PSYCHOSOCIAL FACTORS AND MOBILE HEALTH INTERVENTION: IMPACT ON LONG-TERM OUTCOMES AFTER LUNG TRANSPLANTATION

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Identifying and intervening on modifiable risk factors may improve outcomes in lung transplantation (LTx), which, despite recent improvements, remain suboptimal. Evidence suggests that two modifiable risk factors, psychiatric disorders and nonadherence, may improve LTx outcomes in the short-term; however, neither has been explored in the long-term. Therefore, the overarching goal of this dissertation was to determine the long-term impact of these modifiable risk factors and intervention to attenuate them.

First, we examined the relationship of pre- and early post-transplant psychiatric disorders on LTx-related morbidity and mortality for up to 15 years post-LTx. Our sample included 155 1-year LTx survivors enrolled in a prospective study of mental health post-LTx. We found that depression during the first year post-LTx increased risk of BOS, mortality and graft loss by nearly twofold, and that pre-transplant depression and pre- and post-transplant anxiety were not associated with clinical outcomes.

Next, we examined the impact of a mobile health intervention designed to promote adherence to the post-LTx regimen, PocketPATH, on long-term LTx-related morbidity, mortality and nonadherence. We conducted two follow-up studies to the original yearlong randomized controlled trial in which participants assigned to PocketPATH showed improved adherence to the regimen, relative to usual care. Among the 182 LTx recipients

(LTxRs) who survived the original trial, we found that PocketPATH had a protective indirect effect on mortality by promoting LTxRs' communication with the LTx team during the first year. Among the 104 LTxRs who completed the follow-up assessment, we found that PocketPATH's adherence benefits over the first year were not sustained into the long-term, although LTxRs assigned to PocketPATH were more likely than LTxRs assigned to usual care to perform the home self-care tasks of the regimen at follow-up. Median time since LTx for participants in both follow-up studies was 4.2 years (range, 2.8-5.7 years).

This dissertation presents an important first step toward identifying and intervening on modifiable risk factors to improve long-term LTx outcomes. Mobile health technologies offer limitless potential to target these risk factors and others. More work is needed to determine specific features and long-term patient engagement strategies that will optimize and sustain intervention effectiveness.

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1.0 INTRODUCTION

Modifiable risk factors are important contributors to health outcomes. These risk factors span a range of domains, from psychosocial to behavioral to environmental, and play a role in a range of illnesses. Among individuals with chronic disease, the purpose of intervening on modifiable risk factors is to stop or slow the progression of disease after diagnosis or limit disability after injury. If successful, such intervention may ultimately slow the progression of disease over time and potentially prevent exacerbations. Identifying and subsequently intervening on modifiable risk factors presents a major opportunity to prevent poor outcomes in chronic medical conditions.

Lung transplantation (LTx) is an example of one such chronic medical condition whose outcomes have potential to benefit from the identification of modifiable risk factors. For many individuals with advanced lung disease, LTx is the only viable therapeutic option.[1-6] Since 2009, more than 3,200 lung transplants have been performed annually in the United States and abroad,[7] and the Cardiothoracic Transplant Program at our transplant center, University of Pittsburgh Medical Center (UPMC), has one of the highest LTx volumes of any center in the world, at approximately 100 per year (based on data from the United States Organ Procurement and Transplantation Network as of March 1, 2015). Despite recent advances in surgical techniques and immunosuppression, morbidity and mortality remain high. Fewer than half of lung transplant recipients (LTxRs) survive to five years and fewer than 30% reach 10 years.[7] In contrast, other solid organ recipients survive at rates ranging from 75-91% at 5 years and 55-62% at 10 years.[8]

Poorer outcomes after LTx are driven by higher rates of complications such as infections and acute and chronic graft rejection.[7,9-11] Although many pre- and post-transplant medical factors have been identified as predictors of poor outcomes, few of these predictors are modifiable.

A growing body of evidence suggests that two domains of modifiable risk factors – psychiatric disorders and nonadherence – may impact outcomes in LTx.

Depression and anxiety are the two psychiatric disorders most commonly linked to health outcomes. A large literature shows that they are associated with poor medical outcomes in a variety of chronic illnesses, including heart disease, diabetes and asthma.[12-19] In solid organ transplant populations that do not include LTxRs, there is mixed evidence on such psychosomatic links.[20-36] However, only a handful of studies have investigated this area in LTxRs,[35-38] only one of which examines the impact of post-transplant psychiatric disorders.[34] This leaves a critical gap for the LTx community, as rates of depression and anxiety reach up to 30% during the first several years after transplant.[39-42] Given the high rates of depression and anxiety in LTxRs and the links between these disorders and poor outcomes in other chronically ill populations, it is important to determine whether they contribute to poorer health outcomes in LTx as well.

A large literature also shows that nonadherence is associated with poor outcomes following LTx. Adherence to a complex medical regimen is a crucial and lifelong aspect of managing post-transplant health, as the regimen is designed to involve recipients in prevention and detection of complications.[43-48] It involves following treatment recommendations, monitoring signs and symptoms of disease progression, and communicating changes in condition promptly with the transplant care team. Nonadherence is a significant problem because (a) it has been reliably linked to poor post-LTx clinical outcomes[11,43,48-52] and (b) short-term rates of non-adherence (i.e., up to two years after LTx) remain unacceptably high among LTxRs.[53] Long-term nonadherence (i.e.,

beyond two years post-transplant), however, has been relatively unexplored, except for one study that looked specifically at medication nonadherence through up to three years.[54] Promoting better adherence – especially in the long-term, when complications are likely to arise and clinical follow-up becomes sparse – is thus an important step toward reducing the potentially preventable morbidity that drives high mortality in this population.

This dissertation comprises three distinct papers that investigate the impact of psychiatric disorders and nonadherence on long-term outcomes in LTx. Psychiatric disorders are potentially modifiable by means of treatment and preventive intervention, and nonadherence is potentially modifiable by means of targeted behavioral intervention. In fact, this dissertation presents a follow-up study of one of the only interventions designed to target nonadherence in LTxRs. Examining the impact of these modifiable risk factors fills a critical and clinically important gap that may ultimately improve long-term outcomes in this medically complex population.

Paper 1 explores the impact of pre- and post-transplant depression and anxiety disorders on 15-year morbidity and mortality in a cohort of 155 LTxRs that was enrolled between 1999 and 2004.[42] Our study is the first to prospectively examine the impact of post-transplant psychiatric disorders on long-term morbidity and mortality in LTxRs, and its nearly 15-year follow-up is the longest follow-up period in studies of these risk factors to date.

Papers 2 and 3 take advantage of a unique cohort of LTxRs who participated in a randomized controlled trial of a mobile health (mHealth) intervention designed to enhance patient self-management. This intervention, called Pocket Personal Assistant for Tracking Health (Pocket PATH®), is a customized smartphone application (app) that assists with three major areas of self-management: adhering to the post-transplant regimen, self-monitoring and communicating appropriately with the transplant team. Pocket PATH was one of the first – and is still one of the

few – mHealth interventions to be developed and tested using rigorous scientific methods. In the 1-year trial, which randomized recipients to receive the Pocket PATH device or standard paper-and-pencil tracking logs, Pocket PATH was associated with improved adherence, self-monitoring and communication with the transplant team, relative to usual care.[55] Now several years beyond completion of the original randomized controlled trial, we conducted follow-up studies to assess the impact of Pocket PATH on clinical outcomes (Paper 2) and nonadherence (Paper 3) up to 5.8 years post-transplant. Our work provides nonadherence data gathered over the longest-term to date, as well as novel insights into long-term maintenance of mHealth intervention effects.

2.0 PAPER 1: PSYCHIATRIC PREDICTORS OF LONG-TERM TRANSPLANT-RELATED OUTCOMES IN LUNG TRANSPLANT RECIPIENTS

2.1 INTRODUCTION

Despite improvements in long-term survival after lung transplantation (LTx), lung transplant recipients (LTxRs) continue to have the highest morbidity and mortality of all solid organ recipients.[8] Only half of LTxRs survive to five years after transplant, and by 10 years, this rate drops to 31%.[7,8] Chronic rejection, manifested as bronchiolitis obliterans syndrome (BOS), is prevalent and remains the major obstacle to long-term survival.[7,10,56] Identifying reliable risk factors for BOS is thus a necessary step toward optimizing patient survival. Although clinical predictors of BOS as well as long-term survival have been identified,[57-59] few of those identified to date are currently preventable or modifiable.

Psychosocial risk factors – which are often modifiable through preventive interventions and treatment – may also have key roles in predicting these outcomes in LTxRs. Among such factors, psychiatric characteristics, in particular, warrant investigation as potential predictors given their association with poor outcomes in a range of non-transplant general medical illness and chronic disease populations.[12-19] Moreover, the high prevalence of depression and anxiety disorders among lung recipients during the first several years after transplant (occurring in up to 30% of recipients)[39-42] underscores their potential importance as risk factors for poor transplant outcomes.

However, psychiatric disorders have often only been considered as outcomes rather than as risk factors for health and survival in transplant recipients. The scant evidence from existing

studies that explore the role of psychiatric disorders as risk factors for medical outcomes in transplant populations is mixed and inconsistent.[20-31,33] In lung transplant populations in particular, the evidence is especially slim and appears inconsistent depending on whether morbidity or mortality outcomes are considered.[32-38] Furthermore, lung recipient studies have generally focused on the first few years post-transplant. To date, no studies have examined the specific impact of psychiatric disorders on morbidity and mortality over a long-term follow-up period.

In this study, we sought to determine whether depression or anxiety disorders occurring before or during the first year after transplant increased subsequent risk for transplant-related morbidity and mortality during the period up to 15 years after lung transplantation. We considered not only psychiatric history prior to transplant, but also disorders present during the first year after transplant because this latter period is the time during which post-transplant depression and anxiety are most likely to emerge.[42,60] The outcomes we examined – time to BOS onset, patient mortality and graft loss – are common metrics used to determine transplant success.

2.2 METHODS

2.2.1 Study population

We prospectively enrolled 178 adults (aged ≥18 years) receiving their first lung transplant between November 1999 and August 2004 in the Cardiothoracic Transplantation Program, University of Pittsburgh Medical Center. The cohort has been described previously.[42] Ninety-five percent of all individuals transplanted during this timeframe agreed to enroll. The eligibility criterion was survival beyond the post-transplant surgical recovery period (defined as the first six weeks after

surgery). Ten recipients (5.6%) died within one year of transplantation and were excluded from the present analyses because a goal was to ascertain whether psychiatric disorders during the first year post-transplant predicted subsequent outcomes. Thirteen recipients (7.3%) did not complete the psychiatric assessments because they were too ill (n=2) or refused (n=11). There were no differences in demographic or transplant-related characteristics between this group of 13 recipients and the recipients who completed study assessments. Our final cohort consisted of 155 lung transplant recipients whom we then followed prospectively for a maximum of 15 years to ascertain study outcomes.

2.2.2 Data collection

The University of Pittsburgh Institutional Review Board approved the prospective collection of both psychiatric interview and medical records data. All participants provided written informed consent. During the first year after transplant, participants were interviewed at 2, 7 and 12 months to assess the history and presence of mood and anxiety disorders, as described further below. Trained clinicians with advanced degrees in behavioral medicine fields conducted the interviews. Transplant-related medical characteristics and information on post-transplant clinical outcomes were obtained in annual reviews from recipients' medical records, with censoring at patient death or at the end date of August 15, 2014.

2.2.2.1 Demographic and transplant-related medical characteristics. Demographic characteristics (i.e., gender, age, race/ethnicity, education, income) were assessed at the initial interview. Transplant-related medical characteristics (i.e., transplant indication, single vs. bilateral

transplant, donor age, ischemia time of the donor graft, recipient/donor CMV mismatch, type of induction immunosuppression received) were ascertained from the medical record.

2.2.2.2 Psychiatric disorders. Depression and anxiety disorders were diagnosed according to standard criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR).[61] We used the Structured Clinical Interview for DSM-IV-TR (SCID)[62] to determine the presence of major depressive disorder and the presence of any of several anxiety disorders (panic disorder, post-traumatic stress disorder related to transplant [PTSD-T] and generalized anxiety disorder). The 2-month interview assessed these disorders since the time of transplant, and the 7- and 12-month interviews covered the period since the previous assessment. At the initial (2-month) interview, we also determined with the SCID whether recipients had a pre-transplant lifetime history of major depressive disorder, panic disorder or generalized anxiety disorder.

2.2.2.3 Outcomes. Three outcomes were considered: (1) onset of BOS, (2) patient survival and (3) graft survival. Medical record abstractors and outcome adjudicators were blinded to recipients' psychiatric status. The earliest date at which each outcome was present was recorded. The outcomes were defined as follows. The presence of BOS, at grade ≥1, was determined according to internationally established criteria.[63] Determinations were based on consensus decisions by two study investigators and a transplant pulmonologist using both pulmonary function tests (PFTs) and medical records of clinical encounters. All recipients received PFTs and clinical follow-up according to the transplant center's standard post-transplant care protocol, including surveillance bronchoscopy with transbronchial biopsy and bronchoalveolar lavage, spirometry, physical examination and blood work. The surveillance protocol included follow-up (including PFTs) every

three to four months during the first two years after transplant. Beyond two years post-transplant, all patients received follow-up every four to six months, with PFTs and any additional testing performed as clinically indicated. The date of the earliest incidence of BOS was recorded. Patient survival was defined as time to patient death, with death date ascertained from the medical record. Graft survival was defined as time to graft loss by patient death or retransplantation.

2.2.3 Statistical analysis

We used descriptive statistics to characterize the demographic and transplant-related medical characteristics of the sample. To determine the impact of pre- and post-transplant psychiatric disorders on each outcome, we used multivariable Cox regression with data censoring due to patient death (for outcomes other than patient survival) or end of follow-up. This approach allowed us to examine the unique impact of each psychiatric disorder while controlling for transplant-related covariates shown previously to be associated with morbidity and mortality outcomes,[7,64] including age at transplant, type of transplant, indication for transplant, ischemia time of the donor graft, CMV mismatch (donor +/recipient -), donor age and whether the recipient received alemtuzumab induction immunosuppression. For each outcome, one analysis was done to assess the impact of pre- and post-transplant major depression, and a separate analysis was done to assess the impact of pre- and post-transplant anxiety disorders. We performed separate analyses to examine depression history and anxiety history because our sample size precluded us from maintaining an adequate ratio of respondents: predictors of close to 20:1,[65] and because the rate of comorbid depression and anxiety was generally low, as discussed below. We assessed regression model assumptions for all models as appropriate.[65]

2.3 RESULTS

2.3.1 Description of study sample

Demographic and transplant-related medical characteristics of the 155 lung recipients in our sample are shown in Table 1. Our sample is similar to the international population of lung recipients transplanted during the same period in terms of gender, age, transplant indication and transplant type.[7] Most patients received tacrolimus-based immunosuppression. The median follow-up time was 12.1 years (range, 10 – 14.7 years).

Table 1 also shows the distribution of pre- and post-transplant depression and anxiety disorders in the sample. Over 40% (n=63) of the sample had a pre-transplant history of depression, and nearly 20% (n=30) had depression during the first year after transplant. Of those with depression post-transplant, 27% of cases were incident cases (i.e., occurring in individuals with no previous history of depression).

As noted in Table 1 (footnote e), the numbers of cases of individual anxiety disorders were relatively small; thus, we focus on whether recipients met criteria for any anxiety disorder. Table 2.1 shows that one-quarter (n=39) of the sample had a pre-transplant history of an anxiety disorder, and 26% (n=40) had an anxiety disorder during the first year post-transplant. In this latter group, 58% of cases were incident cases.

Comorbidity between depression and anxiety was relatively infrequent. Pre-transplant, 16% of the sample had histories of both types of disorders, and post-transplant, 7% of the sample met criteria for both types of disorders.

Table 1. Demographic, transplant-related and psychiatric characteristics of the 155 lung transplant recipients included in the sample

Characteristic	% (No.)
Demographic	
Age, years, mean ± SD	51.8 ± 12.0
Male	49.0 (76)
Caucasian	94.8 (147)
Less than high school education	49 (76)
Transplant-related	
Years since transplant, median (IQR)	12.1 (10.8 – 13.2)
Indication for transplant	
COPD/emphysema (including A1AT)	43.2 (67)
Pulmonary fibrosis (including sarcoidosis and scleroderma)	31.0 (48)
Cystic fibrosis	15.5 (24)
Other	10.3 (16)
Bilateral lung transplant[a]	45.2 (70)
Total length of stay for transplant, days, median (IQR)	21 (12 – 35)
Ischemia time of donor graft, minutes, mean ± SD	308.7 ± 95.6
Induction immunosuppression agent	
Alemtuzumab	30.3 (47)
Daclizumab	29.7 (46)
Rabbit antithymocyte globulin	18.7 (29)
None	21.3 (33)
Maintenance immunosuppression	
Tacrolimus	87.1 (135)
Cyclosporine	12.9 (50)
CMV mismatch (Recipient-/Donor+)[b]	27.4 (42)
Donor age, mean ± SD[b]	36.1 ± 14.3
Psychiatric	
Major depressive disorder	
Pre-transplant[c]	40.9 (63)
Received pharmacologic treatment	44.4 (28)
During first year post-transplant[d]	19.9 (30)
Received pharmacologic treatment	70.0 (21)
Anxiety disorder[e]	
Pre-transplant[c]	25.3 (29)
Received pharmacologic treatment	41.0 (16)
During first year post-transplant[d]	26.5 (40)
Received pharmacologic treatment	57.6 (23)

[a]Includes 4 heart-lung recipients
[b]n=153 because there was missing information on 2 donors
[c]n=154 because there was insufficient information to determine whether 1 recipient had pre-transplant disorders
[d]n=151 because there was insufficient information to determine whether 3 recipients had post-transplant disorders
[e]Pre-transplant, 6 recipients had panic disorder only, 9 had GAD only and 7 had both disorders. Post-transplant, 14 recipients had panic only, 1 had GAD only, 19 had PTSD-T only, 3 had panic and GAD, and 3 had panic and PTSD-T
Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; A1AT, α-1-antitrypsin deficiency; GAD, generalized anxiety disorder; PTSD-T, post-traumatic stress disorder related to transplant

2.3.2 Prediction of study outcomes

2.3.2.1 BOS. For the BOS analysis, the sample excluded three recipients whose BOS preceded the depression and anxiety diagnoses during the first year post-transplant; this ensured that we examined the prospective impact of each psychiatric disorder. There were 106 cases of BOS. Risk of BOS was nearly doubled if recipients experienced post-transplant major depression (hazard ratio [HR], 1.91; 95% confidence interval [CI], 1.10,3.29; p=.021; see first column, Table 2), whereas risk of BOS was not reliably associated with pre-transplant depression (p>.05; Table 2). Figure 1a depicts the association of post-transplant depression with BOS risk.

Risk of BOS did not differ between recipients with and without post-transplant anxiety (HR, .64; 95%CI, .39,1.03; p=.064) (Figure 1b and Table 2). Risk also did not reliably vary between recipients with and without pre-transplant anxiety (p>.05, Table 2).

2.3.2.2 Patient survival. There were 107 deaths during the follow-up period. The most common causes of death were graft failure (25%), infection (24%) and malignancy (21%), followed by pulmonary (11%), cardiovascular (3%) and cerebrovascular (3%) causes. The distribution of causes of death did not differ by psychiatric diagnosis (depression: $\chi^2(6)=6.07$, p=.414; anxiety: $\chi^2(6)=3.70$, p=.717). Risk of patient death was higher for recipients with post-transplant major depression than recipients without (HR, 1.69; 95%CI, 1.01,2.81; p=.046) (Figure 2a), whereas risk of patient death did not differ between recipients with and without pre-transplant depression (p>.05, see second column, Table 2).

Risk of patient death was not related to post-transplant anxiety (HR, 1.01; 95%CI, .63,1.61; p=.966) (Figure 2b and Table 2). Risk was also unrelated to pre-transplant anxiety (p>.05, Table 2).

Table 2. Results from Cox regression analyses of psychiatric predictors of outcomes

	Outcome								
	BOS[a]			Patient survival			Graft survival		
Predictors	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Regression model for major depressive disorder[b]									
Pre-tx depression	0.79	(0.51,1.22)	.281	0.76	(0.48,1.19)	.232	0.75	(0.49,1.17)	.205
Post-tx depression	1.91	(1.10,3.29)	.021*	1.69	(1.01,2.81)	.046*	1.78	(1.08,2.96)	.025*
Regression model for anxiety disorders[b]									
Pre-tx anxiety	0.96	(0.61,1.53)	.870	1.03	(0.64,1.66)	.894	0.97	(0.61,1.54)	.885
Post-tx anxiety	0.64	(0.39,1.03)	.064	1.01	(0.63,1.61)	.966	0.90	(0.57,1.43)	.664

*p<.05

[a]Excludes 3 recipients whose BOS preceded the depression or anxiety diagnosis during the first year post-transplant

[b]BOS analyses controlled for: age at transplant, type of transplant, indication for transplant, ischemia time of the donor graft and whether alemtuzumab induction immunosuppression was received; patient and graft survival analyses controlled for: age at transplant, type of transplant, indication for transplant, ischemia time of the donor graft, whether alemtuzumab induction immunosuppression was received, CMV mismatch (donor + / recipient –) and donor age

Abbreviations: BOS, bronchiolitis obliterans syndrome; tx, transplant

2.3.2.3 Graft survival. There were 112 cases of graft loss during the follow-up period. Risk of graft death was higher for recipients with post-transplant major depression than recipients without (HR, 1.78; 95%CI, 1.08,2.96; p=.025) (Figure 3a), whereas risk of graft loss did not differ as a function of pre-transplant depression history (p>.05, see third column, Table 2). Risk of graft loss also was not reliably related to post-transplant anxiety (HR, .90; 95%CI, .57,1.43; p=.664) (Figure 3b). Pre-transplant anxiety did not affect risk of graft loss (p>.05, Table 2).

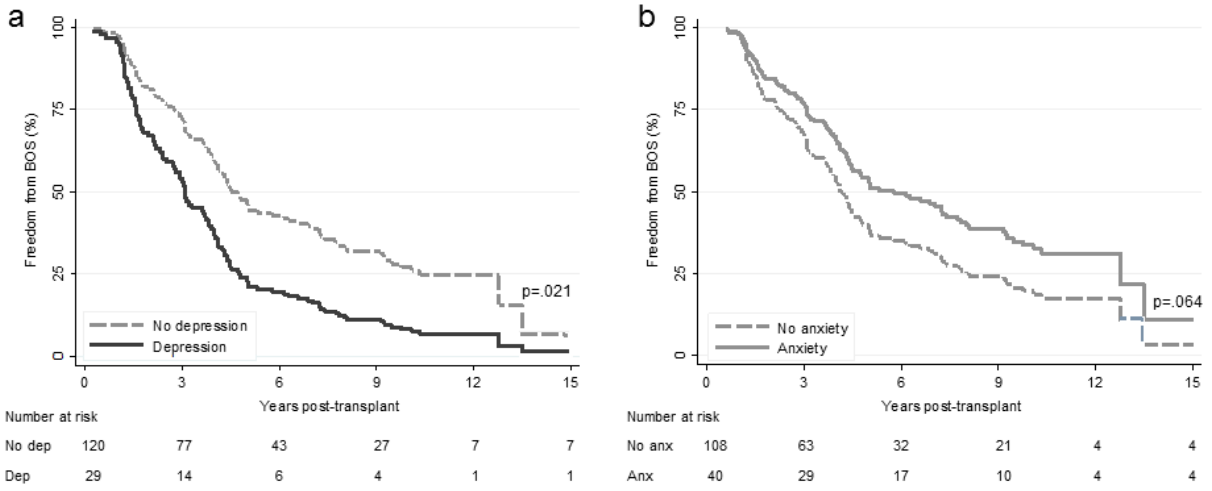


Figure 1. Cox regression curves depicting freedom from BOS. Freedom from BOS in lung transplant recipients with and without (a) depression and (b) anxiety during the first year after transplant is shown. p values refer to tests of significance between recipients with and without the psychiatric disorder. Abbreviations: BOS, bronchiolitis obliterans syndrome; dep, depression; anx, anxiety

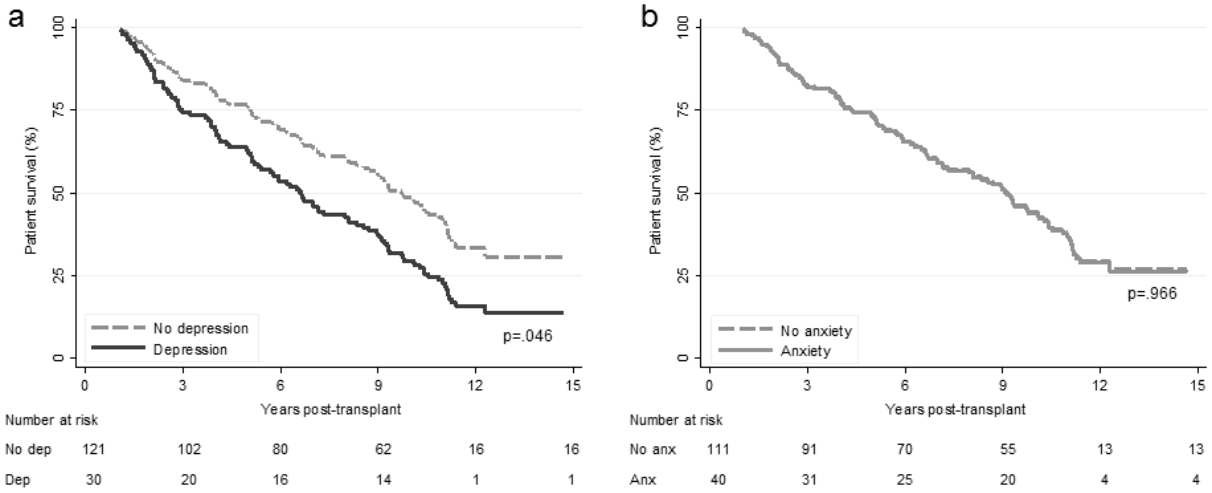


Figure 2. Cox regression curves depicting patient survival. Patient survival in lung transplant recipients with and without (a) depression and (b) anxiety during the first year after transplant is shown. p values refer to tests of significance between recipients with and without the psychiatric disorder. Abbreviations: dep, depression; anx, anxiety

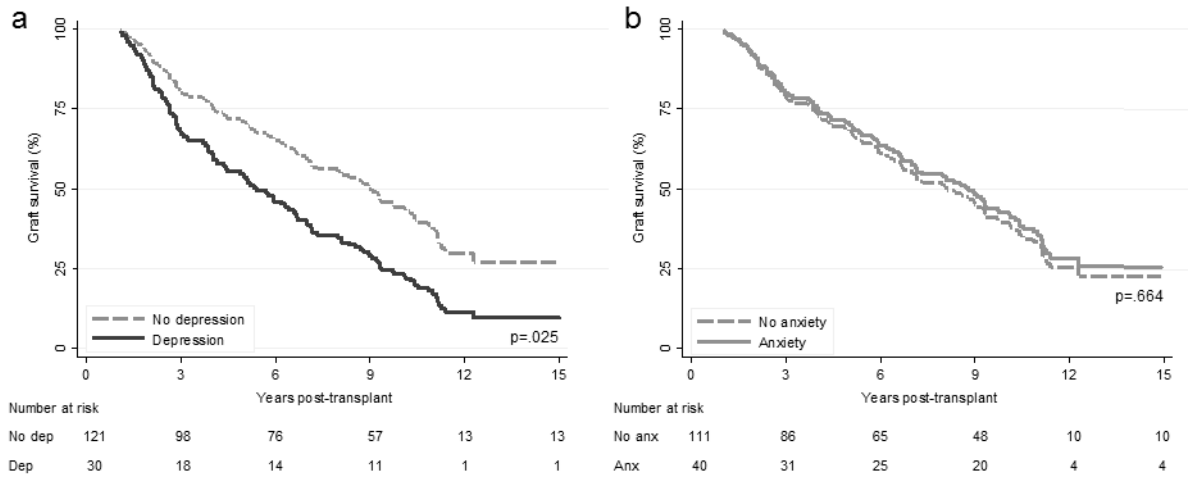


Figure 3. Cox regression curves depicting graft survival. Graft survival in lung transplant recipients with and without (a) depression and (b) anxiety during the first year after transplant is shown. p values refer to tests of significance between recipients with and without the psychiatric disorder. Abbreviations: dep, depression; anx, anxiety

2.4 DISCUSSION

Identifying modifiable predictors of poor outcomes is an important step toward reducing long-term morbidity and mortality after lung transplantation. Although the link between psychiatric distress and mortality (and to a lesser extent, morbidity) has been studied in recipients of other solid organs, this issue has received little attention in lung recipients. The handful of existing studies in lung recipients have examined transplant-related morbidities as predictors of psychiatric distress,[32,39,40] or pre-transplant or early post-transplant psychiatric symptoms as predictors of health outcomes in the early years after lung transplantation.[33-37] Findings from the latter studies have been inconsistent. Moreover, most examined relatively short follow-up periods after transplant. Our study is the first to prospectively examine the impact of post-transplant psychiatric disorders on

long-term morbidity and mortality in lung transplant recipients, and its nearly 15-year follow-up is the longest follow-up period in studies of these risk factors to date. Studying the prospective impact of psychiatric disorders on transplant-related outcomes is a distinct and important question given that depression and anxiety are prevalent in lung recipients and are largely modifiable through medical and behavioral intervention.

Our main finding is that major depression during the first year after transplant reliably increases the risk for long-term morbidity and mortality. This is consistent with a large body of work in general medical illness and chronic disease populations.[12-16] In non-lung transplant populations, studies have reported mixed findings on the link between depression in the early aftermath of transplant and mortality.[20-25,29,30] With respect to morbidity outcomes, several studies have found an association with post-transplant depression in non-lung transplant populations,[22,27,30,31,66] although the number of studies that have examined morbidity outcomes remains very small. In lung recipients, to our knowledge only one study has examined the impact of post-transplant depression on subsequent morbidity, showing an association between depression and the development of BOS over the following year.[33] Our finding thus adds an important contribution to the growing body of literature suggesting that depression, particularly when present after transplant, increases risk for mortality.

Although the literature linking anxiety and medical outcomes is smaller than that which focuses on depression, the existing evidence suggests that anxiety also has a clinically important and harmful role in a range of non-transplant medical illnesses.[17-19] However, the few studies in transplant populations that have investigated the impact of post-transplant anxiety have reported mixed findings: one relatively large study of heart recipients found strong links between post-transplant PTSD-T and mortality,[27] whereas three other studies of heart recipients have not shown

similar associations.[24,25,67] To account for our finding of a counterintuitive, albeit nonsignificant, trend toward reduced risk of BOS in recipients with post-transplant anxiety, we examined relationships between anxiety and other demographic and transplant-related factors. We found that anxiety was associated with female gender, likely driven by the strong relationship between female gender and panic disorder reported in a previous study of the same cohort,[42] but not any of the other factors. Given that gender has not been shown to be related to morbidity and mortality in lung recipients, it is unlikely that gender was driving the relationship we observed between anxiety and BOS. As the first study to examine the impact of anxiety on long-term outcomes after lung transplantation, our findings are an important first step toward understanding whether post-transplant anxiety should be considered a risk factor for subsequent poor outcomes, although more work in this population is needed to reliably determine whether any link does (or does not) exist.

It is notable that neither pre-transplant depression nor anxiety was associated with morbidity or mortality across our 15 years of follow-up. This is consistent with four of the five previous studies examining the impact of pre-transplant psychiatric symptoms and disorders on post-transplant physical health in lung recipients,[35-38] although it is notable that most of their follow-up periods were considerably shorter. The one study that did find a relationship between pre-transplant anxiety and post-transplant survival found that recipients with anxiety were more likely to survive to the end of the first year post-LTx;[34] this may not be comparable with our findings, however, because our sample only included recipients who survived at least one year. One explanation for why depression *after* but not *before* transplant might have an impact on outcomes in the present cohort is that post-transplant depression is more proximal to the outcome and thus more likely to have a stronger effect. Another explanation might be that recipients with a pre-transplant history of depression may have sought mental health treatment before transplant

and were therefore better prepared to cope with the stresses of transplantation. In any case, these findings suggest that a history of a previous psychiatric disorder at the transplant evaluation stage does not necessarily portend poorer post-transplant outcomes, which is an important consideration for candidate selection and pre-transplant management.

The question of whether treatment of psychiatric illnesses can attenuate the risk of poor outcomes in recipients with depression is an important one. This is especially pertinent in light of evidence from liver recipients suggesting that adequate treatment of depression may improve outcomes.[66] We have already described our cohort's patterns of help-seeking for the psychiatric conditions.[42] In our cohort, the majority of recipients with depression and anxiety, 70% and 58%, respectively, had received psychotropic medications by the end of their first year post-transplant. Our sample size precludes definitive analyses of the impact of treatment receipt, but if we stratify the sample with depression by whether or not they received psychotropic medications, there is no evidence that receipt of medication was associated with improved survival. Similarly, we discerned no evidence of medication effects in recipients with anxiety disorders. However, the numbers of cases and events in each stratum are too small to power these analyses for reliable interpretation.

Although our study was not designed to address the mechanisms underlying the links between post-transplant depression and subsequent morbidity and mortality, we were able to examine several behavioral elements that may have had a role in these pathways. Some evidence suggests that transplant recipients with psychiatric disorders, particularly depression, have poor medical adherence after transplant.[68] However, previous analyses with the present cohort did not find any evidence that recipients' pre- or post-transplant psychiatric status was associated with adherence levels, at least through the first two years post-transplant (adherence was not monitored

beyond this time point).[53] Another possibility is that recipients with depression were less likely to request and subsequently undergo pulmonary biopsies and PFTs, which might have delayed detection and treatment of complications. However, upon additional medical record reviews, we found that recipients' likelihood of undergoing these procedures was the same regardless of whether they experienced depression, anxiety or neither disorder. Furthermore, we have previously reported that recipients with and without psychiatric disorders did not differ in their number of missed clinic visits,[53] suggesting that psychiatric status did not impact the consistency of post-transplant clinical follow-up in the first two years after transplant.

Our study has several limitations. First, we report only a single-center experience. However, our findings are still potentially generalizable because our cohort's clinical and demographic characteristics are similar to those of the international lung transplant population, and our center's protocol for surveillance biopsies and PFTs is similar to that used in other centers across the United States. Second, our selection of outcomes was limited to BOS, patient death and graft loss. Although these are among the most important outcomes for lung recipients, we were unable to examine two other major post-transplant outcomes: infections, because they are not consistently documented in our transplant center's medical record beyond the first few years post-transplant (i.e., patients may not return to our center for care of every infection), and malignancies, because too few cases occurred over our follow-up period. Third, while our study design followed recipients prospectively after transplant, our assessment of pre-transplant psychiatric disorders was retrospective. In addition, as noted earlier, we were unable to directly assess the impact of psychiatric treatment. This was due not only to the relatively small total number of cases of the disorders we assessed but also because, while we have information on psychotropic medication receipt, we did not collect information on the range of other psychiatric interventions patients may

have received (e.g., psychotherapy). Moreover, due to sample size limitations that precluded subgroup analyses, we were unable to assess whether varying patterns of onset of the psychiatric disorders, which have been described previously,[42] had a differential impact on risk for the outcomes. Finally, our study was not designed to isolate the causal pathways underlying the link between psychiatric disorders and physical outcomes. It is clear that future exploration of mechanistic hypotheses – not only behavioral but also pathophysiologic – will be important for understanding this relationship and identifying potential targets for intervention.

In sum, major depression during the first year after transplant appears to be an important risk factor for poor long-term outcomes, nearly doubling the risk of BOS and increasing the risk of patient death and graft loss over 1.5-fold. This underscores the need to screen all recipients for psychiatric disorders after transplant, which is not currently standard practice in most transplant centers. Identifying and treating depression should be a major priority for transplant teams; this is not only because effective depression treatments exist but also because treating depression may be a means of preventing long-term morbidity and mortality. Although anxiety during the first year after transplant does not appear to be associated with morbidity and mortality, transplant teams should nonetheless screen for, monitor and treat anxiety as well, since it factors largely into quality of life. The opportunity for mental health screening and intervention during the first post-transplant year should not be missed, as this is when post-transplant psychiatric disorders are most likely to emerge[42,60] and when the transplant team has most contact with recipients. Heightened mental health surveillance during this critical period may yield benefits that ultimately extend beyond quality of life to improved post-transplant health over the long-term.

3.0 INTRODUCTION TO THE POCKET PATH SAMPLE

Papers 2 and 3 report findings from two related studies that are long-term follow-ups of a cohort of LTxRs that were enrolled in a randomized controlled trial evaluating the Pocket Personal Assistant for Tracking Health (Pocket PATH) intervention. This chapter will briefly describe the Pocket PATH intervention, the procedures of the original Pocket PATH trial and the flow of patients between the original trial and the two long-term follow-up studies reported here.

3.1 THE POCKET PATH INTERVENTION

Pocket PATH is a mobile health (mHealth) technology in the form of a smartphone application (app) that was designed to enhance lung transplant recipients' involvement in their post-transplant regimen. The app provides customized data recording and graphing programs, alerts and reminders, and decision support about communicating condition changes to the transplant team. Pocket PATH was developed using principles of user-center design[69] and subsequently pilot tested during the first two months following hospital discharge.[70]

3.2 PROCEDURES OF THE ORIGINAL POCKET PATH TRIAL

Between December 2009 and January 2011, Pocket PATH was formally evaluated in a randomized controlled trial that enrolled 201 LTxRs during their index hospitalization for the lung transplant procedure at the Cardiothoracic Transplantation Program, University of Pittsburgh Medical

Center, Eligibility criteria included age ≥18 years old, never having received a prior organ transplant, and ability to read and speak English; patients were excluded if they had a condition that precluded hospital discharge after the LTx surgery or limited their ability to be involved in their own post-transplant care.

The procedures for the original trial have been described previously.[55] In brief, the trial used a two-group design in which patients were randomized to the intervention or to usual care prior to discharge after their LTx surgery. Patients in both groups received the same discharge instructions and were interviewed at 2, 6 and 12 months post-LTx to assess their performance of self-management behaviors, as described further below.

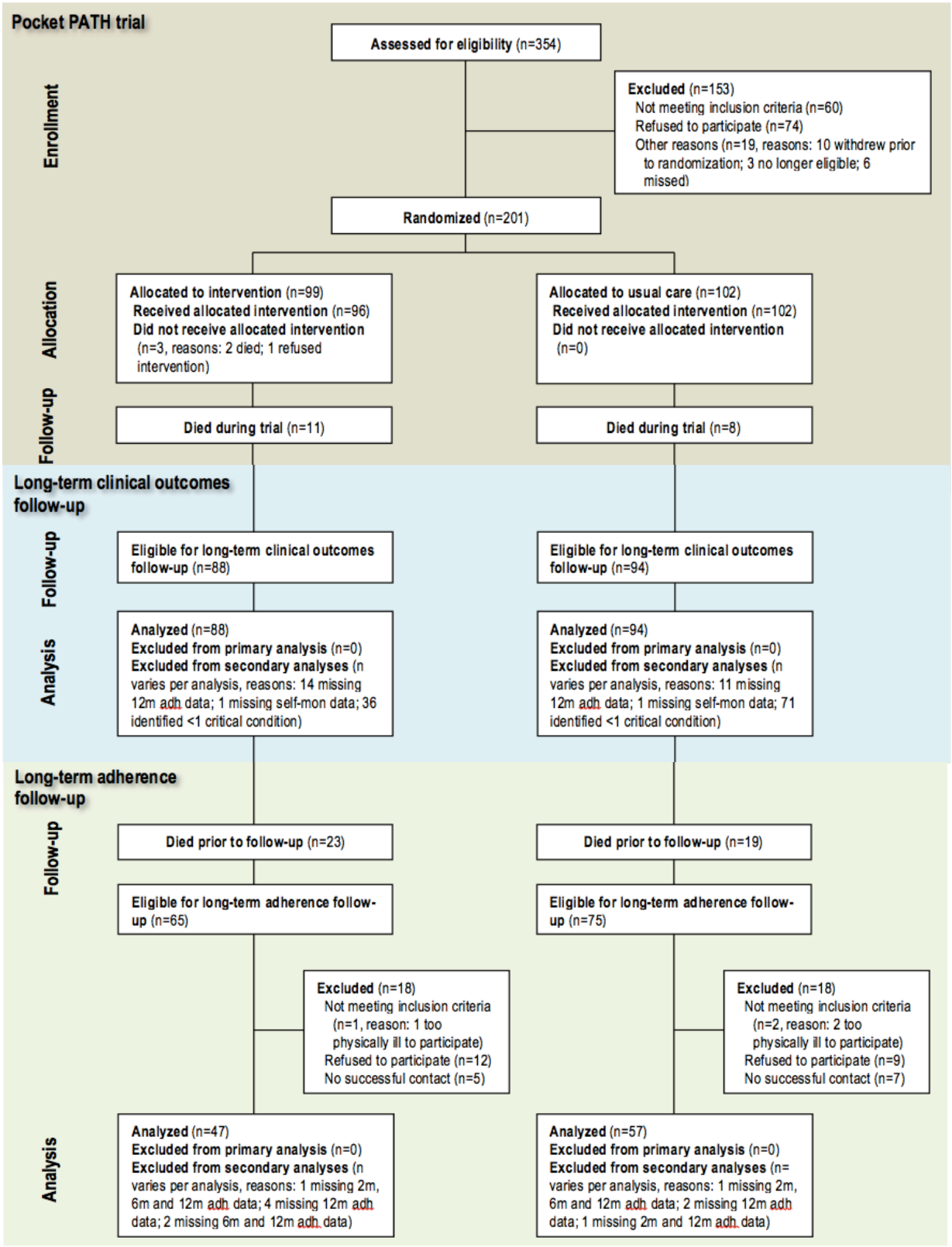
Patients in the intervention group received a smartphone with the Pocket PATH app. The app provided customized data recording and graphing programs, alerts and reminders, and automatic decision-support about communicating condition changes to the transplant team. Trained interventionists performed a scripted review of discharge instructions that included taking immunosuppressants daily as prescribed, self-monitoring health indicators (e.g., spirometry, vital signs and symptoms) everyday, recording the self-monitored values into Pocket PATH, attending all follow-up clinic appointments, exercising at least once a week and refraining from smoking. Patients were also instructed to contact their LTx coordinator if the health indicators they self-monitored were outside a range of pre-established parameters, which suggested a critical condition change warranting clinical attention. Pocket PATH provided automatic decision-support messages to advise patients to report each critical condition change to their LTx coordinator. The decision-support algorithm has been published previously.[71]

Patients in the usual care group did not receive the Pocket PATH device or app. Instead, they received paper-and-pencil tracking logbooks that are given to all LTx patients in our

Cardiothoracic Transplantation Program. Patients in the usual care group received the same interventionist-delivered scripted review of discharge instructions – including information on adhering to medications, self-monitoring, attending appointments, exercising, refraining from smoking and parameters for reporting condition changes to their LTx coordinator – as patients in the intervention group.

3.3 FLOW OF PATIENTS BETWEEN THE ORIGINAL TRIAL AND LONG-TERM FOLLOW-UP STUDIES

The long-term follow-up studies discussed in this dissertation are based on two distinct samples that derive from the sample in the original study. Figure 4 describes the flow of participants from the original study to the studies described in Papers 2 and 3.



Abbreviations: m, month; adh, adherence; self-mon, self-monitoring

Figure 4. Flow of participants from original Pocket PATH trial to follow-up studies

4.0 PAPER 2: IMPACT OF MOBILE HEALTH INTERVENTION ON LONG-TERM TRANSPLANT-RELATED OUTCOMES IN LUNG TRANSPLANT RECIPIENTS

4.1 INTRODUCTION

As smartphones and wireless tablets have become more common over the past several years, the number of mobile health (mHealth) apps has grown exponentially. Defined as "mobile device applications intended to improve health outcomes, deliver health care services, or enable health research,"[72] mHealth apps now number into the tens of thousands.[73] This rapid pace of development and dissemination is largely at odds with the slow pace of conducting and publishing the randomized controlled clinical trials considered to be the gold standard for assessing new interventions.[74-76] As a result, the vast majority of apps reach patients and consumers without undergoing rigorous scientific evaluation,[76-78] unlike any other evidence-based interventions. Moreover, because regulatory agencies have not been able to keep pace with creating guidelines about the level of evidence needed to develop and evaluate an app, patients, clinicians and researchers are left without an overarching framework for how to assess an app's safety and effectiveness.[73] Chief among the questions that arise in this unregulated environment is a concern about long-term clinical effectiveness, especially for the large group of apps targeting patients with chronic illnesses (over 50% of all apps).[79] To this point, there have not been any studies in the small but growing app evaluation literature that have examined the long-term health effects of using an app.

The Pocket PATH for lung transplantation (LTx) provides a unique opportunity to rigorously evaluate the long-term effectiveness of a self-management app for a chronically ill

population. Pocket PATH was designed to enhance lung transplant recipients' (LTxRs) involvement in their post-transplant regimen by providing them with customized data recording and graphing programs, alerts and reminders, and decision-support about seeking clinical assistance. Broadly, the regimen involves taking immunosuppressants daily in order to prevent graft rejection and monitoring lung function routinely in order to alert clinicians to potentially fatal complications such as infection and rejection.[43-48] Despite the regimen's importance for preventing graft rejection and alerting clinicians to early signs and symptoms of potentially fatal complications, sizeable proportions of patients show poor adherence to this regimen, ranging up to 70% for some elements of the regimen during the first three years after LTx.[53,54,80] Clinical outcomes, at least during the two-year post-transplant period that has been most commonly studied, have been shown to suffer as a result.[11,43,48-52] Although Pocket PATH was designed to promote self-management behaviors specifically in LTxRs, its features also stand to improve the similar non-adherence issues that plague many other chronic illness populations.[73,81]

Pocket PATH is one of the few existing self-management apps[79,82] to have undergone a rigorous process of development and testing since its inception. It was developed using principles of user-center design,[69] pilot tested in the immediate post-transplant period[70] and then formally evaluated during a 1-year period of patient observation in a randomized controlled trial with 201 LTxRs.[55] Outcomes from that trial showed that patients who were randomized to Pocket PATH self-monitored more often and adhered to more elements of the post-transplant regimen during the first year post-transplant than patients who received usual care.[55]

The present study collected clinical outcomes follow-up data from LTxRs who participated in the Pocket PATH trial. Follow-up ranged from 2.8 through 5.7 years post-transplant. Our primary goal was to examine whether receipt of the Pocket PATH intervention during the first year

after LTx was associated with longer time to bronchiolitis obliterans syndrome (BOS), the clinical correlate of chronic rejection, and patient mortality. Our study covers the longest follow-up period that has been reported in the mHealth literature to date.

4.2 METHODS

4.2.1 Study participants

Figure 4 describes the flow of participants from the original trial. Participants included 182 LTxRs who survived to the end of the original trial (i.e., until one year after hospital discharge); we selected this subset in order to ensure that all LTxRs included in the follow-up study had an equal length of time to use their assigned tracking method. Of the 182 LTxRs in the present sample, 25 were lost to follow-up during the original trial (14 assigned to Pocket PATH and 11 assigned to usual care) and did not complete the 12-month adherence assessment.

Compared to the 19 LTxRs enrolled in the original trial who died during the first year after LTx (and were therefore excluded from the present study), our sample of 1-year survivors was more likely to have received a double (vs. a single) LTx (37% vs. 63%, p=.029) and to have had a shorter length of stay following the LTx surgery (median [IQR] days, 46 [23-79] vs. 27 [18-42], p=.029).

4.2.2 Procedure

The University of Pittsburgh Institutional Review Board approved the original trial and this long-term follow-up study. All patients provided written informed consent to participate in the original randomized controlled trial and have their medical records reviewed subsequently.

The present long-term follow-up study ascertained clinical outcomes from LTxRs' medical records, beginning at their exit date from the original trial (ranging from January 2010-January 2013) and censoring at the date of patient death or the end date of September 1, 2014.

4.2.3 Measures

4.2.3.1 Clinical outcomes at long-term follow-up. Medical record abstractors and outcome adjudicators were blinded to participants' intervention assignment. The clinical outcomes we examined were patient mortality, which was defined as time to patient death, and onset of BOS, which was defined using criteria established by the International Society for Heart and Lung Transplantation[63] as grade ≥1 (≥20% decrease in forced expiratory volume in 1 second [FEV_1] relative to the mean of the two highest post-transplant FEV_1 values not explained by clinical illness or infection). Death date was ascertained from the medical record. Determinations for BOS were based on decisions by study investigators using both pulmonary function tests (PFTs) and medical records of clinical encounters. All patients received pulmonary function tests (PFTs) and clinical follow-up according to the transplant center's standard post-transplant surveillance protocol for the first two years after LTx; thereafter, they received clinical follow-up every four to six months, with PFTs and additional testing performed as clinically indicated. We recorded the earliest date of BOS grade ≥1. (No patients experienced BOS grade ≥1 before the end of the original Pocket

PATH trial.) Although we collected data on graft survival, which we defined as time to graft loss by patient death or retransplantation, we did not conduct separate analyses with this outcome because only one participant underwent retransplantation during the follow-up period.

4.2.3.2 Performance of self-management behaviors during the first year. In addition to examining whether intervention exposure affected clinical outcomes, we examined whether the degree to which patients performed four self-management behaviors (adhering to immunosuppressants, adhering to spirometry, self-monitoring and communicating critical values to LTx coordinators) during the first year after LTx had an effect on long-term clinical outcomes. These self-management behaviors were assessed as outcomes in the original trial. Thus, by examining these behaviors in the present study, we sought to determine whether the Pocket PATH intervention may have indirectly affected clinical outcomes via its earlier impact on self-management behaviors.

Adherence to immunosuppressants and spirometry was ascertained by self-report using the Health Habits Assessment, a validated instrument that asks about adherence to the elements of the post-transplant regimen.[27] Self-report (either alone or in combination with another source, such as a family caregiver) has been recommended by studies[53] and meta-analyses[83] as a reliable method of detecting non-adherence. In the original trial, adherence to immunosuppressants and spirometry was assessed at 2, 6 and 12 months post-transplant; the 2-month assessment focused on the period since hospital discharge, and the 6- and 12-month assessments focused on the period since the previous assessment. Adherence was defined as meeting our transplant center's requirement of, respectively, missing ≤1 dose of the primary immunosuppressant during the prior month and monitoring spirometry >1 time per week during the prior month. We used the 12-month assessment of adherence in our analyses because this assessment is most proximal to our long-term follow-up.

Twenty-five patients were lost to follow-up during the original trial; thus, 157 patients completed the 12-month adherence assessment (74 assigned to Pocket PATH and 83 assigned to usual care). Each patient's primary family caregiver also provided an additional report of the LTxR's adherence, and discrepancies between LTxR and caregiver reports (i.e., if one person indicated that the recipient was adherent and the other indicated that the recipient was nonadherent) were reconciled by coding the recipient as nonadherent.

Self-monitoring was ascertained by reviewing the health indicators that patients entered into the Pocket PATH app (for the intervention group) or onto paper logs (for the usual care group). Pocket PATH recorded these values automatically, whereas paper logs were photocopied at the 2-, 6- and 12-month assessments for patients in the usual care group. Self-monitoring data were obtained from 180 patients. For each patient, a self-monitoring rate was calculated to indicate the cumulative number of days over the 12-month trial that the patient recorded a value for a health indicator (i.e., spirometry, blood pressure, temperature or weight) (numerator) as a proportion of the number of days during that year in which the patient was home (denominator) (i.e., the denominator was adjusted for any days patients were rehospitalized, as they were not expected to self-monitor under those circumstances). Self-monitoring rates were categorized into groups indicating whether patients self-monitored on <25% of days, 25%-<50% of days or ≥50% of days. These cut-points are clinically meaningful and ensure sufficient numbers of patients in each group.

Communicating critical condition changes to the LTx coordinator was ascertained by (1) reviewing the health indicators that patients entered into the Pocket PATH app (for the intervention group) or onto paper logs (for the usual care group) to identify the number of critical conditions that were recorded and (2) reviewing LTx coordinators' progress notes in the medical record to determine whether patients reported these condition changes to the LTx coordinator. For each

patient, a communicating critical conditions rate was calculated to indicate the number of critical condition changes that the patient reported to his or her LTx coordinator (numerator) as a proportion of the number of critical values patients the patient identified (denominator) cumulatively over the 12-month trial. Because patients had to have identified a critical condition change in order to be eligible to report the change, this variable only included the 75 patients who identified at least one critical condition change during the first year (52 assigned to Pocket PATH and 23 assigned to usual care).

4.2.3.3 Clinical outcomes during the original trial. Number of re-hospitalization days and number of acute rejection episodes graded A2 or greater during the original 12-month trial were ascertained from the medical record. Number of re-hospitalization days was considered as a continuous variable, and acute rejection episodes were dichotomized based on whether patients experienced any vs. no episodes.

4.2.3.4 Baseline characteristics. The original trial collected data on sociodemographics, LTx-related medical factors (e.g., recipient age at transplant, LTx indication, LTx type) and computer use characteristics.

4.2.4 Statistical analysis

4.2.4.1 Clinical outcomes. We used an intention-to-treat approach to examine the effect of intervention assignment on each long-term clinical outcome. We used descriptive statistics (i.e., χ^2 or Fisher exact tests for dichotomous variables and t tests or Mann-Whitney rank-sum tests for

continuous variables) to compare baseline sociodemographic, LTx-related and computer use characteristics between the intervention and usual care groups. (We replicated the baseline group comparisons that were done in the original trial to ensure that the groups remained balanced in our sample of 1-year survivors.) To estimate group differences in time-to-event rates for each clinical outcome, we used Kaplan-Meier methods with the log-rank test. We then used Cox proportional hazards regression to compare group differences in risk for each long-term clinical outcome outcome when adjusting for covariates with known associations with each outcome.[7] The Cox models estimated hazard ratios (HRs) and 95% confidence intervals (CIs). For the BOS analyses, patients were censored at their time of death.

To meet our secondary goal of examining the association between performing the self-management behaviors targeted by Pocket PATH and each long-term clinical outcome, we conducted additional Cox regressions with each self-management behavior as a predictor variable.

4.2.4.2 Links between intervention assignment, self-management behaviors and clinical outcomes. A growing literature on mediation analysis recommends investigation of the effect of intervening variables even in the absence of a significant main effect, which, in the traditional Baron and Kenny approach to mediation,[84] is a prerequisite for mediation analysis. The alternative approach posits that indirect effect analyses are warranted when (a) the direct effect is greater or less than zero, regardless of statistical significance; and (b) there is a reasonable expectation that the intervening variable is in the causal chain between the independent and dependent variables, based on ruling out the majority of potential confounders.[85,86]

In accordance with this literature, we explored whether intervention exposure had an indirect impact on long-term clinical outcomes by promoting LTxRs' performance of self-management behavior by examining the links between: (1) intervention exposure and long-term

clinical outcomes, (2) performance of self-management behaviors during the original trial and long-term clinical outcomes, and (3) intervention exposure and performance of self-management behaviors. Our analysis of the first two links is described above. The analysis of the third link was the subject of the original trial; however, we re-analyzed this link in the present sample to determine whether relationships between intervention exposure and each self-management behavior also exist in our sample of 1-year survivors. We compared the performance of the four self-management behaviors between the intervention and usual care groups using χ^2 tests for dichotomous and categorical variables (i.e., adherence to immunosuppressants at the 12-month assessment, adherence to spirometry at the 12-month assessment, self-monitoring on <25% of days, 25%-<50% of days or ≥50% of days during the original trial) and Mann-Whitney rank-sum tests for the continuous variable (i.e., the percentage of condition changes that patients communicated to the LTx coordinator during the original trial). We considered a significant indirect effect to have occurred if links 2 and 3 specified earlier reached statistical significance.

Statistical significance for all tests was considered a 2-tailed $p<.05$. Analyses were conducted with STATA Version 13.

4.3 RESULTS

4.3.1 Patient characteristics

Table 3 shows the demographic, LTx-related and computer use characteristics of the sample of 182 LTxRs that were included in the present long-term follow-up sample. At the time of long-term follow-up, median time since transplant was 4.2 years (range, 2.8-5.7). Our sample is similar to

the international population of LTxRs transplanted during the same time period in terms of demographics, LTx indication and type of transplant.[7] The intervention and usual care groups in our sample were also similar on most baseline characteristics; however, as in the original trial, the intervention group had a longer and more severe hospital course than the usual care group upon discharge from the LTx surgery. Nevertheless, despite these baseline imbalances, both groups were balanced in terms of 1-year clinical outcomes (Table 3).

4.3.2 Early post-transplant predictors of long-term clinical outcomes

4.3.2.1 Effect of intervention exposure. Our primary goal was to determine whether exposure to Pocket PATH improved survival and delayed onset of BOS over the long-term follow-up period, relative to usual care.

During follow-up, the actuarial mortality rate was 29% in the Pocket PATH group (23 deaths) and 27% in the usual care group (19 deaths). Intervention group assignment did not impact mortality risk in unadjusted analyses (HR, 1.29; 95% CI, .71,2.38; p=.403) or analyses adjusted for recipient age at transplant, indication for transplant and type of transplant (HR, 1.37; 95% CI, .74,2.56; p=.320) (Table 4).

During follow-up, the actuarial rate of BOS onset was 65% in the Pocket PATH group (28 cases) and 66% in the usual care group (29 cases). These rates are lower than cumulative rates of BOS within five years post-transplant reported in international registry data.[7] Intervention group assignment did not impact risk of BOS in unadjusted analyses (HR, 1.01; 95% CI, .60,1.71; p=.958) or analyses adjusted for recipient age at transplant, indication for transplant, type of transplant and ischemia time of the donor graft (HR, 1.04; 95% CI, .61,1.75; p=.890) (Table 4).

Table 3. Baseline characteristics of the 182 lung transplant recipients included in the follow-up clinical outcomes study

Characteristic	Pocket PATH (n=88) % (No.)	Usual Care (n=94) % (No.)	p value
Sociodemographics			
Age at transplant, mean ± SD, y	57 ± 13	58 ± 14	.778
Men	51 (45)	56 (60)	.252
White race	92 (81)	83 (88)	.397
Married	74 (65)	67 (71)	.696
Transplant-related			
Transplant indication			
Non-α-1-antitrypsin deficiency COPD	42 (37)	32 (30)	.157[a]
Pulmonary fibrosis	27 (24)	40 (38)	
Cystic fibrosis	11 (10)	12 (11)	
Other	20 (17)	16 (15)	
Double lung transplant	84 (74)	83 (78)	.840
Ischemia time of donor graft, median (IQR), min	320 (271 – 374)	318 (275 – 364)	.739
Recipient/donor CMV mismatch, (R-/D+)	6 (5)	7 (7)	.661
Intensive care unit length of stay, median (IQR), days	4 (3 – 10)	7 (3 – 13)	.084
Re-intubated	14 (12)	29 (27)	.013*
Length of stay for transplant surgery, median (IQR), days	24 (16 – 37)	32 (21 – 47)	.004**
Computer use characteristics			
Previous computer use	86 (76)	79 (74)	.176
Previous handheld device use	20 (17)	22 (21)	.644
Self-management behaviors			
Adherent to immunosuppressants at 12 months[b]	97 (72)	91 (76)	.123
Adherent to monitoring spirometery at 12 months[b]	47 (35)	29 (24)	.018*
Self-monitoring during year 1[c]			
<25% of days	40 (35)	80 (74)	<.001*
25-<50% of days	26 (23)	9 (8)	**
≥50% of days	33 (29)	12 (11)	
Communicating critical condition changes, median (IQR) percentage of identified changes that were reported[d]	100 (91 – 100)	80 (10 – 100)	.018*
Clinical outcomes during year 1			
Re-hospitalization days, median (IQR), days	12 (3 – 30)	14 (3 – 32)	.346
≥1 episode of A2 or greater rejection	63 (55)	59 (55)	.582

*p<.05, **p<.01
[a]Significance test was based on the comparison of non-α-1-antitrypsin deficiency COPD vs. all other groups (Yusen)
[b]n=157
[c]n=180
[d]n=75

Table 4. Early post-lung transplant predictors of long-term clinical outcomes

Predictors[a]	Long-term clinical outcomes			
	Mortality[b]		BOS[c]	
	HR (95%CI)	p	HR (95%CI)	p
Intervention assignment				
Pocket PATH	1.37 (.74,2.56)	.320	1.04 (.61,1.75)	.890
Usual care	*Reference group*		*Reference group*	
Adherence to immunosuppressants	1.80 (.23,13.77)	.572	.77 (.27,2.16)	.612
Adherence to spirometry	1.31 (.63,2.68)	.466	.59 (.33,1.08)	.087
Rate of self-monitoring				
<25%	*Reference group*		*Reference group*	
25-<50%	.97 (.43,2.16)	.936	1.34 (.69,2.60)	.390
≥50%	.47 (.20,1.09)	.077	.86 (.43,1.74)	.684
Rate of communicating critical conditions[d]	.17 (.05,.64)	.008**	.46 (.16,1.31)	.145

**p<.01
[a]Adherence to immunosuppressants and spirometry reflect the month prior to the 12-month assessment; rates of self-monitoring and communicating reflect the entire first year after LTx
[b]Adjusted for age at LTx, LTx indication and type of LTx
[c]Adjusted for age at LTx, LTx indication, type of LTx and ischemia time of donor graft
[d]Sample only includes patients who identified ≥1 critical condition change; thus, n=52 in Pocket PATH group and n=23 in the usual care group

4.3.2.2 Effect of self-management behaviors during the first year. Our secondary goal was to determine whether performing the self-management behaviors targeted by Pocket PATH during the first year after LTx reduced long-term mortality and delayed subsequent onset of BOS. Of the four self-management behaviors, adherence to immunosuppressants, adherence to spirometry and rate of self-monitoring were not associated with patient mortality or time to BOS (all p's >.05) (Table 4). However, communicating critical condition changes to the LTx coordinator was inversely associated with patient mortality: among patients who identified a critical condition change, those who reported more of these changes to their LTx coordinator had a lower risk of

death (HR, .17; 95% CI, .05,.64; p=.008). The percentage of critical condition changes reported was not associated with time to BOS (Table 4).

4.3.3 Links between intervention assignment, self-management behaviors and long-term clinical outcomes

During the original trial, exposure to Pocket PATH improved performance of self-monitoring (self-monitored for ≥50% of days, 33% of Pocket PATH group vs. 12% of usual care group, p=.001) and communicating critical condition changes to LTx coordinators (median [IQR] critical values reported, 100 [91-100] in Pocket PATH group vs. 80 [10-100] in usual care group, p=.018) in our sample of 1-year survivors (Table 3). Moreover, as discussed above, communicating critical condition changes was associated with a lower risk of death (Table 4). Taken together, these associations suggest that, although there was no direct intervention effect on long-term clinical outcomes (Table 4), exposure to Pocket PATH may have had an indirect effect on long-term mortality by promoting LTxRs' communication of critical condition changes. We further explored this relationship by adding the communicating critical condition changes variable to the adjusted Cox model of patient mortality. Although this model does not show an effect for intervention assignment (HR, 2.08; 95% CI, .61,7.10; p=.241), it does indicate that reporting more critical condition changes is associated with a lower risk of death (HR, .097; 95% CI, .02,.50; p=.005), independent of intervention group assignment. Thus, receiving Pocket PATH may have had a protective indirect effect on mortality by promoting patients' communication with the LTx team during the first year after LTx.

4.4 DISCUSSION

This study leverages a unique opportunity to evaluate the long-term clinical effectiveness of Pocket PATH, an mHealth intervention developed specifically for LTxRs. We address an underlying, but often understudied, goal of behavioral interventions in healthcare: to create behavior change that results in improved health.[87] We found that receipt of the Pocket PATH app did not have a direct impact on morbidity and mortality through up to 5.7 years post-LTx, specifically time to patient death and onset of BOS. However, we also found that LTxRs who reported more critical condition changes to the LTx team during the original trial, who were more likely to be in the Pocket PATH than the usual care group, had a lower odds of long-term mortality. In other words, despite the absence of direct effects, Pocket PATH appeared to have an indirect effect on risk of long-term mortality by promoting better communication between LTxRs and the LTx team. This finding holds broad significance for future mHealth apps because it identifies the feature of Pocket PATH most likely to be responsible for its clinical effect – the clinical decision support system.

Pocket PATH's clinical decision support system falls under the category of "push" factors that have been described as important for enhancing an mHealth intervention's effectiveness.[88,89] Push factors refer to the "pushiness" of an intervention, which falls along a spectrum. Less pushy interventions are passive and do not guide users' behavior (e.g., electronic monitoring logs), whereas more pushy interventions actively prompt users to perform intended actions (e.g., medication-taking alarms, automatic calls from a care coordinator). A study of patients with poorly controlled hypertension showed that the more pushy components of its internet-based intervention, including electronic messaging by clinicians in response to poor home blood pressure recordings, were responsible for the intervention's positive effect.[90] Similarly, several studies in LTxRs have demonstrated patient acceptability and sensitivity of an automatic event detection system based on

home spirometry.[91-93] Pocket PATH's many features can also be plotted along a pushiness spectrum. Its most pushy factor is its clinical decision support system, which provided feedback messages to patients about how to manage values they had self-monitored as exceeding pre-defined thresholds indicating the need for clinical attention.[71] Our finding that the clinical decision support system, but not increased self-monitoring or medication-taking, had an indirect effect on long-term mortality may be interpreted similarly to the hypertension study: Pocket PATH's most pushy component was associated with its clinical effect.

Two possible pathways may be responsible for the benefit associated with Pocket PATH's clinical decision support system. In one pathway, the decision support system may have prompted patients to alert clinicians to a condition change earlier than they typically would have, thus initiating quick clinical action and maximizing the chances that treatment would have an effect. In this case, the decision support system circumvented any knowledge barriers that may have prevented LTxRs from recognizing and subsequently acting on critical condition changes. In another pathway, the decision support system may have created a positive feedback loop that reinforced the consistent use of Pocket PATH's self-monitoring features. Receiving a decision support message may have served as an additional demonstration of Pocket PATH's utility and thereby encouraged LTxRs to continue using the device to self-monitor. Similar reinforcement has been described in relation to users of wearable activity tracking devices, who "quickly abandon wearables that don't help them make positive changes."[94]

There are many possible explanations for the lack of a direct intervention effect on morbidity and mortality. First and foremost, the extended time period between intervention assignment and the long-term study endpoints creates many opportunities for confounding factors to impact outcomes. Second, our study examines the impact of exposure to, rather than use of,

Pocket PATH. Data from the original trial indicate that there was wide variation in use of Pocket PATH.[55] Future research should aim to develop a metric to capture intensity of use in order to determine whether a higher intensity of use is associated with improved clinical outcomes. Finally, although Pocket PATH was associated with improved adherence to the regimen during the first year, evidence on adherence patterns during the first two to three years after transplant[53,54] suggests that these benefits would be expected to decline over time. Therefore, any clinical benefit of higher adherence to the regimen during the first year – for instance, because more frequent self-monitoring and communication with the transplant team might have initiated clinical action earlier in any disease process – would also be expected to decline over time. Short-term and cross-sectional data support these linkages,[45,48] but our study is the first to explore them over a prolonged follow-up period. Ultimately, then, without data on each LTxR's adherence during the period closest to a clinical event, the only conclusion our data can suggest is that early adherence does not have a direct impact on long-term clinical outcomes.

It is also important to consider Pocket PATH's intended use, which was to increase patients' involvement in their self-management regimen during the first year after LTx. In other words, Pocket PATH was not designed to have a long-term effect. Although patients were able to continue using Pocket PATH beyond the original trial, its decision support system was not available after the original trial ended. Therefore, any long-term Pocket PATH users were using a less potent intervention, specifically lacking the feature shown in the present study to be associated with an indirect clinical effect.

Our study was limited by lack of data collection about the interim period between the end of the original trial and the long-term follow-up. Changes in the frequency of performing self-management behaviors during the interim may have influenced outcomes. Future work evaluating

the long-term clinical impact of mHealth interventions should thus follow participants continually over time and assess both clinical and self-management outcomes in order to obtain a more comprehensive account of the interventions' impact on outcomes. Moreover, future work should also explore mHealth's impact on alternative clinical outcomes that may be more sensitive indicators of health status than mortality and BOS, such as infections. Finally, we were unable to perform subgroup analyses given our small sample size and a relatively small number of morbidity and mortality events.

To our knowledge, this is the only existing study to investigate the long-term clinical impact of a self-management app. Our findings are generalizable beyond LTxRs to the large and growing population of chronic illness sufferers, who face many of the same challenges such as performing a daily self-management regimen and interpreting and acting on the clinical information they self-monitor. Moreover, Pocket PATH is, in many ways, an exemplar mHealth intervention with features that are common to many existing self-management apps. Whereas many self-management apps target only one element of self-management, such as medication taking or tracking self-monitoring data,[95] Pocket PATH employs a multipronged approach by including multiple features that target the various components of self-management. As this and other findings show, the more pushy intervention components are likely to be responsible for the largest clinical impact. Thus, identifying the push factors that encourage action for specific patient populations should be a key consideration for app developers in the future. Although mHealth interventions appear to hold promise for improving clinical outcomes, more work is needed to understand whether, how and for whom they work.

5.0 PAPER 3: IMPACT OF MOBILE HEALTH INTERVENTION ON LONG-TERM NONADHERENCE IN LUNG TRANSPLANT RECIPIENTS

5.1 INTRODUCTION

Mobile health (mHealth) technologies have transformed today's health and wellness landscape. Virtually unheard of a decade ago, these smartphone applications (apps) and devices are now commonplace in consumer markets and healthcare settings.[79,94,96] Individuals with chronic illnesses have become a major focus of mHealth technologies,[79] as many of the behavioral tasks required to manage a chronic illness (e.g., self-monitoring, tracking diet and exercise, adjusting medication doses, communicating with clinicians) are amenable to the type of algorithmic assistance offered by programs on portable devices. However, unlike most other interventions in healthcare, the vast majority of existing mHealth technologies have not been evaluated in rigorous clinical trials.[76-78] This lack of evidence raises critical questions about whether mHealth interventions are effective and whether any effects are sustained into the long-term. There has also been some concern that, for some patient populations, using an untested (and potentially ineffective) mHealth intervention instead of an evidence-based non-mHealth alternative may actually be harmful.[78] Given that the growth of mHealth shows no signs of abating, the need for research on its effectiveness is now more pressing than ever.

To be effective for chronically ill patients, who must manage their disease daily for the duration of their lives, mHealth interventions must improve adherence to their targeted behavior over the long-term. However, the few mHealth interventions that have been rigorously evaluated[79,82] observed participants for less than 1.5 years. This leaves major gaps regarding the

duration of patient engagement with mHealth interventions as well as the duration of any intervention effect. To our knowledge, the only existing data on long-term mHealth engagement comes from a large nationwide survey of relatively healthy individuals who own a wearable fitness tracking device aimed at promoting health, such as Jawbone or Fitbit.[94] This survey reported that one-third of individuals stopped using their device within six months of receiving it and that fewer than half of individuals continued to use their device at two years. Clinical trials report dropout rates up to 65%; however, these rates do not differentiate between dropout due to typical trial loss-to-follow-up or discontinued use of the intervention.[88,97] In any case, the impact of such attrition on the effect of mHealth interventions is unknown.

The present study examines the long-term effectiveness of an exemplar self-management app, Pocket PATH, which was designed to enhance performance of self-management behaviors after LTX, by involving LTxRs in prevention and detection of complications. This regimen requires adherence to strict guidelines about the frequency of performing tasks related to taking medications, monitoring lung function routinely and alerting clinicians to signs and symptoms of lung function decline, and following a healthy lifestyle.[43-48] Pocket PATH assists with these tasks by providing LTxRs with customized data recording and graphing programs, alerts and reminders, and automated decision support about when to seek clinical assistance. Although designed to promote self-management behaviors specifically in LTxRs, Pocket PATH's features also stand to improve the similar nonadherence issues that plague many other chronic illness populations.[73,81]

Nonadherence to the post-LTx regimen, which Pocket PATH is designed to reduce, remains a central problem of lung transplantation. Despite the regimen's importance for preventing graft rejection and alerting clinicians to early signs and symptoms of potentially fatal complications, sizeable proportions of patients show poor adherence to this regimen, ranging up

to 70% for some elements of the regimen during the first three years after LTx.[53,54,80] Studies show that nonadherence tends to be lowest immediately following LTx, increases over the subsequent one to two years and then plateaus around year two.[53,54] Clinical outcomes, at least during the two-year post-transplant period that has been most commonly studied, have been shown to suffer as a result of such nonadherence.[11,43,48-52] There are limited data on nonadherence patterns beyond two to three years post-LTx. This gap in evidence is clinically significant because the longer-term post-LTx years are when self-motivated adherence to the regimen carries the most weight. Unlike during the early post-LTx period, when the transplant team is highly involved in infection and rejection surveillance during LTxRs' frequent clinical follow-up, LTxRs must take on more responsibility for such surveillance during the later post-LTx years when their clinical follow-up becomes less frequent. Identifying, and subsequently intervening on, short-term predictors of longer-term nonadherence is therefore critical for maintaining a seamless transition between primarily clinician-driven and primarily patient-driven surveillance of complications. However, evidence about predictors of nonadherence, at least during the short-term periods that have been studied, is mixed and inconsistent.[53,54,68,80,98,99]

Pocket PATH is one of the few[79,82] existing self-management apps to have undergone a rigorous process of development and testing since its inception. It was developed using principles of user-center design[69], pilot tested during the two months after discharge from the transplant surgery[70] and then formally evaluated during the first post-transplant year in a randomized controlled trial with 201 LTxRs.[55] Outcomes from that trial showed that patients who received Pocket PATH self-monitored more often and had lower nonadherence to the post-LTx regimen as a whole during the first year after LTx than patients who received usual care.[55]

We conducted a long-term follow-up study of LTxRs who participated in the original Pocket PATH trial in order to evaluate the app's long-term effectiveness. Our primary goals were to describe long-term nonadherence in this population and determine whether assignment to the Pocket PATH intervention reduced long-term nonadherence relative to usual care. At the time of follow-up, all LTxRs ranged from 2.8 to 5.7 years since LTx; this is the longest follow-up period reported in both the mHealth and the transplant-related nonadherence literatures to date.

5.2 METHODS

5.2.1 Study participants

Figure 4 describes the flow of participants from the original trial. Of the 201 patients enrolled in the original trial, 140 were alive at the long-term follow-up. Among these, three patients were too ill to participate, 21 refused and 12 could not be contacted. The present sample thus comprised 104 patients.

Among the 140 participants enrolled in the original trial who were alive at the long-term follow-up, those who completed the follow-up did not differ from those who did not complete the follow-up on sociodemographic and transplant-related baseline characteristics, performance of self-management behaviors during the first year after LTx and clinical outcomes since LTx. The only difference we observed was that completers reported higher satisfaction with their assigned tracking method during the first post-LTx year than non-completers (mean ± SD score on satisfaction scale, 2.0 ± 1.1 vs. 2.6 ± 1.5, p=.010; possible score range 1-7 with lower scores indicating higher satisfaction).

5.2.2 Procedure

The University of Pittsburgh Institutional Review Board approved the original trial and this long-term follow-up study. Written informed consent was obtained at the time of the original trial and again from those who agreed to participate in the long-term follow-up study. The long-term follow-up consisted of a cross-sectional assessment. Data on patient adherence and psychosocial status were collected via individual 30- to 45-minute structured telephone interviews or a secure internet-based form (Qualtrics, LLC). Interviews were conducted by trained interviewers. Each patient determined his or her preferred method of completing the assessment; there were no significant differences due to interview mode for any variable. Each patient's primary family caregiver (identified by the patient as person who provides the most care and assistance on a daily basis) also completed an assessment of the patient's adherence. All assessments were completed between March 1, 2014 and September 17, 2014.

The procedures in the original trial are described in Chapter 3.

5.2.3 Measures

5.2.3.1 Nonadherence at follow-up. The adherence literature has identified self-report as the strategy that identifies the highest rates of nonadherence,[80,83,100] though it also recommends combining multiple methods of assessment.[101] Consistent with these recommendations, we assessed patient nonadherence to the post-LTx regimen using a combination of patient and family caregiver report. Most patients (78%) identified a caregiver at the follow-up assessment.

We used the Health Habits Survey to assess nonadherence; this is the same instrument used to assess nonadherence in the original Pocket PATH trial.[55] It was developed for kidney transplant

recipients[102] and has been successfully adapted for and administered to cardiothoracic recipients.[27,70,99] The Health Habits Survey assesses post-LTx nonadherence to nine elements that make up the post-LTx regimen: (a) taking the primary immunosuppressant, (b) taking other prescribed (non-immunosuppressant) medications, (c) performing home spirometry, (d) attending follow-up clinic appointments, (e) completing labwork, (f) monitoring vital signs at home, (g) following a prescribed diet, (h) following a prescribed exercise plan, and (i) abstaining from tobacco use. Responses were given in an ordinal format that indicated how often patients completed each element. We dichotomized responses based on whether or not patients met our Cardiothoracic Transplant Program's requirement for frequency of performing each element. Patients were asked to consider the prior month when completing the survey.

The vast majority (84%) of caregivers also completed the Health Habits Survey regarding the patient's adherence behaviors. Patients and caregivers were largely concordant in their responses. For discordant responses to any item, we created a single item measure by considering any report of nonadherence from either the patient or the caregiver as evidence of nonadherence for that element. For patients whose caregiver did not complete the nonadherence assessment, we used the patients' responses on their own as measures of nonadherence.

We considered two types of nonadherence outcomes: (1) nonadherence to the overall regimen and (2) nonadherence to specific self-management areas. The former was a count of the number of elements of the regimen (out of a possible nine) to which patients were nonadherent. The latter comprised the following four areas of related elements: (a) taking medications (immunosuppressants and non-immunosuppressants); (b) performing home spirometry; (c) clinical follow-up (attending clinic appointments, completing labwork); and (d) home self-care (self-monitoring vital signs, following a diet, exercising). The elements of the post-LTx regimen

have been grouped this way in other studies examining nonadherence.[53] We considered each self-management area as a dichotomous variable that indicated whether or not patients were nonadherent to any of the elements in that area.

5.2.3.2 Potential predictors of long-term nonadherence. We selected the variables to examine as potential predictors of long-term nonadherence based on the World Health Organization's model of nonadherence[103] and evidence from adherence research in cardiothoracic transplant populations.[53,54,68,80,98,99]

Sociodemographic characteristics and transplant-related medical factors. The original trial collected data on patients' gender, age, race/ethnicity and education at the initial interview. It also reviewed medical records to obtain data on LTx-related medical factors (e.g., LTx indication, LTx type).

Psychosocial factors. Caregiver support was measured at the baseline assessment in the original trial using the Dyadic Adjustment Scale,[104,105] which was administered to patients at the initial interview to assess the quality of the patient-caregiver relationship. Because scores on this instrument were highly skewed, we dichotomized responses at the lowest quartile to distinguish patients with a low level of caregiver support from all other patients. Psychological distress was measured at the 1-year assessment in the original trial using the depression and anxiety subscales of the Symptom Checklist 90-Revised (SCL-90).[106] We dichotomized scores on each subscale based on whether they indicated a clinically significant symptom level, defined as >1 standard deviation above the gender-specific normative mean.[106] Because scores on each subscale were moderately and

significantly intercorrelated (r=.39, p<.001), we created a composite variable to indicate whether or not patients experienced clinically significant symptoms of either depression or anxiety.

Clinical and nonadherence outcomes at 1 year. The original trial reviewed medical records to ascertain whether patients experienced any acute rejection episodes graded ≥A2 for the duration of the original 12-month trial. The original trial also assessed nonadherence using the Health Habits Survey at 2, 6 and 12-months post-LTx. The same procedures for determining nonadherence for each element and reconciling discrepant patient and caregiver reports were used. Six patients were missing data from the 12-month assessment but had completed the 2- and 6-month assessments; in order to include them in the analyses of predictors of nonadherence in the long-term study, these missing 12-month values were imputed by carrying the value ascertained in the 6-month assessment forward. Five patients were missing adherence data from more than one assessment and were excluded. We constructed variables to represent nonadherence at the 12-month assessment to the overall regimen and to each of the four self-management areas (i.e., taking medications, performing home spirometry, clinical follow-up and home self-care) using the same approach as that employed to examine nonadherence at follow-up.

5.2.3.3 Potential correlates of long-term nonadherence. We examined patient reports of caregiver support and psychological distress at the long-term follow-up as potential correlates of long-term nonadherence. We assessed caregiver support using the Dyadic Adjustment Scale and psychological distress using the SCL-90-R. Both variables were handled as described above. We

also examined presence of a caregiver as a potential correlate. We determined that a caregiver was present if the patient reported that s/he relied on a family member or friend to assist with daily care. In the original trial, all patients had a caregiver (this is a requirement for transplantation); however, not all patients had a caregiver at the time of follow-up because they may have become self-sufficient with respect to their daily care or their family situations may have changed.

Current self-monitoring practices. We asked all patients who reported that they self-monitored spirometry or vital signs (i.e., blood pressure, temperature and weight) how they recorded the values. For descriptive purposes, we categorized the open-ended responses to this question into the following categories: (a) paper log; (b) electronic system (including apps or online programs accessed on a smartphone or tablet, or documents or spreadsheets saved on a computer, phone or tablet); (c) Pocket PATH; automatic recording by the self-monitoring instrument (e.g., blood pressure cuff or digital thermometer); or (d) does not record. We also asked all patients assigned to Pocket PATH whether and how they continued to use it.

5.2.4 Statistical analysis

We used descriptive statistics (i.e., χ^2 or Fisher exact tests for dichotomous variables and t tests or Mann-Whitney rank-sum tests for continuous variables) to examine baseline differences between groups. To compare nonadherence between groups at the long-term follow-up, we used χ^2 or Fisher exact tests to compare proportions of each group that were nonadherent to each element of the regimen and t tests to compare each group's overall level of nonadherence (i.e., the number of elements to which patients were nonadherent). We adjusted for differences in time elapsed since

LTx using logistic and linear regression, respectively. We also compared nonadherence rates at both timepoints using McNemar's test (with the exact binomial test as applicable) and paired t tests.

We examined potential risk factors and correlates of long-term nonadherence in separate analyses to maintain temporal consistency with respect to when the variables were measured (i.e., risk factors were measured prior to the follow-up whereas correlates were measured at the time of follow-up). We examined associations with the overall regimen using linear regression and with each of the four self-management areas using logistic regression. We ensured that all variables tested met analytic assumptions and that our final models maintained an observation-to-variable ratio within the recommendations of 10:1.[65]

We also examined descriptive data about how patients recorded their self-monitoring data. To explore the impact of intervention assignment on recording, we used descriptive statistics to compare proportions of each intervention group that recorded the data they self-monitored using various recording methods.

Statistical significance for all tests was considered a 2-tailed $p<.05$. Analyses were conducted with STATA Version 13.

5.3 RESULTS

5.3.1 Patient characteristics

Table 3 shows the baseline characteristics and 1-year outcomes of the 104 LTxRs who completed the long-term follow-up. Our sample is similar to the international population of LTxRs transplanted during the same time period in terms of demographics, LTx indication and type of transplant.[7] At the time of long-term follow-up, median time since transplant was 4.2 years (range, 2.8 to 5.7). The intervention and usual care groups in our sample were similar with respect to most baseline characteristics; the only exception was consistent with baseline group differences observed in the original trial, in that the usual care group had a longer length of stay following the LTx surgery than the Pocket PATH group (Table 5). Both groups were balanced in terms of 1-year clinical outcomes (Table 5).

5.3.2 Cross-sectional nonadherence rates at the long-term follow-up

Our primary goal was to compare rates of nonadherence between the Pocket PATH (intervention) and usual care groups at the long-term follow-up. Table 6 shows the proportions of patients in each study group who were nonadherent to each element of the post-LTx regimen at the long-term follow-up. Rates of nonadherence varied widely between elements, ranging from nearly zero for missing labwork to nearly 90% for monitoring vital signs. In addition, groups had an equivalent level of overall nonadherence at the long-term follow-up (mean number of elements to which LTxRs were nonadherent ± SD, 2.9 ± 1.6 in Pocket PATH vs. 3.1 ± 1.2 in usual care, p=.517).

Table 5. Baseline characteristics of the 104 lung transplant recipients who completed the follow-up assessment

Characteristic	Pocket PATH (n=47) % (No.)	Usual Care (n=57) % (No.)	p value
Sociodemographics			
Age at transplant, mean (SD), y	56 ± 12	56 ± 14	.842
Men	49 (23)	60 (34)	.275
White race	94 (44)	91 (52)	.454
Married (at the time of LTx)	70 (33)	68 (39)	.844
Transplant-related			
Transplant indication			
COPD (non-α-1-antitrypsin deficiency)	47 (22)	28 (16)	.125
Pulmonary fibrosis	17 (8)	32 (18)	
Cystic fibrosis	13 (6)	18 (10)	
Other	23 (11)	23 (13)	
Double lung transplant	91 (43)	89 (51)	.729
Length of stay for transplant surgery, median (IQR), days	24 (15 – 38)	31 (20 – 46)	.021*
Computer use characteristics			
Previous computer use	87 (41)	81 (46)	.370
Previous handheld device use	17 (8)	23 (13)	.498
Outcomes during first year after transplant			
Satisfaction with assigned tracking method, mean (SD)[a]	1.7 ± .98	2.1 ± 1.2	.062
Re-hospitalization days, median (IQR)	12 (3 – 32)	8 (3 – 21)	.577
≥1 episode of A2 or greater rejection in year 1	70 (33)	63 (36)	.449
Health Habits Assessment at 2m, mean (SD), no. elements[b]	8.0 ± 1.0	7.7 ± 1.1	.172
Health Habits Assessment at 6m, mean (SD), no. elements[c]	7.9 ± 1.2	7.2 ± 1.3	.019*
Health Habits Assessment at 12m, mean (SD), no. elements[d]	7.2 ± 1.4	6.7 ± 1.4	.048*
Outcomes after year 1			
BOS	21 (10)	32 (18)	.238
Time to long-term assessment, mean, SD,y post-LTx	4.2 ± .9	4.2 ± .8	.657

*p<.05
[a]n=93; score ranges from 1-7, with lower scores indicating higher satisfaction
[b]n=101; [c]n=97; [d]n=93

We also considered whether time since LTx was related to nonadherence at follow-up. However, even after adjusting for time since LTx, all but one of the relationships between group assignment and nonadherence to the overall regimen or to any individual element were unchanged (all p's>.05). The exception was tobacco use, for which there was an increased odds of nonadherence associated with time (OR=7.4, 95% CI 1.3,43.7, p=.027); however, the small sample of five patients who reported smoking precludes sound interpretation of these odds.

5.3.3 Comparison of nonadherence rates at the 1-year assessment and long-term follow-up

We compared proportions of patients in each study group who were nonadherent at the 1-year assessment and the long-term follow-up to determine whether nonadherence rates had changed since the end of the original trial. Table 6 shows proportions of patients in each study group who were nonadherent to each element of the post-LTx regimen at both time points.

Although both groups had similar rates of nonadherence to each element at the long-term assessment, at the 1-year assessment, the Pocket PATH group had a lower rate of nonadherence for monitoring vitals (57% vs. 84%, p=.003) and a trend toward lower nonadherence for performing spirometry (52% vs. 71%, p=.057). In addition, the Pocket PATH group had lower nonadherence to the overall regimen at the 1-year assessment (mean ± SD, 1.5 ± 1.4 vs. 2.2 ± 1.5, p=.018). Rates of nonadherence for all but two elements (getting labwork and following a diet) increased at the long-term follow-up relative to the 1-year assessment in the Pocket PATH group (Table 6).

For the sample as a whole, nonadherence was higher at the long-term follow-up than at the 1-year assessment for the elements of attending clinic appointments (McNemar's χ^2=31.0, p<.001), spirometry (McNemar's χ^2=9.3, p=.002), monitoring vitals (McNemar's χ^2=5.8, p=.027) and exercise (McNemar's χ^2=17.2, p<.001). There was no difference in nonadherence between the two assessments for the other elements of the regimen (all p's >.05) (Table 7).

Table 6. Cross-sectional rates of nonadherence to elements of the post-lung transplant regimen at the 12-month assessment and the long-term follow-up by intervention assignment[a]

	Long-term follow-up[b]					12-month assessment[c]				
	PPATH N=44		Usual care N=55			PPATH N=47		Usual care N=57		
Elements of the post-LTx regimen	**%**	**(No.)**	**%**	**(No.)**	**p**	**%**	**(No.)**	**%**	**(No.)**	**p**
Primary immunosuppressant medication (missed > once per month)	9	(4)	18	(10)	.179	5	(2)	9	(5)	.381
Non-immunosuppressant medications (missed > once per month)	20	(9)	26	(15)	.388	9	(4)	18	(10)	.197
Clinic appointments (missed ≥1 visit)	40	(19)	26	(15)	.127	0	(0)	2	(1)	.369
Labwork (missed ≥1 appointment)	0	(0)	2	(1)	.357	7	(3)	2	(1)	.209
Spirometry (< several times per week)	81	(38)	84	(47)	.682	52	(23)	71	(39)	.057
Monitoring vitals (< several times per week)	86	(30)	90	(45)	.546	57	(25)	84	(46)	.003
Diet (went off diet at least occasionally)	13	(6)	20	(11)	.349	18	(8)	18	(10)	1.0
Exercise (≤ once per week)	57	(27)	56	(32)	.894	25	(11)	29	(16)	.650
Tobacco use (any)	6	(3)	4	(2)	.495	2	(1)	0	(0)	.261
Number of nonadherent elements, mean ± SD	2.9 ± 1.6		3.1 ± 1.2		.517	1.5 ± 1.4		2.2 ± 1.5		.018

[a] χ^2 tests examined differences in nonadherence to each element between intervention assignment groups, and t tests examined differences in nonadherence to the overall regimen (measured as the number of elements to which patients were nonadherent) between intervention assignment groups.
[b] The sample included the 104 patients who completed the long-term follow-up assessment.
[c] The sample included 99 patients who had data for both 1-year and long-term assessments.

Table 7. Cross-sectional rates of nonadherence to elements of the post-lung transplant regimen at the 12-month assessment and the long-term follow-up for the entire sample

	Long-term follow-up[a]		12-month assessment[b]		McNemar's	
Elements of the post-LTx regimen	**%**	**(No.)**	**%**	**(No.)**	**χ^2**	**p**
Primary immunosuppressant medication (missed > once per month)	14	(14)	7	(7)	2.27	.227
Non-immunosuppressant medications (missed > once per month)	24	(24)	13	(14)	1.96	.161
Clinic appointments (missed ≥1 visit)	34	(34)	1	(1)	31.00	<.001
Labwork (missed ≥1 appointment)	1	(1)	4	(4)	1.80	.375
Spirometry (< several times per week)	86	(85)	60	(62)	9.26	.002
Monitoring vitals (< several times per week)	76	(75)	68	(71)	5.76	.027
Diet (went off diet at least occasionally)	27	(17)	17	(18)	0.18	.670
Exercise (≤ once per week)	60	(59)	26	(27)	17.16	<.001
Tobacco use (any)	5	(5)	1	(1)	4.00	.125

[a] The sample included the 104 patients who completed the long-term follow-up assessment.
[b] The sample included 99 patients who had data for both 1-year and long-term assessments.

5.3.4 Risk factors for and correlates of long-term nonadherence

Table 8 shows the variables we examined as risk factors for long-term nonadherence and their respective associations with the nonadherence outcomes (i.e., nonadherence to the entire regimen and nonadherence to each of the four self-management areas). Each analysis included a variable to represent 1-year nonadherence to the same group of elements as those that comprised the given outcome. Table 8 shows that sociodemographic characteristics, psychosocial factors and 1-year clinical outcomes did not predict risk for nonadherence to the overall regimen or to any of the four self-management areas. Nonadherence at 1 year predicted higher long-term nonadherence to the overall regimen (β=.30, 95% CI .10 to .51, p=.004) and to the home self-care area (OR=4.33, 95% CI 1.03 to 18.21, p=.045). Moreover, when adjusting for potential risk factors, assignment to Pocket PATH reduced the odds of nonadherence to the home self-care area at long-term follow-up (OR=.17, 95% CI .04 to .74, p=.019).

Table 9 shows the variables we examined as correlates of long-term nonadherence. Clinically significant psychological distress was associated with higher long-term nonadherence to the overall regimen (β=.76, 95% CI .21 to 1.32, p=.008) and increased odds of nonadherence to clinical follow-up (OR=2.56, 95% CI 1.08 to 6.05, p=.033). Having an identified family caregiver was not associated with any of the nonadherence outcomes. Sensitivity analyses showed that the quality of recipients' relationship with their caregiver (if they had one) was not associated with any of the outcomes, either. Assignment to Pocket PATH was associated with reduced odds of nonadherence to home self-care (OR=.14, 95% CI .04 to .56, p=.005) when adjusting for potential correlates.

Table 8. Regression analyses examining potential risk factors for long-term nonadherence[a]

	% or mean ± SD for sample	Entire regimen		Taking medications		Performing spirometry		Clinical follow-up care		Home self-care	
		β	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Potential risk factors											
Age at LTx, years	55±13	.001	-.02,.03	1.01	.97,1.05	.97	.92,1.02	.99	.95,1.02	.99	.94,1.04
Caregiver support, lowest quartile on DAS	22	.32	-.40,1.04	1.01	.26,3.93	2.08	.39,11.24	1.02	.31,3.37	2.65	.27,25.42
Acute rejection, ≥1 episode graded ≥A2 during year 1	66	.37	-.21,.94	1.52	.49,4.71	2.59	.76,8.85	.43	.16,1.15	3.91	.97,15.74
Psychological distress at 1 year, clinically significant	40	.23	-.36,.83	1.00	.32,3.14	1.16	.34,3.95	2.16	.79,5.89	.85	.20,3.63
Nonadherence at 1 year[b]	1.9±1.5	.30**	.10,.51	3.51	.94,13.08	1.41	.44,4.53	.53	.05,6.16	4.33*	1.03,18.21
Time since transplant, years	4.2±.8	.27	-.07,.60	1.57	.81,3.03	1.61	.78,3.32	.88	.49,1.60	1.17	.53,2.56
Group assignment, PPATH	45	.01	-.56,.60	.86	.29,2.56	.78	.25,2.44	2.12	.81,5.56	.17*	.04,.74
Adjusted R^2 or pseudo R^2		.094		.063		.083		.071		.232	

[a] Linear regression was used to examine nonadherence to the entire regimen, while logistic regression was used to examine presence or absence of nonadherence to each of the 4 areas of the regimen. Regressions were based on the sample of n=93 for whom we had complete data (missing data included n=11 for psychological distress). The associations of potential risk factors (shown in this table) were examined in separate regressions from potential correlates (shown in Table 9).

[b] Each analysis included a different variable to indicate nonadherence at 1 year that was consistent with the given outcome. 1-year nonadherence variables were constructed the same way as the respective outcomes using data from the 12-month assessment.

*p<.05, **p<.01

Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; LTx, lung transplant DAS, Dyadic Adjustment Scale, PPATH, Pocket PATH

Table 9. Regression analyses examining potential correlates of long-term nonadherence[a]

	% or mean ± SD for sample	Entire regimen		Taking medications		Performing spirometry		Clinical follow-up care		Home self-care	
		β	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Potential risk factors											
Psychological distress at follow-up, clinically significant	37	.76**	.21,1.32	1.80	.71,4.54	1.66	.54,5.14	2.56*	1.08,6.05	2.06	.56,7.63
Presence of a caregiver at follow-up, yes	78	-.04	-.66,.59	1.02	.34,3.02	1.11	.34,3.59	.89	.34,2.35	.72	.19,2.71
Time since transplant, years	4.2±.8	.03	-.29,.36	1.08	.62,1.89	1.18	.64,2.20	.97	.58,1.61	.67	.34,1.34
Group assignment, PPATH	45	-.18	-.73,.37	.61	.23,1.59	.84	.29,2.40	1.78	.75,4.22	.14**	.04,.56
Adjusted R^2 or pseudo R^2		.039		.025		.015		.050		.134	

[a] Regressions examining nonadherence to the entire regimen (continuous outcome) were multivariate linear regressions, while regressions examining nonadherence to each of the 4 areas of the regimen (dichotomous outcomes) were multivariate logistic regressions. Regressions were based on the entire sample of 104 patients that completed the long-term follow-up. The associations of potential correlates (shown in this table) were examined in separate regressions from potential risk factors (shown in Table 8).
*p<.05, **p<.01
Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; LTx, lung transplant DAS, Dyadic Adjustment Scale, PPATH, Pocket PATH

5.3.5 Use of Pocket Path at the long-term follow-up

At the long-term follow-up, two of 47 patients were still using Pocket PATH. Both of these patients were more than 5.4 years post-LTx. One patient used the medication-taking reminder feature of Pocket PATH, while the other used Pocket PATH to record spirometry, blood pressure, temperature and weight.

5.3.6 Recording of self-monitoring data at the long-term follow-up

Figure 5.1 shows the numbers of patients who currently self-monitor spirometry, blood pressure, temperature or weight, and the method they use to record these data. For spirometry, blood pressure and temperature, approximately one-third of patients do not record the data they monitor, while

nearly 60% of patients who monitor weight do not record it (Figure 5.1). These proportions did not differ by intervention assignment (all p's >.05). The most common method of recording self-monitoring data is a paper log (Figure 5.1). Small numbers of patients use an electronic system (including apps, websites and computer-, tablet- and phone-based logs) or rely on the automatic data-saving function of the self-monitoring instrument itself to save data (e.g., electronic blood pressure cuff or digital thermometer).

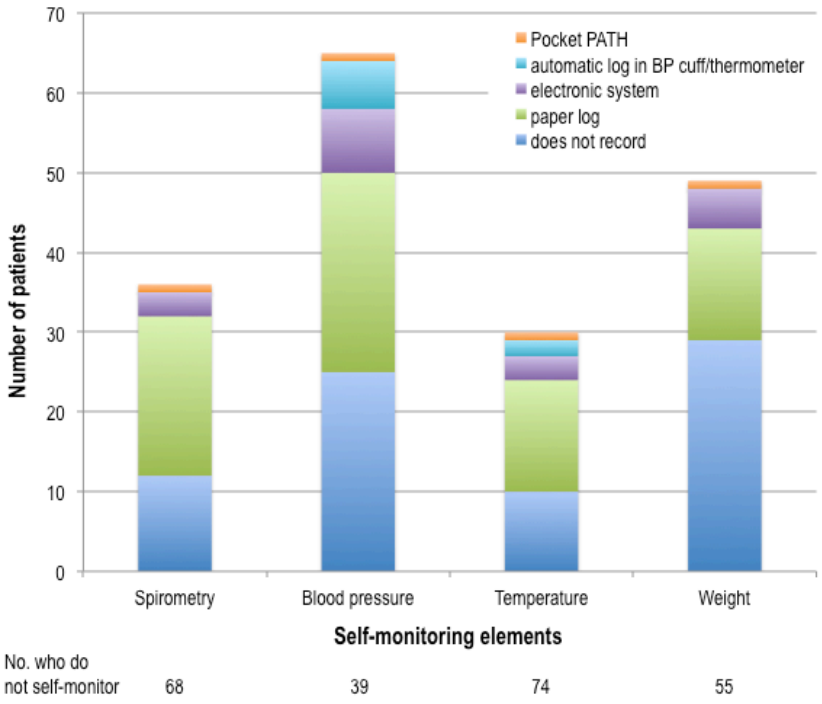


Figure 5. Methods of recording self-monitoring data among lung transplant recipients who completed the follow-up assessment. Each bar represents the number of patients who currently record each self-monitoring element using various methods: Pocket PATH (orange bar), automatic log in blood pressure cuff or thermometer (turquoise bar), electronic (i.e., computer-, internet- or smartphone-based) system (purple bar), paper log (green bar), does not record (blue bar). Abbreviation: BP, blood pressure

5.4 DISCUSSION

The recent explosion of mHealth has left today's medical landscape in a unique situation: mHealth interventions are being created and disseminated faster than science can evaluate them. As a result, many patients may be relying on mHealth interventions that may ultimately be ineffective. Our study makes an important contribution to the mHealth literature because it is one of the first to rigorously evaluate the long-term effectiveness of an mHealth intervention. This intervention, the Pocket PATH app for LTxRs, was associated with short-term reductions in nonadherence relative to usual care during the first year after LTx.[55] However, our long-term follow-up study showed that these short-term benefits were generally not sustained into the long-term. Yet, when we considered the regimen as four groups of related elements rather than as nine individual elements, adjusted analyses indicated that patients who received Pocket PATH had lower odds of nonadherence to performing home self-care tasks (self-monitoring vital signs, following a diet, exercising) at the long-term follow-up.

The finding that Pocket PATH's early benefits were largely not sustained may be explained by the small number of LTxRs who continued using the device. Only two LTxRs still used Pocket PATH at the long-term follow-up, one to record self-monitoring values and the other for medication-taking reminders. While disappointing in terms of absolute numbers, this may be representative of the natural course of declining patient engagement that has been observed with other mHealth technologies.[88,94] The reasons for this engagement decline may be somewhat paradoxical: patients might stop using these technologies because (a) they are not effective or (b) they are so effective that patients no longer need them to carry out the behaviors targeted by the technologies. Our data suggest that this second hypothesis is not true: if it were, we would expect nonadherence to be lower in the Pocket PATH group than in the usual care group because strong

adherence habits would have been sustained to the long-term follow-up. On the other hand, some LTxRs might have stopped using Pocket PATH because their self-management needs changed over time and Pocket PATH no longer met these new needs. Alternatively, the small number of sustained Pocket PATH users may reflect the post-trial procedures in the original trial. Although LTxRs were given the Pocket PATH device to keep and told that they could continue using the device to record and view trends for as long they desired, the data plan that allowed Pocket PATH to run its clinical decision support feature was not continued. For some patients, Pocket PATH may have lost its utility without this feature.

Another explanation for Pocket PATH's general lack of sustained benefit is related to whether using Pocket PATH in the short-term created lasting habits. The finding that LTxRs who received Pocket PATH were more adherent to performing home self-care tasks than recipients who received usual care suggests that, for these elements at least, Pocket PATH may have facilitated habit formation. It is not surprising that this was not the case for the majority of elements of the regimen, as health behavior models suggest that consistent reinforcement may be necessary for sustaining habits facilitated by mHealth interventions.[107] Alternatively, anecdotal evidence suggests that patients' opinions on the need for self-management may have changed over time, with less value placed on self-management in the long-term than in the immediate post-LTx period. For these patients, a lower perceived importance of self-management may be a stronger driver of long-term nonadherence than poor habit formation in the short-term.

Regardless of the mechanism, our study indicates that nonadherence in the long-term is a problem. Rates of nonadherence were unacceptably high for two of the most important elements of the regimen – taking the primary immunosuppressant (14%) and spirometry (86%). Nonadherence to both of these elements is associated with chronic rejection, which becomes an

increasing concern as patients progress farther post-LTx. Moreover, although only 2% of LTxRs were nonadherent to getting labwork, over one-third missed clinic appointments, which indicates that LTxRs are experiencing gaps in their care at a time in which consistent follow-up is critical.

Another aim of this study was to identify predictors and correlates of long-term nonadherence. To this end, we found that nonadherence during the first year post-LTx and concurrent psychological distress, respectively, were the only factors that were significantly associated with long-term nonadherence. The relationship between past behavior and future behavior has been demonstrated in many health scenarios, including recent data showing that pre-LTx nonadherence predicts post-LTx nonadherence.[54] These links suggest that efforts to minimize nonadherence must be implemented early on and sustained in order to have the greatest impact on reducing nonadherence. Moreover, although the relationship between perioperative psychological distress and nonadherence in the short-term has been described previously in heart and liver transplant recipients,[99,108] our study presents the first data in LTxRs to indicate a link between concurrent psychological distress and nonadherence. Given that both psychological distress and nonadherence have been shown to be associated with poor clinical outcomes, these findings suggest that screening and intervention in both of these areas during the longer-term post-LTx years may have a role in improving outcomes.

Our study had several limitations. First, we were unable to examine differences in nonadherence based on duration of Pocket PATH use. Because Pocket PATH no longer uploaded use data to the study website once the trial ended, we attempted to obtain information about duration of Pocket PATH use from participants; however, we found that recall was poor over such a long-term period. We also found that many participants did not understand that they were able to continue using Pocket PATH beyond the original study. Thus, even though there appeared to be

wide variations in how and how often LTxRs in the Pocket PATH group reported continuing to use the device, we were unable to conduct analyses based on intensity or duration of Pocket PATH use. Moreover, since we analyzed participants in the group to which they were originally assigned, our analyses could not capture the impact of using alternative tracking methods beyond the Pocket PATH trial. Future work should investigate the impact of different intensities, durations and types of Pocket PATH use and reasons for abandonment in order to gain a better understanding of how to encourage use that leads to long-term adherence. Lastly, we did not explore whether changes in insurance coverage since the original trial impacted long-term nonadherence. Cost-related immunosuppression nonadherence has been identified as a barrier to adherence in LTxRs[53] and kidney transplant recipients,[109] and similar interruptions in insurance coverage in LTxRs may have contributed to the high rates of nonadherence to medications observed in our sample.

Ultimately, this work provides lessons for optimizing the effects of mHealth interventions. Most importantly, sustaining a short-term benefit over the long-term likely requires consistent reinforcement. Future research should explore the configuration and impact of booster sessions, including such issues as booster session mode of delivery (e.g., electronic vs. in person) and frequency. Future work would also benefit from qualitative research that explores patients' beliefs about the importance of long-term self-management in order to understand how to adapt mHealth interventions so that they remain relevant and useful to patients. Additionally, broadening the scope of mHealth interventions so that they target psychosocial factors in addition to nonadherence that have been shown to impact clinical outcomes, may increase their impact even further. For instance, our finding that psychological distress is associated with long-term nonadherence suggests that LTxRs using mHealth interventions over the long-term might benefit from psychological screening and intervention as well as self-management assistance. The field of

mHealth offers limitless possibilities to target various elements of health and wellness in a single program or device, such as nonadherence and psychological symptoms. However, the field as a whole must also develop a commitment to rigorous and ongoing evaluation. It is this combination of technological innovation and evidence-based medicine that will allow mHealth to reach its full potential to improve health.

6.0 CONCLUSION

The papers in this dissertation work toward the goal of identifying and intervening on modifiable risk factors in LTx. The need for evidence on modifiable risk factors is pressing given that, despite many recent medical advances, long-term LTx outcomes remain poor. In order to minimize the many complications that typify the post-transplant course, cross-disciplinary work in such areas as surgery, immunology, infectious disease and, our focus, psychiatry and behavioral medicine is needed. These latter fields have the unique ability to identify risk factors that can be attenuated with psychosocial intervention and therefore play a critical role in improving outcomes for this medically complex population.

Overall, our findings reinforce the need for continuous psychosocial screening and intervention to target modifiable risk factors after LTx. In Paper 1, we identified depression during the first year after LTx – a potentially modifiable risk factor because effective treatments exist – as a predictor of mortality, chronic rejection and graft loss over a 15-year post-transplant period. We did not find any evidence that pre-transplant depression or pre- or post-transplant anxiety were associated with these outcomes. In Paper 2, we identified the clinical decision support feature of Pocket PATH as the intervention component that may be responsible for its indirect effect on improving longer-term mortality. Taken together, the findings from Papers 1 and 2 suggest that the year after LTx is a critical time for taking action to improve long-term health. Finally, in Paper 3, we showed that Pocket PATH's improvements in self-management during the first year after LTx were not sustained into the long-term. Despite this, however, we also showed that LTxRs who were assigned to Pocket PATH were more likely than LTxRs assigned to usual care to perform tasks in the home self-care area of the post-LTx regimen.

mHealth technologies represent an exciting intervention method that is feasible to implement during (and beyond) this important first year. Lessons learned from our work and others' can help refine the next generation of mHealth. Here, we briefly outline areas of consideration in the development, design, implementation and evaluation of mHealth technologies for increasing patients' involvement in their healthcare.

Development: engage patients and stakeholders early on. Ultimately, "[s]uccess [of mHealth technologies] is defined by the degree to which these devices and services make a long-term impact on their users' health and happiness."[94] This type of impact can only be achieved with the early and sustained input of patients, clinicians and healthcare system leaders.[110] Approaches to engaging all of these stakeholders, while still works in progress, have been outlined by the Patient Centered Outcomes Research Institute[111,112] and in recent reviews.[113,114] With these approaches, technology developers increase their likelihood of designing products that are relevant, useful and feasible to implement – all of which are necessary for a technology to impact patients' lives.

Design: adopt the most current technologies to create "pushy" one-stop-shops. In many ways, patients have a more seamless view of their medical experience than the compartmentalized approach in which most healthcare is provided and studied. The same can be said for many of the existing apps for patients with chronic illness, which have tended to focus on single elements of self-management rather than the entire self-management regimen or patients' social experience of living with their illness.[79] Patients' desires for practical mHealth technologies that integrate their many healthcare needs into a single program are evident in several studies of transplant populations that explored patient perspectives on mHealth. These studies show that patients are interested in apps that: reduce the time burdens of self-management by automating

repeated tasks such as pharmacy refills and insurance updating; integrate with other smartphone functions such as alarms, physical activity monitoring and calendars; integrate with digital instruments that can link to smartphones such as blood pressure cuffs and peak flow meters; enhance communication with the medical team for responding to clinical questions and making medication adjustments; facilitate social networking with others with their disease; and can be customized to meet individual health goals.[115,116] It is encouraging that patients express interest in "push" factors, since these have been shown to increase app effectiveness in chronic illness[90,92] and lung transplant populations,[91,92,117] including the Pocket PATH follow-up cohort (Paper 3). By integrating new sensing technologies that can retrieve and instantly process behavioral, physiological and contextual data, push factors make it possible to deliver "just-in-time" interventions that can initiate preventive or clinical action faster than has been possible ever before.[78] Finally, given the quick pace of technology change, researchers developing mHealth technologies should partner with app developers using open-source platforms to prevent their programs from becoming "outdated, obsolete, and clinically ineffective."[115]

Implementation: reinforce use of mHealth technologies regularly. Our data (Paper 2) and others'[88,94] show that discontinuing use of an mHealth technology after six months to one year is the rule, not the exception. This is problematic because, unless a technology's effect is strong enough to result in permanent behavior change, a technology must be used in order for it to sustain its effect. Automated event detection and clinical decision support systems are one form of reinforcement, as patients must use the technology in order to benefit from these features. Enlisting clinicians in reinforcing patients' use of mHealth technologies may also increase mHealth's effectiveness, especially if providers discuss the technology with patients during or between clinic visits. Anecdotal evidence from our Pocket PATH follow-up cohort suggests that patients are more

willing to use an app to self-monitor if their clinicians ask to see their self-monitoring data at clinic visits or send them feedback on the data they self-monitor between visits. If the technology is not conducive to being incorporated into clinical care, clinical programs should consider implementing booster sessions to re-engage patients who have discontinued use and celebrate the engagement of sustained users.

Evaluation: be attuned to unique considerations in trial design. Designing a relevant clinical trial to evaluate an mHealth intervention presents several unique challenges. First, because mHealth technologies are so readily available to patients commercially, patients in the usual care comparison condition may not necessarily be using the usual care (i.e., the paper-and-pencil tracking logs given to them by the transplant program) exclusively. This raises the potential for misclassification bias: if participants are assigned to a paper-and-pencil comparison group but are actually using a commercial mHealth intervention that is more effective than paper-and-pencil logs, the intervention's effect size may be underestimated. mHealth intervention trials should consider stratifying participants based on whether they already use an mHealth technology or, at the very least, conducting subgroup analyses based on participants' use of mHealth technologies outside of the study. Second, researchers should consider whether their sample should include all patients with the condition of interest or only the subsample of patients at high risk for poor self-management.[87] Although restricting the sample to a high risk subset would likely require a larger sample to reach adequate statistical power, this strategy may reflect a more feasible approach to "real world" implementation of mHealth technologies, particularly in settings with limited resources. Third, researchers should develop a metric for intensity of intervention use and then conduct per-protocol-like analyses that group participants based on this metric. These analyses would help determine whether a dose-response relationship exists for mHealth technologies, which

will be important for counseling patients about how to adequately use these technologies. Finally, participant observation periods in trials of mHealth interventions must be long enough to capture the duration over which participants' use naturally waxes and wanes. This information will be important for designing the next generation of technologies and determining when to provide booster sessions to reinforce technology use.

Ultimately, mHealth technologies have limitless potential to impact health, not only for LTxRs but also for the growing number of individuals who suffer from chronic illnesses. mHealth's ability to target multiple areas of disease management and integrate seamlessly into an individual's daily life makes it uniquely suited to chronic disease management. mHealth technologies are also well suited to the recent movement to increase and improve communication between patients and providers, given mHealth's ability to integrate seamlessly into patient portals and electronic health records. However, mHealth technologies must develop an evidence base before they can be considered safe and effective. Thus, the mHealth field must switch its focus from demonstrating its versatility and reach to evaluating its impact. It is only through this interdisciplinary approach that mHealth will be able to achieve its full potential.

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