ allows users to navigate easily and perform tasks in a reasonable time, leading to the satisfactory achievement of intended aims [30]. *Usability testing* typically identifies problems users encounter when working with a tool. Data collection involved video observation and think-aloud reporting [30, 35, 36].

Design

We assessed clinicians' evaluations using ratings, as well as qualitative content analysis of patients' think-aloud recordings, observations and interviews (Figure 2). Data were collected from December 2005 to September 2006. The study protocol was approved by the "Beider Basel" cantonal ethics committee, and all participants provided written informed consent.

Figure 2: Overview of the study's design



Note: the arrows indicate the sequence of the 4 steps (i.e., 1 = first, 4 = last) undertaken during the study period. Clinicians reviewed the original OTIS™ version (step 1), which we then revised regarding content (step 2), which resulted in an adapted OTIS™ version (step 3), which was tested by patients (step 4).

Sample and Setting

We employed purposive sampling using the following patient/subject characteristics: age (older), computer experience (little or none), and time since kidney transplantation (various). We assumed that older patients with little or no computer experience would experience significantly more usability problems [37] than would a group of younger, computer-literate patients, since inexperienced computer users are more likely to struggle if the navigational structure of a program is not intuitive and self-explanatory [35]. Furthermore, involving patients at various times after transplantation demands that the content of the program contains material useful to patients with varying degrees of experience living with their transplants. The purposive sampling strategy ensured that patients representing an appropriate mix of characteristics reviewed each module pair. Patient inclusion criteria were: being either a kidney transplant candidate or kidney transplant recipient, receiving either treatment for end stage renal disease or post-transplant follow-up at the Basel University Hospital (USB), being adult, speaking German, being fully cognizant, literate and able to read a computer screen without difficulty, and having no functional impairments which would hinder navigation on a tablet personal computer (e.g., the inability to hold a stylus). We included eight specialized nephrological care clinicians. The study took place at the USB Transplant Immunology & Nephrology unit.

Variables and Measurements

Clinicians' recorded demographics were *age*, *gender*, and *profession*. *Nephrology experience* figures reflected years working in nephrology. Clinicians' notes were written using a structured paper format to record their perspectives regarding the software's content validity, and to identify content deviations from USB clinical practice guidelines (clinicians' critical review). Two items (see Table 2, "Results") assessed clinicians' ratings of the software's educational value to patients, and the relevance of the program regarding implementation into daily clinical practice.

Patients' recorded demographics were *age*, *gender*, and *formal education*. Medical variables were *type of renal replacement therapy*, and *date of transplantation*. Computer variables were *prior computer experience*. Usability data included tape-recorded think-aloud verbal responses and videotaped observations. Patients' perspectives regarding content validity were obtained through transcripts of tape-recorded structured interviews asking how fully the program met their health and illness management needs (see Table 1 for specific questions).

Table 1: Content validity of the program from the patients' perspectives: Structured interview questions

1. A. What did you like about the program? B. What did you not like?
2. A. What was easy in using the program? B. What was difficult?
3. Does the content of OTIS™ meet your information and learning needs?
    A. If no, what would you recommend?
    B. What topics should be included in the program?
    C. What topics should be skipped?
4. Would you use this program to learn about your illness, the transplantation and follow-up care, and your self-care?
    A. If yes, on which occasions?
    B. If no, why not?
5. Would you recommend OTIS™ to others?
6. Should your relatives or significant others also use OTIS™ to learn?
    A. If yes, what topics should be integrated into the program?
    B. If no, why not?
7. What would you like to say that I haven't asked about so far?

Data collection procedures

Clinicians' evaluations

To assess content validity data from the clinicians' perspectives, the interviewer (a master's degree level nurse with clinical expertise in renal transplantation) wrote comments while

reviewing the software modules. Clinicians provided feedback on two modules each, and each module was reviewed by either two or three clinicians. Next, the interviewer noted their two-item interview responses concerning the value of the program and its relevance regarding clinical implementation. Content validity data from the clinicians' critical reviews were used to adapt the content before testing it on patients (see Figure 2).

Patients' evaluations

After explaining the study, the interviewer obtained written informed consent, then demographic and medical data from interested patients. She then instructed patients by demonstrating how to speak one's thoughts while working with the software. Patients settled in front of the computer screen, where the interviewer showed them how to use the touch-screen and stylus to navigate through the software, the touch-sensitive on-screen fields to access the software modules and sub modules, and the previous-page and next-page icons. A one-page summary of instructions was also provided, which specified the two modules the patient should work through (e.g., "Before Your Transplant", and "Your Transplant") as well as a personal password to log on to the software. The interviewer remained available while the patient worked through the software. The patients' think-aloud responses were tape-recorded and transcribed. The computer monitor and the patient were video-recorded, which helped to link the patients' responses to the respective software screens, and captured the details of the patients' navigation, along with system responses. The video-recorded observations of the patients captured the patients' gestures, movements and facial expressions. These observations were reviewed and selected passages referring to usability problems transcribed. The structured interview following the completion of the two modules was also tape-recorded and transcribed verbatim. To save time, patients worked with only two modules each. After a maximum of 100 minutes, the interviewer terminated the think-aloud reporting, and continued with the structured interview, in which the patients' impressions were elicited to assess the program's content validity. The structured interview was tape-recorded and transcribed verbatim.

Data analysis

Demographic and clinical data were summarized using frequencies, medians and ranges. Usability data analysis involved grouping response transcript excerpts according to issue type: *interface related*, *content related* or *other* [38]. The analysis of the video-taped observations focused on movements/gestures, and facial expressions with regard to agreement/comfort, and

disagreement/discomfort [32]. The interview transcripts were analyzed using Mayring's content analysis techniques: text-bearing tracts were marked, then paraphrased; paraphrases were then generalized, summarized and grouped into inductively emerging categories [39]. The analysis was conducted by the first author, who met regularly with a group of senior expert researchers to discuss all findings.

Results

Clinicians' perspective

The Organ Transplant Information System program was critiqued by four nephrologists, three registered nurses and one renal dietician with a median of 10 years' (min 2.5 – max 20) professional experience in nephrology. They invested a median total time of 95 minutes (range: 30-190) to review their allocated program segments. Six clinicians completed the review. The two who terminated their reviews cited the perceived poor quality of the OTIS™ information, combined with the perceived lengthiness of the modules as their reasons for doing so.

We summarized and grouped the clinicians' critical evaluation notes into three main categories: content provided; language used; and information structure within OTIS™. The clinicians identified sections of OTIS™ information that did not correspond to current medical practice. Table 2 depicts the categories, illustrated with examples of the negatively appraised material. Besides the negative criticism, positive comments were given to the following elements of the program: videos of patients narrating first-hand experiences and giving advice, and an interactive exercise on composing medication dosages. Five clinicians considered it important for patients to know the content of "an optimized" OTIS™ program, but most (7 of 8) found OTIS™ insufficiently relevant for clinical implementation (see Table **2**).

Table 2: Clinicians' perspective of OTIS™

Categories of the clinicians' critical evaluations		**Clinicians' ratings in view of the relevance and importance of OTIS™**	
Category	**Critique**	**Item**	**Clinician ratings**
Content	Many sections…	Importance for patients to know	5 important
	a) did not correspond to current medical practice	the content of "an optimized"	1 neutral
	b) were medically incorrect	OTIS™ program	1 not important
	c) contained lengthy text with low meaning		1 no answer
Language	The language was perceived to…	Relevance of implementing	1 relevant
	a) be negatively burdened (with a potential to provoke anxiety)	OTIS™ (original version) into	7 not relevant
	b) consist of long complicated sentences	clinical practice	
	c) be burdened with complex medical terminology		
Structure	A lack of a clear conceptual framework, leading to confusing information flow		

Modifications to the original program

Integrating the clinicians' recommendations entailed reducing text, simplifying the remaining information, and adapting text to current medical practice. We reorganized information throughout for clarity and consistency.

Patients' perspectives

The purposive 14-patient sample (9 male) had a median age of 60 years (range 41-75y) and included 4 kidney transplant candidates (3 on hemodialysis and 1 on CAPD) and 10 kidney transplant recipients (median time since kidney transplantation 37 months, range 5-426 months). All had at least nine years' formal education, and one had completed four years' higher education. Eight had no computer experience, four used computers during leisure time only, and two used them for both work and leisure (median usage = 2 hours (range 0.5-20) per week). Nine patients required a median time of 89 minutes (range 31-97 minutes) to go through two modules of the program, and five did not complete the modules within the predefined maximum of 100 minutes.

Usability

We grouped participants' responses and our observations of their difficulties during the cognitive tour of the program into three categories: interface related; content related; and other issues [38]. All participants encountered difficulties, mostly with the OTIS™ interface. After 14 participants had completed the testing, we deemed the data's redundancy level sufficient regarding the detection of usability problems, as the last three involved patients encountered no new issues.

<u>Interface related problems</u>

Interface related problems involved misinterpretation of navigation tools, inconsistency within the response cycle (see below), or non-comprehension of the structure and orientation of the modules and sub modules. For example, several participants were confused by buttons displaying people's names (indicating videos of patients' narratives), since buttons with functional labels (e.g., "start program") had been used earlier in the program. The following quote illustrates this problem (quotes are in italic, observations in brackets)**:** *who is this Mr. Miller? Is this the writer of the program?* [looks at interviewer] interviewer responds: *He is one of the other patients who tell about their experiences* [participant touches forward icon, backward icon, but not the button itself]. *And how should that be functioning?*

The goal-action-system feedback cycle (i.e., user ponders how to answer or move to next page – user clicks the appropriate button – system signals correctness/incorrectness or presents next screen) was also problematic. In one quiz, if the participant attempted to change an answer, the system would neither respond nor load the next question. The only functional option was to return to and re-answer the preceding question: *Well, it* (my answer) *can only be wrong* [participant touches button next to alternative answer: no response from system; participant looks astonished, touches this button again: no response from the system, participant sits back, breaths deeply, examines the screen]. *Well, now, I can't get any further.* This requirement to go backward to proceed (and receive a response from the system) was inconsistent with the navigation in previous quizzes and beyond the scope of several participants to solve the situation and proceed.

The structure and orientation of the modules and sub modules also consistently caused confusion: *Now we are again through. Shall I continue with the menu button?* [participant touches menu button, looks astonished] *Well, we've already had that, haven't we?* [touches on introduction; (…) goes again into the same section that he has just completed; pauses] *do they repeat everything?* [long pause] *Now, you have to help me.* Irrespective of the specific module or sub module, participants consistently became disoriented. This became evident both through participants' questions to the interviewers (often for information as to whether particular material had already been visited), and through observed behavior such as jumping from one sub-module to another or to unrelated material, or even terminating the program prematurely, having concluded (falsely) that they had completed it.

Content related problems

Content related problems applied both to meaningful learning aims and to medical terminology. They were present in an interactive exercise concerning viruses and diseases, a section on antiviral medications, and a section on possible complications following transplantation. Regarding antiviral medications and medical terms, problems occurred when participants recognized a particular virus (e.g., cytomegalovirus) they had contracted, but not the treatment indicated in the module (e.g., gancyclovir). This may have resulted from the program's use of generic drug names, or from the patients having forgotten their treatment details. Further, some participants struggled with inadequately explained medical terms (e.g., acute tubular necrosis).

Other issues

Other issues were linked to the software's navigational structure or to the physical environment. Navigation related issues included shortages of links to related information pages or to alternative responses following quiz errors. Only one participant repeated several pages of information – which involved answering all questions again – in order to answer a question with which he was struggling. All other participants answered by trial and error, i.e., they touched the button next to the alternative answer and proceeded without repetition. Finally, environmental problems included various physical distractions (e.g., a fly in the room, noisy discussions in the corridor).

Content validity

Structured interviews (see table 1 for specific questions) were designed to learn whether the program met the participants' information and learning needs regarding health and illness management. Emerging categories were *gaining knowledge*, *managing the illness*, and *forming partnerships*.

Gaining knowledge

Most participants believed that the program covered all relevant themes well and presented information unknown to them before. As one respondent commented, *all important things are included: where I have to take precautions, what I need to do. Everything is well explained.* This was the case for most participants, unless their stage within the illness trajectory did not correspond to the content of the modules in the program (e.g., if a patient who was seven years post-transplantation went through "Transplantation medicines", which provides information regarding immunosuppressive drugs and other transplant related medications). In such cases the program had limited relevance, and was considered, at best, a useful review. However, participants spoke of the possibility to repeat modules at their own discretion as an important learning feature, which was supported if the content was perceived as easily readable, clearly explained and well-illustrated.

New information was generally welcomed by participants, many of whom reported sometimes feeling they were informed about complications only if they were about to experience them and only if they asked explicitly for information. On the other hand, one participant explained that she would rather not know about every possible complication. She consequently read the pages of the program quickly and selectively.

Managing the illness

Participants perceived that the program would help them to understand their illness, treatment, and follow-up care, and would increase their self-sufficiency regarding their conditions. Other patients' narratives, presented through videos, contributed to this perception, as these narratives were affirmed to be "so true". Viewing the videos, participants could identify, often very strongly, with the filmed patient, as each patient in the video had experienced waiting for and/or living with a transplant. Some participants realized that these patients had concerns similar to and sometimes more serious than their own. Thus, most perceived the videos as helpful. The program's list of signs of infection and rejection was further perceived as helpful for knowing when to ask for assistance: *According to this program, there can be noticeable signs* (of rejection)*. If I felt such signs, I would go into the program to read again. And if they indeed had something to do with it, I would call my doctor.* Concrete strategies and advice to monitor such signs, to prevent infections or skin cancer, and to support general health increased the sense of developing proficiency in managing the illness.

Forming partnerships

The participants agreed that the program facilitated communication with both health care professionals and significant others, including relatives and friends. Several believed the program would help them to address individual issues with their healthcare professionals, or to explain their illness and illness related events to their relatives and friends. Using the program would also develop their vocabulary, or fill time waiting or on dialysis with meaningful content.

Some participants who applauded the program's helpfulness for managing their illness concurrently emphasized that they did not wish to criticize their current courses of care. Some participants talked about doctors' and nurses' lack of time to inform and teach, and remarked critically that they had received information on some topics only following adverse outcomes.

The participants considered their relationships with their healthcare professionals crucial. Where the program deviated from their doctors' advice, then, they were confused. For example, one participant was puzzled by the program's comment that immunosuppressive drugs could be taken with meals, as her doctor had advised her to take them between meals: *I was informed and I asked again and I was clearly told yes, take Prograf® either one hour before or 1.5 to two hours after the meal. And you know, I have arranged it and this is not easy at all, I can say.* Thus, conflict arose where the program deviated from, questioned or contradicted clinical counseling or the patient's established routines.

Discussion and Conclusion

Discussion

This study evaluated the content and usability of OTIS™, a computer-based patient information and training program for transplant candidates and recipients. Although OTIS™ had already been launched internationally in transplant clinics, this study was the first to evaluate it systematically from the perspectives of both clinicians and patients.

Content validity from the clinicians' perspectives

The potential to use the OTIS™ Editor to tailor content to a transplant center's needs regarding medications is one of the software's main strengths. However, the clinicians were disappointed by the large investment of staff time necessary before the package's information could approach the standard provided by the clinic. This may explain why the majority of involved clinicians rated OTIS™ as "irrelevant" regarding clinical practice.

Several other explanations also warrant consideration. First, while other groups [5, 40-43] involved multidisciplinary teams as well as target patients early in the development of their programs, our clinicians expected a user-ready package designed in accord with current medical practice (i.e., based on current literature, and in cases of insufficient literature, expert opinion), which would allow, if necessary, customization of the content to match local practice. Where such expectations existed, however, they clearly went unfulfilled. Another possible explanation for the clinicians' negative reactions is that, in many transplant clinics, a focus on acute care prevails, including a paternalistic relationship between clinicians and patients. Such a paradigm may explain – in part – why clinicians rated OTIS™ as irrelevant. A shift towards a chronic illness management approach [2], whereby support of patient self-management is considered a component of current medical practice [21], may make computer-assisted patient education a more valued addition to traditional clinical transplant care. It is, however, imperative that such programs offer information reflecting evidence based practice, which is often not the case [44-50].

Usability

Aided by a group of patients who are potential end users of the OTIS™ software, this study further investigated the program's usability. The data collection instrument combined observations with cognitive interviews, in which think-aloud responses allowed the researchers to map the mental activities of users while working with the software. This mix

very likely revealed more problems than would have been found by assessing patients' reported perceptions alone.

The study's analyses highlighted a variety of usability issues, mostly related to the program's user interface. These included misinterpretation of icons, loss of orientation within the modules, and inconsistency of system responses to user input. Some of these problems would be easily correctable (e.g., functional expressions of button labels). Others would be more difficult or unfeasible to solve in the OTIS™ software. Disorientation within the modules, for example, may lead to skipped information, inadvertent repetition, anger, frustration, or becoming trapped and prematurely ending the learning session. None of these outcomes supports mastery experiences, an important factor both of learning [51] and of enhancing perceived self-efficacy [52]. Unfortunately, a suggested design revision to improve user orientation was deemed unworkable (P. Kaiser, personal communication, July 24, 2006).

The significance of the encountered problems also warrants consideration. What happens when patients encounter the program in a clinical setting rather than a study? Based on the data gathered here, we strongly believe that several participants would be trapped in confusing situations. Such confusion would be actively counterproductive to the learning process [51, 53]. Furthermore, in a real learning situation, no clinician should be required to resolve usability issues: the goal of implementing the software is, after all, to leave clinicians free to help patients translate the presented information into productive behavior.

Content validity from patients' perspectives

This study's patients regarded the program as a valuable tool to complement current care at our transplant centre by facilitating learning, illness management, and partnership with healthcare professionals and significant others. These perceptions indicate some measure of success: becoming a knowledgeable partner and developing the ability to participate actively in one's own care are key features of chronic disease management models [2]. Relevant information, motivation, and skill building are mutually beneficial factors influencing behavioral change [54]. These favorable perceptions could also result from under-representation of highly-educated participants, who would potentially be more critical. An interviewer bias is also possible, since the interviewer was also known to the study participants as a healthcare provider. However, the favorable perceptions could also reflect the successful revision of OTIS™ based on the clinicians' evaluations.

Limitations of the study

First, although the study's sample can be considered adequate for usability testing [55, 56] (as evidenced by data redundancy regarding problems), it was certainly small. Second, to better understand the educational and informational needs of patients and their significant others (that can be translated into the content of such programs), further research is clearly warranted. For such a study, a larger sample of the target population would be advisable. Finally, we do not know how significant the usability problems were in terms of their effect on patients' learning. However, we argue that such programs need to be carefully developed, leaving little room for problems when used. To facilitate learning, a user should be free to concentrate on and interact with the target content rather than with usability issues.

Conclusion

This study's findings suggest that any IHCA's content and usability both require testing and validation before such programs are launched for clinical use. Our formal testing revealed that the original OTIS™ program was problematic. The revised OTIS™ program was perceived as helpful to gain knowledge of the illness, treatment and necessary self-care to develop proficiency in managing the long-term condition of kidney transplantation. Regarding the achievement of this goal, studies of IHCAs' long-term effects are necessary.

Practice Implications

Because patients take health information seriously, IHCAs' content needs to be of high quality: a program offering wrong or useless information could result in counterproductive or even dangerous behavior.

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Chapter 7
Discussion, Conclusion, and Perspectives

While recent decades have seen phenomenal advances in short-term graft survival, long-term perspectives have long been at an apparent impasse. Despite numerous improvements to immunosuppressive medication and other aspects of transplant management over the past 30 years, 10-year graft survival rates have remained virtually static since the 1990's [1]. The current challenge within transplantation is to improve those rates. Investing in transplant recipients' self-management and medication adherence may clear the path for further progress.

It is hoped that the current research program will play a meaningful part in this task. The following are the program's contributions:

First, using a chronic illness management care paradigm, we have defined and operationalized the elements of kidney transplant recipient self-management by summarizing evidence from the transplant literature. The resulting description provides a comprehensive framework including detailed transplant specific self-management activities and core skills for successful self-management. It is hoped that it will serve as a research and clinical guide for increasingly long-term management of transplant recipients.
Besides numerous disease specific activities related to medical regimen management, patient self-management deals with emotions and new life roles, as well as with core patient skills (e.g., problem solving, decision making). Finally, it occurs in a broad context of interactions with family, community and the health care system. Still, while patient self-management obviously encompasses much more than adherence, adherence to the medical regimen has proven importance as a behavioral pathway to improve patient outcomes after transplantation.

Second, in order to better understand medication adherence, we have provided a literature based overview of its correlates and interventions. This is complemented by a case study offering a practical approach to applying adherence enhancing strategies.

Third, we have assessed the diagnostic accuracy of immunosuppressive drug assay, patient self-reports, clinicians' collateral reports, and composite adherence scores, as tools to assess medication non-adherence. The results confirm previous evidence that current state-of-the-art

measures do not accurately assess medication non-adherence, particularly when used as single measures. Furthermore, our study provides evidence that diagnostic accuracy improves when measures are combined, as compared to single measures – a strategy suggested in a recent NEJM article [2], which we have now confirmed with empirical evidence from the transplant literature.

Fourth, we conducted a pilot randomized controlled trial of a theory-based educational-behavioral intervention and social support program designed to enhance medication adherence in non-adherent kidney transplant recipients. The study found an inclusion effect resulting in higher medication adherence in both intervention and usual care group, while the interventions also increased adherence. This pilot study adds to the very limited number of adherence enhancing intervention studies in transplantation using an appropriate methodological approach.

As the fifth part of this research program, we evaluated e-health technology designed for transplant patients to learn about their illness, treatment and self-management activities. It is essential that technical interventions be tested, in view of usability, content validity and effectiveness, before their dissemination into clinical practice. Our examination focused on usability and content validity, both of which involve clinicians and patients who are potential end users of the program, and found major drawbacks regarding both content validity and usability.

The following paragraphs discuss the main findings of the research program's studies.

Measuring medication adherence

Using a convenience sample of 249 kidney transplant recipients, this cross sectional study used electronic monitoring as a reference standard to test the diagnostic accuracy of immunosuppressive assays, patient self-reports, clinicians' collateral reports, and constructed composite adherence scores. Medication non-adherence's prevalence across the measurement methods varied from 12.4% for self-reports to 38.9% for composite adherence scores. Of all the measures tested, the composite adherence score showed both the highest sensitivity (72.1%) and the highest likelihood ratio of a positive test (2.74), while collateral reports of at least three clinicians showed the highest specificity (93.1%). While no measures showed high sensitivity alongside high specificity, combining measures increased diagnostic accuracy,

indicating the relevance of combined measures for clinical and research purposes. This study thus confirms previous observations [3] that non-adherence rates are influenced by measurement methods, and also, as a review by Dew et al. [4] recently demonstrated, by operational non-adherence definitions and overall study quality. Furthermore, our study's empirical evidence confirmed a previously suggested strategy [2] of combining several measures to produce superior diagnostic values. This is a suggestion that could doubtlessly be applied to numerous transplant studies, as only 17% currently use multiple methods [4], but none combined them. The majority of studies in the transplant literature surveyed used patient self-reports [5-28], while others immunosuppressive drug assays [8, 9, 18, 24, 26, 29-31], or, more recently, electronic monitoring [19, 23, 24, 32-39]. Small numbers preferred collateral reporting [24, 26], pharmacy refill records [29, 30, 40], or pill counts [26, 28, 41]. Further, until the current program, no study has combined adherence data from diverse sources to construct a composite adherence score. Adequate assessment tools are vital to medication non-adherence research, and thus to the development of interventions to improve related clinical outcomes.

One often-problematic measurement method is the patient self report: patients tend to underreport non-adherence because of social desirability bias or simply because they forget [2]. Our study confirmed this method's low sensitivity. In contrast, other work in transplantation [4, 24] and in other fields [42] have found patient self-reports a source of high non-adherence rates, possibly owing to more sensitive self-report methodologies (e.g., confidential in-depth interviews [24]) or different operational definitions of non-adherence [4]). The low expense and high feasibility of patient self reports in clinical settings certainly make them attractive as measures of medication adherence, especially when strategies are employed to maximize their reliability (e.g., building up a trusting atmosphere, conducting a confidential interview, detaching the occurrence of non-adherence from the concept of failure). Validation of specific self-reporting instruments will be the final hurdle to their widespread acceptance.

Other non-adherence assessment instruments are subject to bias from sources other than the subjects themselves. Immunosuppressive blood assay levels are influenced by the drug's half-life, metabolic rates, drug-drug interactions, and white-coat adherence (i.e., greater adherence before a clinical visit) [43-45]; pill counts are invalidated when patients hoard or discard drugs [44, 46]; collateral reporting depends on the reporter's familiarity with the patient [44, 46]; and the fill frequency of prescriptions is problematic when patients use a number of non-networked pharmacies [46-48]. Even the validity of electronic monitoring, although

justifiably used as a reference standard, can be compromised by incorrect use [49], by negatively impacting established adherence routines, or by improving normal adherence through an intervention effect [49]. No one perfect method has yet been devised. Based on our data, though, we recommend combining two or more measurement methods, including electronic monitoring. The combination of various methods to construct a final composite adherence score may be the most comprehensive technique to date, as each measurement method potentially assesses different aspects of non-adherence behavior. Taking or not taking medication is, after all, a behavior to be measured retrospectively–a task subject to a wide range of obstacles, few of which are easily seen.

In summary, reliable measurements of medication non-adherence are essential to the discovery and correction of related problems in the transplant population. As no single perfect method is yet available, any information suggesting non-adherence, regardless of its source, should be taken seriously as a possible non-adherence indicator, and should be followed up with an in-depth adherence assessment. If non-adherence is confirmed, the clinician should then offer adherence-enhancing interventions.

Medication adherence enhancing interventions

In the literature on adult solid organ transplantation, research is rare on the efficacy of interventions to increase immunosuppressive medication non-adherence. Suggested interventions refer to educational approaches [29, 50, 51], internet-based interventions [52], financial support programs for medications [30, 53], electronic monitoring feedback [54], and self-medication administration program as part of discharge planning [53]. Few are randomized controlled trials and design issues (e.g., dimensional limitations, insufficient study periods, lack of theoretical support) limit their applicability.

Our pilot intervention study used theory driven interventions and was built upon state-of-the art knowledge in view of adherence research. It is a pilot randomized controlled trial, testing the efficacy of an educational-behavioral intervention, including feedback on electronically monitored medication taking, in addition to enhanced social support to increase medication adherence in non-adherent renal transplant recipients. The results showed a remarkable decrease in non-adherence in both the intervention group and the enhanced standard care group over the first three months (IG, p=.04; EUCG, p=.06). The interventions appeared to benefit medication adherence levels more in the IG (which showed the greatest decrease in non-adherence). However, post-hoc power analysis (alpha set at 0.05, power set at 0.80, χ^2

effect size of 1.05) revealed that 100 patients more than the sample used would have been required to detect a significant difference in non-adherence between the two groups.

Despite this shortfall, the demonstrated effect that, for both study groups, inclusion in the intervention study decreased non-adherence remains significant. Combined with other findings, this implies that medication non-adherence should be regularly monitored and feedback provided based on a variety of non-adherence measures (e.g., patient self-reports, blood assay, clinicians' collateral reports).

It also warrants discussion that the inclusion effect was small. This finding is in line with a recent Cochrane review [55], which confirms previous evidence [56-59] that even the most effective interventions do not result in large improvements in adherence and treatment outcomes. However, any improvements in adherence levels are crucial, as evidence suggests that, for kidney transplant recipients, even small deviations from perfect adherence have a negative effect on clinical outcomes [40, 60].

While all of the above mentioned experimental intervention studies were classified as weak using the CONSORT quality appraisal instrument, our study was appraised as strong [61]. In fact, the majority of intervention studies in adult transplantation show major shortcomings related to methodology and/or intervention content. Content related shortcomings include the lack of a theoretical framework, unidimensionality (e.g., education) and unifactorial interventions (e.g., patient risk levels) not tailored to the individual situation. Methodological shortcomings include the use of non-randomized samples, the use of non-clinically-relevant operational definitions (e.g., of non-adherence), the use of invalid (e.g., single) measurement methods, the lack of a description of usual care, the lack of a control group, the lack of baseline adherence assessment, and the lack of an adequate sample size [61]. Subsequent trials will need to address all of these issues.

Furthermore, besides resolving shortcomings related to intervention content and study methodology, future intervention studies may need to invest in the development and validation of innovative systems of assisting patients to follow long-term medication regimens [55]. The need for special care strategies to improve long-term patient outcomes motivates the current request to move towards a chronic care model for the management of long-term patient outcomes [62]. Such care models may integrate components such as technological interventions to support patients in managing their chronic illness in daily life [62-65]. Employing new technology to support transplant recipients' self-management may be of particular help in current transplant clinics, as they are characterized by an acute care

paradigm, which allows insufficient resources (especially time) to invest in chronic illness management.

Using technology systems to support transplant recipient self-management

Information technology systems are becoming increasingly important in the health care system: e-health is believed to have great potential to benefit the management of chronically ill patient populations (Strategic health innovations in Oh, et al., [66]). In acutely driven health care systems such as transplantation, e-health related methodology to support patients in their self-management could be an instrument to optimize the use of clinicians' time. The effectiveness of using technology to assist learning (e.g., using computer or web based educational software packages) has been widely demonstrated in educational science [67]. In health care, current evidence [68, 69] demonstrates that computer assisted or web based patient education is an effective tool to improve patient knowledge, social support, clinical outcomes (e.g., shortness of breath, pain, fatigue, and health distress), perceived self-efficacy (i.e., the confidence in one's own ability to perform a certain task in a certain situation) and health behavior.

Our first steps towards using e-health technology involved evaluating the content validity and usability of a computer-based patient information and training program proposed for use with transplant patients. The Organ Transplant Information System (OTIS)^{TM} was evaluated from the perspectives of both clinicians and patients.

The majority of the clinicians rated the original OTIS^{TM} version as "irrelevant" regarding clinical practice, a finding that reflected the lack of clinicians' and patients' involvement in the OTIS^{TM} development phase, as well as the clinicians' perception that the program's information was not relevant for patients, deviating fundamentally from their own clinical care, which includes providing patients with individualized (e.g., tailored, relevant, easy to understand) information in line with current medical care.

Even programs currently in wide use may not often fulfil these criteria [70, 71]. For example, a systematic review of 79 empirical studies assessing the quality (i.e., accuracy, completeness, readability, design, disclosures, and references) of health information delivered via the worldwide web (www) found that 70% and 21% of the studies concluded that the quality was, respectively, poor or neutral; only 9% received a positive rating [70].

Furthermore, our OTIS^{TM} study found inadequate readability of the presented material. Readability is a central quality issue of patient information/education [72-74], a problem new technologies appear to have inherited from traditional print media [71, 75]. This is evidenced

by studies reviewing the readability level of web-based patient education materials [71, 76]. Wallace et al. found that 75% of patient e-health information offered by the Academy of Family Physicians were pitched above an 8th grade level, which is considered the average reading level in the US [76]. A further review of 100 websites offering patient information on mamma, prostate and colon cancer found that the articles' average reading grade level was 12.9 – roughly the level necessary for university entrance. Further, the information was generally assessed as difficult according to the Flesh Reading Ease Index [71].

These studies suggest that a major effort is still necessary to provide patients with easily understandable health information, whether written or oral. Additionally, illustrative visual materials should be central to patient education, as they support attention, recall, comprehension, intention and behaviour [77]. This principle applies to all patient educational resources, regardless of whether they are delivered as printed documents, CD/ROM/DVD's, or over the worldwide web.

While the majority of clinicians found OTIS™ irrelevant for clinical practice, the majority of patients perceived the reworked program as a valuable tool to complement current care at our transplant centre. The discrepancy between the clinicians' evaluation and patients' perceptions regarding the content value of OTIS™ could be the result of successfully reworking the content of the program based on the clinicians' feedback. Patients perceived the program useful to facilitate learning, management of the illness, and partnership-building with healthcare professionals and significant others. Becoming a knowledgeable partner and developing the ability to participate actively in one's own care are key features of a chronic disease management model [62]. The patients clearly saw OTIS™ as a step in that direction. However, the study revealed major usability problems within the OTIS™ software. Some of these were easily correctable while others would have been time intensive or impossible to resolve without a complete overhaul of the software. Such insoluble problems (e.g., user disorientation within the modules) led to skipped information, inadvertent repetition, anger, frustration and premature termination of learning sessions. These outcomes support neither self-management nor mastery experience – a factor vital both to learning and to enhancing perceived self-efficacy [78, 79].

Other usability studies conducted during the development of educational material also involve groups of potential end users, who generally identify significant usability issues [80-83]. However, providing that these studies are conducted during the development phase of the program, these issues can be resolved with a minimum of expense before testing the program's effect on patient outcomes.

To conclude, a computer or web based intervention tool to enhance transplant patient self-management support should include only content with established validity, including both current disease specific, research based information and the training of disease and non-disease specific skills. Furthermore, the development should be guided by proven software development methodology [81], including recently published research based usability guidelines [84], and involving clinicians and potential end users from the earliest possible stages. The development of the intervention is, after all, an intermediate aim: testing its effect on patient outcomes should be the focus of an intervention study.

Strengths and limitations of the research program

As investing in transplant recipients' self-management and medication adherence is a potential pathway to improving long-term outcomes, one strength of this research program is that it represents a step towards developing a kidney transplant recipient self-management program. Additionally, exploring the field of e-health technology, it made progress toward resolving constraints on healthcare professionals' ability to improve patient's self-management and medication adherence. Finally, the research program was comprehensive in applying various methods to answer the specific research questions. These included a cross sectional design study, a pilot randomized controlled trial, and also qualitative work.

A limitation of the research program was its focus on medication management as a single example of kidney transplant recipient self-management of the medical regimen, and within this, the focus on measuring and improving medication adherence. However, medication adherence is an essential element of patient self-management, and is clearly linked to patient outcomes in transplantation. The studies on medication adherence addressed existing gaps in this field of research.

A further limitation was that we only conducted a pilot randomized controlled trial to assess the efficacy of an adherence enhancing intervention, which limited the statistical inferences. Nevertheless, this study added to the scant information available in the transplant literature regarding the efficacy of medication adherence enhancing interventions. Furthermore, this pilot study was useful to design the "medication adherence enhancing strategies in transplantation and ophthalmology - MAESTRO-Tx" randomized controlled trial study which now runs in Leuven, Belgium [85].

Finally, the study evaluating the usability and content validity of the OTIS^{TM} educational software resulted in the decision, given its major drawbacks, that no further investment in this program was advisable. Therefore, it will be necessary to develop a new computer based or

web based patient self-management tool. Further work is also warranted to study kidney transplant recipient self-management with regard to managing emotions and life roles, and to address methodological challenges in adherence research in transplantation.

Future research

Future research should be performed to develop and test a patient self-management support intervention, and to address the current methodological challenges in transplantation regarding adherence research.

To develop and test a patient self-management support intervention will require the following research steps. First, a systematic literature review is necessary to elaborate the most effective intervention in terms of improving patient outcomes. As no such interventions exist in the transplant literature, the literature of other chronic patient populations should be systematically reviewed with respect to components that are most effective in improving patient self-management. A special focus should thereby be given to intervention elements that belong to the development of knowledge or of patient skills, as patient self-management support systems that entail problem solving skills seem to be superior to interventions that train knowledge alone [86].

Second, future studies need to further develop the conceptual model employed here to include descriptions of managing emotions and managing (new) life roles. Complemented by clinical expertise, a review of the transplant literature with regard to these skills should result in a comprehensive understanding of all components of kidney transplant recipient self-management. Such an understanding is essential before adequate measures can be developed and validated, and before content information can be drafted. The development of intervention content should be based on research based knowledge (i.e., based on the renal transplant recipient self-management model) and include the perspectives of transplant patients and their families.

More specifically, further studies should include representative samples of the target population to assess which of the transplant recipients' and their families' informational and educational needs can be translated into information content. Finally, the intervention program must be developed using proven software development methodology, including several rounds of usability testing [81, 84].

Further studies are also warranted regarding the current methodological challenges to transplantation adherence programs. To allow the simultaneous examination of adherence,

risk factors and outcomes, these should use longitudinal and prospective designs (e.g., transplant cohort studies).

Second, future studies need a clinically meaningful definition of non-adherence, and the methods of assessing non-adherence should be derived from clear, explicit definitions of the domains to be measured. These, in turn, should be highly standardized and expressed as rates adjusted for follow-up duration (i.e., cases/100 persons/year) [4], while calculations should be based on data derived from multiple methods [2]. Additionally, in order to strength our grasp of the most reliable measurement methodologies, it will be necessary to design further studies that can compile and assess the value, appropriateness, and validity of a wide range of related strategies, both objective and subjective [42].

Third, to ensure statistical power, statistical considerations (i.e., significance issues) imply that multicenter studies are needed to guarantee sufficient sample size and the possibility to perform analyses on subgroups whose outcomes might differ. Additionally, future studies should include random samples (rather than a convenience sample) to allow generalizability to the target population.

Fourth, as only 3 of 7 intervention studies in the adult transplant literature included randomized controlled trials, the designs of future intervention studies clearly need to be improved. Additional design considerations in transplant intervention studies imply that baseline adherence should be assessed using a run-in period and a follow-up period to test a wash-out effect. The sustainability of the intervention should be included as a result, the collection of outcomes should be blinded, and a factorial design should be applied to disentangle the effects of the various intervention components. Regarding the content of adherence enhancing interventions, future studies should use literature based and theory driven interventions, and interventions based on available meta-analyses of chronically ill patient populations, specifying the intervention dose and duration.

Fifth, to assess the clinical and economic relevance of non-adherence to immunosuppressive drugs, future intervention studies in transplantation should also include clinical and economic outcomes as primary results.

Finally, data analyses should include time dependent analyses and should imply survival analysis or mixed effects models for repeated measurements, taking any missing data into account. Also, analyses of intention to treat should be performed rigorously, and effect sizes should be reported for all outcomes, as they are the basis for meta-analysis as well as for the evaluation of clinical significance. Such efforts clearly have the potential to deal with the methodological challenges currently facing transplant medication adherence research [87-89].

Conclusion

We conclude that our research program was innovative, offering, for the first time, a definition of kidney transplant recipient self-management. It adds to the existing knowledge regarding the diagnostic values of state-of-the-art measures of medication non-adherence, as well as of interventions to enhance medication non-adherence. Doing so involved entering the promising field of e-health technology as it applies to kidney transplant patient care and support. This research program has also enabled us to outline specific issues and additional topics of interest for further research to understand and support patient self-management in the kidney transplantation population.

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CURRICULUM VITAE

PERSONAL DATA

Name	Petra Schäfer-Keller
Date and place of birth	April, 8th 1971, Schaffhausen, Switzerland
Nationality	Swiss
Civil status	Married to Simon Schäfer
Children	Sebastian Robin, Sept, 24th 2007

ADRESSES

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EDUCATION

GRADUATE EDUCATION

2005-present	PHD MEDICAL SCIENCES-NURSING
	Institute of Nursing Science, Faculty of Medicine
	University of Basel, Basel, Switzerland
2000-2004	MASTERS IN NURSING SCIENCE
	Institute of Nursing Science, Faculty of Medicine
	University of Basel, Basel, Switzerland
1993-1994	ETHNOLOGY (1st year, not completed)
	University of Basel, Basel, Switzerland
1992	VETERINARY MEDICINE (1st semester, not completed)
	University of Basel, Basel, Switzerland

UNDERGRADUATE EDUCATION

1995-1998	BASIC NURSING DEGREE (R.N.)
	School of Nursing, St. Clara Hospital, Basel, Switzerland

1986-1992	MATURITÄT TYP B
	Kantonsschule Schaffhausen, Schaffhausen, Switzerland
1978-1986	PRIMARSCHULE
	Primary school, Wilchingen and Neunkirch, Switzerland

APPOINTMENTS AND POSITIONS

ACADEMIC

04/2005-present	Institute of Nursing Science, University of Basel
	Research assistant
01/2001-03/2005	Institute of Nursing Science, University of Basel
	Research help assistant

NON-ACADEMIC CLINICAL APPOINTMENTS

2004-present	Transplant Immunology and Nephrology
	University Hospital Basel, Basel, Switzerland
	Advanced practice nurse
2001	Surgery
	Cantonal Hospital Bruderholz, Basel, Switzerland
	Staff nurse
1999-2000	Surgery and Medical Unit
	Cantonal Hospital Oberengadin, Samedan, Switzerland
	Staff nurse
1998-1999	Oncology Medical Unit
	St. Clara Hospital, Basel, Switzerland
	Staff Nurse
1994	Oncology Medical Unit
	St. Clara Hospital, Basel, Switzerland
	Trainee in Nursing

LICENSURE AND CERTIFICATION

1998	Nursing License Switzerland
	Registered nurse, AZ 9804a/44910

MEMBERSHIP PROFESSIONAL AND SCIENTIFIC ORGANIZATIONS

2004-present	International Transplant Nurses Society

2004-present	Swiss Transplant Society
2004-present	Alumni Nursing Science, University of Basel
2001-present	Member, Association for the Promotion of Nursing Science and Nursing Research, Switzerland (VFP = Verein zur Förderung der Pflegewissenschaft und –forschung Schweiz)
1995-present	Member, Swiss Nurses Association

RESEARCH GRANTS

CONTRACTS / GRANTS (PI ONLY)

12/2005

3. **Schäfer-Keller P,** De Geest S. Computerized patient education in kidney transplantation. Testing the content validity and usability of the Organ Transplant Information System™. International Transplant Nurses Society: Direct costs: USD 2.500. *Role: Primary-investigator.*

2005, 2006

2. **Schäfer-Keller P**, Denhaerynck K, Steiger J, De Geest S. Testing the content validity and usability of a Computer Assisted Transplant Patient Self-Management Tool (OTIS™ - Organ Transplant Information System). A Pilot study. 2005-2006. Roche Pharma (AG) Schweiz: Direct costs: 24.500 CHF. *Role: Primary-investigator.*

12/2004

1. **Schäfer-Keller P**, Denhaerynck K, Steiger J, **De Geest S**. Testing the effectiveness of a Computer Assisted Transplant Patient Self-Management Tool (OTIS™ - The Organ Transplant Information System). A Pilot study. Schweizerischen Nierenstiftung (Swiss Renal Foundation). Direct costs: 30.000 CHF. *Role: Primary-investigator.*

PUBLICATIONS

PEER REVIEWED JOURNALS

8. **Schäfer-Keller P**, Dickenmann M, Berry D, Steiger J, Bock A, De Geest S. Computerized patient education in kidney transplantation: Testing the content validity and usability of the Organ Transplant Information System (OTIS™). Patient Education and Counseling, in press.
7. Denhaerynck K, **Schäfer-Keller P**, Young J, Steiger J, Bock A, De Geest S. Examining assumptions regarding valid electronic monitoring of medication therapy: development of a validation framework and its application on a European sample of kidney transplant patients. BMC Med Res Methodol. 2008;8:5.
6. **Schäfer-Keller P**, Steiger J, Bock A, Denhaerynck K, De Geest S. Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. Am J Transplant. 2008 Mar;8(3):616-26.
5. De Geest S, Denhaerynck K, **Schäfer-Keller P**, Bock A, Steiger J. Supporting medication adherence in renal transplantation--the SMART study. Swiss Med Wkly. 2007 Mar 2;137 Suppl 155:125S-7S.

4. Denhaerynck K, Steiger J, Bock A, **Schäfer-Keller P**, Köfer S, Thannberger N, De Geest S. Prevalence and risk factors of non-adherence with immunosuppressive medication in kidney transplant patients. Am J Transplant. 2007 Jan;7(1):108-16.
3. **Schäfer-Keller P**, Lyon S, Van-Gelder F, De Geest S. A practical approach to promoting adherence to immunosuppressive medication after renal transplantation. Curr Opin Nephrol Hypertens. 2006 Aug;15 Suppl 2:S1-S6.
2. De Geest S, **Schäfer-Keller P**, Denhaerynck K, Thannberger N, Kofer S, Bock A, Surber C, Steiger J. Supporting medication adherence in renal transplantation (SMART): a pilot RCT to improve adherence to immunosuppressive regimens. Clin Transplant. 2006 May-Jun;20(3):359-68.
1. Denhaerynck K, Dobbels F, Cleemput I, Desmyttere A, **Schäfer-Keller P**, Schaub S, De Geest S. Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review. Transpl Int. 2005 Oct;18(10):1121-33.

OTHER JOURNALS

1. **Schäfer-Keller P**, Huber E, Conca A, Thannberger N, Steiger K, Winterhalder D, Haupt K, De Geest S. Der Beitrag der Pflege am Transplantationszentrum Basel. Das Management chronischer Erkrankung bei TransplantationsempfängerInnen (German). The contribution of nursing at the transplant program Basel: Chronic illness management in kidney transplant recipients. Bulletin de Swiss Transplant. 2003;17(9).

THESIS

MASTER'S THESIS

Institute of Nursing Science, University of Basel, Switzerland
"A comparison of different methods of measuring medication adherence in patients after kidney transplantation"

RESEARCH REPORTS (FIRST AUTHOR ONLY)

2. **Schäfer-Keller P**, De Geest S. Computer-based patient education in kidney transplantation: Testing the content validity and usability of the Organ Transplant Information System (OTIS)^{TM}. Final scientific report for the International Transplant Nurses Society. Basel, Switzerland: Institute of Nursing Science, University of Basel; 2007.
1. **Schäfer-Keller P**, De Geest S. Computer-based patient education in kidney transplantation: Testing the content validity and usability of the Organ Transplant Information System (OTIS)^{TM}. Final scientific report for Schweizerische Nierenstiftung (the Swiss Nephrology Foundation). Basel: Institute of Nursing Science, University of Basel; 2007.

PRESENTATIONS

INTERNATIONAL

14. **Schäfer-Keller P**, Denhaerynck K, Steiger J, Bock A, De Geest S. Cardiovascular disease and risk factors in kidney transplant recipients: Sub-analysis from the SMART study ITNS Symposium; 2007 4.-6. Oct.; Denver; 2007 (oral presentation).
13. Denhaerynck K, Steiger J, Bock A, **Schäfer-Keller P**, Kofer S, Thannberger N, De Geest S. Prevalence and Risk Factors of Non-Adherence with Immunosuppressive

Medication in Kidney Transplant Patients. Am J Transplant. 2006 Nov 15 (poster presentation).

12. **Schäfer-Keller P**, Bock A, De Geest S. Supporting medication adherence in renal transplantation: The SMART-Study. A case study of applying effective adherence enhancing interventions. 15th annual symposium of the International Transplant Nurses Society; 2006 October, 5.-7.; Rotterdam; 2006 (oral presentation).
11. **Schäfer-Keller P**. Computerized patient education in kidney transplantation. Part 1: Testing the usability of the Organ Transplant Information System™. 15th annual symposium of the International Transplant Nurses Society; 2006 October, 5.-7.; Rotterdam; 2006 (invited oral presentation).
10. **Schäfer-Keller P**. ANP Role Development in Switzerland: the 2 Year experience from a single kidney transplant outpatient clinic. 15th Annual symposium of the International Transplant Nurses Society; 2006 October, 5.-7.; Rotterdam; 2006 (invited oral presentation).
9. Thannberger-Brun N, **Schäfer-Keller P**, Denhaerynck K, Köfer S, De Geest S. Which medication aids are used by renal transplant recipients? 15th Annual symposium of the International Transplant Nurses Society; 2006 October, 5.-7.; Rotterdam; 2006 (oral presentation).
8. **Schäfer-Keller P**, Steiger J, Denhaerynck K, Bock A, De Geest S. Using electronic monitoring as reference standard: how well do state of measurement methods measure medication adherence in kidney transplant recipients? American Transplant Congress; 2005; Seattle: American Journal of Transplantation; 2005. p. 331 (abstract 685) (poster presentation).
7. Denhaerynck K, **Schäfer P**, Steiger J, Bock A, De Geest S. Prevalence and correlates of nonadherence with immunosuppressive regimen in adult renal transplant recipients. American Journal of Transplantation. 2005;5(Suppl 11):331 (poster presentation).
6. **Schäfer-Keller P**, Denhaerynck K, Steiger J, Bock A, De Geest S. Cardiovascular disease and risk factors in kidney transplant recipients: Sub-analysis from the SMART study 5th Annual Spring Meeting of the Working Group on Cardiovascular Nursing of the European Society of Cardiology; 2005 11-12 March, 2005; Basel: European Journal of Cardiovascular Nursing; 2005. p. 85-6 (poster presentation).
5. **Schäfer-Keller P**, Denhaeryck K, Bock A, Steiger J, De Geest S. Supporting Medication Adherence in Renal Transplantation (SMART): a pilot RCT to improve adherence with immunosuppressive regimen. 14 ITNS Symposium; 2005 22-24 Sept; Orlando, Florida; 2005 (oral presentation).
4. **Schäfer-Keller P**, De Geest S, Steiger J. Nonadherence with cystagon before kidney transplantation - overcoming ambivalence and supporting readiness for treatment. 14 ITNS Symposium; 2005 22-24 Sept; Orlando, Florida: Number K04; 2005 (poster presentation).
3. Denhaerynck K, Steiger J, **Schäfer-Keller P**, Bock A, Köfer S, Thannberger N, Surber C, De Geest S. Prevalence and determinants of nonadherence with immunosuppressive regimen in renal transplant recipients. International Conference of Behavioral Medicine; 2004; Mainz; 2004 (poster presentation).
2. **Schäfer-Keller P**. Evidence based Nursing. Österreichische Kardiologische Gesellschaft / Jahrestagung der Arbeitsgruppe für Kardiologisches Assistenz- und Pflegepersonal; 2004 Juni 4th; Salzburg 2004.
1. **Schäfer-Keller P**, Denhaerynck K, Thannberger N, Köfer S, Bock A, Surber C, Steiger J, De Geest S. Supporting Medication Adherence in Renal Transplantation. The SMART-study: Pilot findings. Eighth Lowlands Mini-symposium on Drug Exposure and Compliance 2003 November 6th; Utrecht, the Netherlands; 2003 (oral).

NATIONAL

9. **Schäfer-Keller P.** Computerunterstützte Patientenedukation (German). Computerized patient education. Kolloquium, Institute of Nursing Science, University of Basel, Switzerland, 6.Feb.2007 (oral presentation).
8. **Schäfer-Keller P**, Dickenmann M, Steiger J, De Geest S. Computerized patient education in kidney transplantation. Testing the content validity and usability of the Organ Transplant Information System™. Preliminary findings. Swiss Med Wkly. 2006;136(S154):52 (poster).
7. Thannberger-Brun N, **Schäfer-Keller P**, Denhaerynck K, Köfer S, De Geest S. Which medication aids are used by renal transplant recipients? Swiss Med Wkly. 2006;136(Suppl 154):18S (poster).
6. **Schäfer-Keller P**, for the Basel-Leuven Transplant Compliance Group. SMART: A randomized controlled pilot study to improve adherence with immunosuppressive regimen. Fortbildung Nephrologie; 2005 January 17th; University Hospital Basel; 2005 (oral).
5. **Schäfer-Keller P**. Eindrücke über die Ausbildung zum Master in Pflegewissenschaft am Institut für Pflegewissenschaft, Medizinische Fakultät, Universität Basel. Generalversammlung VfP; 2004 May 6th; Bern; 2004.
4. **Schäfer-Keller P**. Supporting Medication Adherence in Renal Transplantation (SMART): A pilot study. De Geest S, Schäfer-Keller P, Denhaerynck K, Bock A, Steiger J. 35 Congress Society of Nephrology; 2004 18-21 September; Basel; 2004 (poster presentation).
3. **Schäfer-Keller P**. Erweiterte und wirksame Pflegepraxis: Einblick in Advanced Nursing Practice (ANP) im Ambulatorium Nephrologie am Universitätsspital Basel (German). Advanced Nursing Practice: Insights into ANP at the outpatient clinic at the University Hospital Basel. 35 Congress Society of Nephrology; 2004 18-21 September 2004; Basel, Switzerland; 2004 (oral presentation).
2. **Schäfer-Keller P**. Impressions de la formation de Master in Nursing Science. Institute de la sciènce des sois infirmiers, faculté de Medicine, Université de Bãle.; 2004 Nov. 1.; Lausanne; 2004.
1. **Schäfer-Keller P**, for the Basel-Leuven Transplant Compliance Group. Supporting Medication Adherence in Renal Transplantation. The SMART-study: Pilot findings. De Geest S, Schäfer-Keller P, Denhaerynck K, Thannberger N, Köfer S, Bock A, Surber C, Steiger J. 35th Annual Meeting of the Swiss Society of Nephrology; 2003 December 4th-5th; Luzern 2003 (oral presentation).

RADIOBROADCAST

1. Grolimund T, Nicca D, Schaffert-Witvliet B, **Schäfer-Keller P**. Co-Abhängikeit - eine verhängnisvolle Verstrickung (German). Co-addiction - A fatal involvement. *Kontext*. Basel: Schweizer Radio DRS 2 2003.

REVIEWER ACTIVITIES

2005-present Reviewer: Journal of Cardiovascular Nursing

TEACHING / EDUCATION

ACADEMIC

2003-2006 Introduction in quantitative research methods I

	Co-teacher, lectures, seminars Master's Degree of Nursing Science curriculum Institute of Nursing Science, University of Basel, Switzerland
2003-present	Introduction in quantitative research methods II Co-teacher, lectures, seminars Master's Degree of Nursing Science curriculum University of Basel, Institute of Nursing Science
2003-present	Advanced Nursing Practice Co-teacher Action learning group Master's Degree of Nursing Science curriculum Institute of Nursing Science, University of Basel, Switzerland
2003-present	Living with chronic illness Co-teacher, lecture, seminar Master's Degree of Nursing Science curriculum Institute of Nursing Science, University of Basel, Switzerland
2005-present	Student Advisor and Student Mentor Advice of students, support of students in research practicum University Basel, Institute of Nursing Science
2003-2006	Public Health Co-teacher, lecture Master's Degree of Nursing Science curriculum Institute of Nursing Science, University of Basel, Switzerland
2004, 2005	Summer School Co-teacher, seminars Competence through evidence University of Basel, Institute of Nursing Science
2001-2003	Statistics Co-teacher, Tutorial Master's Degree of Nursing Science curriculum Institute of Nursing Science, University of Basel, Switzerland