# ADHERENCE TO THE POST-TRANSPLANT MEDICAL REGIMEN IN LUNG TRANSPLANT RECIPIENTS

by

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## ABSTRACT

## ADHERENCE TO THE POST-TRANSPLANT MEDICAL REGIMEN IN LUNG TRANSPLANT RECIPIENTS

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Adherence to the post-transplant medical regimen could maximize outcomes in lung transplant recipients (LTRs). This dissertation addresses three major gaps in the LTR adherence literature: 1) the need to synthesize evidence on adherence to medical regimen, 2) a lack of evidence concerning longitudinal patterns and correlates of adherence to self-monitoring, a challenging issue for LTRs, and 3) the need to understand longitudinal patterns and correlates of self-care agency (SCA, one's willingness and ability to perform self-care), a potentially important theoretical construct for adherence.

Study 1. To synthesize the current state of science on adherence in LTRs, a systematic review was conducted. Findings indicated that nonadherence rates varied greatly across the elements of the regimen and between studies, and could not be consistently attributed to any single factor. Effect sizes of interventions designed to promote adherence ranged from .05 to .45. There was a weak correlation between nonadherence to home spirometry and patient mortality.

Study 2. To better understand longitudinal patterns and correlates of SCA, a trajectory analysis was conducted. Findings revealed 3 patterns for SCA: *persistently low*, *persistently moderate,* and *persistently high*. Requiring re-intubation post-transplant (p=.043), discharged to a facility rather than home (p=.048), and endorsing a higher baseline anxiety level (p=.001) were associated with membership in the *persistently low*

*SCA* group. Higher anxiety and depression levels were associated with memberships in the *persistently moderate* and *persistently low SCA* groups over 12-months (*p*s<.05).

Study 3. To advance the field's understanding of patterns and correlates of adherence to self-monitoring, a trajectory analysis was performed. Findings revealed two patterns of adherence to self-monitoring: *moderately adherent with slow decline* and *persistently nonadherent*. Baseline correlates for being *persistently nonadherent* included female gender (p=.035), higher anxiety (p=.008), and lower sense of personal control over health (p=.005). Lower physical component scores of quality of life over 12 months were associated with membership in the *persistently nonadherent* group (p=.004).

This dissertation points to the need for more strategies to promote and sustain adherence over time in LTRs. Future interventions should target reducing psychological distress and reinforcing the sense of control over one's health in LTRs.

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# PREFACE

As the old saying goes, Rome wasn't built in a day. I think pursuing a PhD requires effort, time, perseverance, and mostly importantly, support from many individuals. I would like to take this opportunity to express my gratitude to those who played a key role in my PhD journey. First, I would like to sincerely thank every member of my dissertation committee for their helpful feedback, unconditional mentoring, and continuous support along my PhD journey. Thank you to Dr. Jennifer Lingler, my advisor and dissertation chair, for invaluable guidance and mentoring on every aspect of my predoctoral training and this dissertation study. Through participating in her NIH-funded study, she provided me with hands-on experience in various aspects of the research process, from idea conceptualization to results dissemination. Thank you to Dr. DeVito Dabbs for generously sharing data for my dissertation study and providing critical critique to my study. Thank you to Dr. Sereika for the tremendous guidance and mentoring on data analyses, data interpretation, and data presentations of the project. Thank you to Dr. Dew for providing insightful comments and generously sharing expertise in adherence behaviors among transplant population.

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Lastly, I want to thank my family, friends, and PhD fellow students, who provide invaluable support during my PhD journey. Thanks to my parents for unconditional support and sharing the joys and sorrows in my life. Thanks to my older sister, younger brother, and my boyfriend for continuous encouragement along the way. Thank you to my friends and PhD fellow students, who are very generous to share their knowledge and serve as a source of inspiration. All of you have made this journey more enjoyable!

# 1.0 INTRODUCTION

Lung transplantation is one of the most effective treatments for extending survival and improving quality of life for persons with end-stage lung diseases (Kugler et al., 2005; Rodrigue, Baz, Kanasky, & MacNaughton, 2005; Vasiliadis, Collet, & Poirier, 2006). While the first year survival rate among lung transplant recipients (LTRs) is similar to recipients of other solid organ transplants (International Society for Heart & Lung Transplantation, 2015), the 5-year survival rate for LTRs is much lower due to higher risks of complications, such as graft rejection and infection (Studer, Levy, McNeil, & Orens, 2004; Yusen et al., 2014). For example, the first year survival rate for LTRs is about 80%, compared to 85% for heart transplant recipients (International Society for Heart & Lung Transplantation, 2015; Yusen et al., 2014). Yet, for LTRs this rate is only 65% for 3-year survival and 53% for 5-year survival. In contrast, for heart transplant recipients, 5-year survival is around 70% (International Society for Heart & Lung Transplantation, 2015; Yusen et al., 2014).

To allow for early detection and prompt intervention on post-transplant complications, LTRs are expected to adhere to a complex lifelong medical regimen (De Geest et al., 2005; DeVito Dabbs et al., 2009; Dew et al., 2007; Dew, DiMartini, et al., 2008). The science of adherence to the medical regimen in the context of lung transplantation is a continuously expanding area with much potential to positively impact

post-transplant care for LTRs. However, several gaps in our understanding remain. As described in what follows, this dissertation project contributes to the science of adherence behaviors among LTRs using three complementary approaches: 1) a systematic review, 2) an analysis of self-care agency, a critical theoretical concept thought to be of importance to adherence behaviors, and 3) an analysis focusing on a particularly challenging area of adherence for LTRs, which is adherence to self-monitoring.

**Study 1.** While there is a growing body of literature on adherence behaviors among LTRs, translating this body of research to practice requires a systematic examination of the evidence. To date, one meta-analysis and two reviews have examined prevalence and risk factors of nonadherence among adult heart and lung transplant recipients (De Geest et al., 2005; Dew et al., 2007; Korb-Savoldelli et al., 2010). However, the number of studies pertaining to LTRs was few, thus limiting the ability to draw conclusions about adherence after lung transplantation. While LTRs and heart transplant recipients may share some similarities in post-transplant care given that both belong to the cardiothoracic transplant groups, there are unique challenges and barriers for LTRs to be adherent because of greater complexity of post-transplant medical regimen and higher risks for infection and graft rejection. Without a systematic review of the up-to-date evidence, it is challenging for clinicians to apply research evidence into their care for LTRs. Therefore, the first study of this dissertation project aimed to systematically review the evidence regarding the 1) prevalence of nonadherence; 2) risk factors for nonadherence; 3) impact of interventions for promoting adherence; and 4) outcomes of nonadherence, among LTRs (see Chapter 2).

While this review is a distinct study within the dissertation project, it also provides a foundation for the other two studies in this dissertation, both offering additional

justification for conducting those studies and informing the discussion of implications from their findings. I will provide such connections at the beginning of manuscripts 2 and 3 to explicitly describe how they complement this one.

**Study 2.** The second study of this dissertation project focused on a potentially important theoretical construct for adherence in LTRs, which is self-care agency (SCA). SCA is defined as one's willingness and ability to engage in self-care behaviors (Orem, 2001). The rationale for focusing on SCA was that this concept has emerged in research on other chronic diseases management as an important theoretical construct to be considered in interventions to promote adherence to medical regimen (Baker & Denyes, 2008; Dale, Söderhamn, & Söderhamn, 2012; Wang, Lau, Loo, Chow, & Thompson, 2014; Wong, Ip, Choi, & Lam, 2015), but it has received little attention in the context of LTRs. To date, only one study has described levels of SCA and examined its correlates among LTRs prior to discharge from their transplant surgery (DeVito Dabbs et al., 2013). DeVito Dabbs and colleagues (2013) found that LTRs reported higher levels of SCA than patients with other chronic diseases and suggested one possible explanation was that prior to discharge when SCA was assessed, LTRs might be overly confident about their capability to perform self-care behaviors at home. Thus, DeVito Dabbs and colleagues (2013) called for future work to explore the longitudinal patterns of SCA among LTRs. To address this gap, study 2 of this dissertation aimed to 1) describe distinct patterns of SCA and 2) identify correlates of SCA among LTRs over the first 12-months post-hospital discharge after transplant (see Chapter 3).

**Study 3.** One key issue in the field of adherence is the need for advanced approaches to understand longitudinal adherence patterns within individuals and to identify

groups of individuals with similar patterns (Dunbar-Jacob & Sereika, 2001). While this issue is beginning to receive attention with respect to medication taking among other chronic disease populations (Gonzalez et al., 2007; Greenley et al., 2015; Gueorguieva, Wu, Krystal, Donovan, & O'Malley, 2013), little is known of longitudinal patterns of adherence in the context of LTRs. The need to understand longitudinal patterns of adherence in LTRs is especially important for self-monitoring, a critical aspect of the post-transplant medical regimen that has been reported to be particularly difficult for LTRs (Dew, DiMartini, et al., 2008). Self-monitoring has been defined as "an awareness of symptoms or bodily sensations that is enhanced through periodic measurements, recordings and observations to provide information for improved self-management" (Wilde & Garvin, 2007, p. 343). In the case of LTRs, self-monitoring is expected to be performed daily and encompasses monitoring a variety of health indicators, including lung function, vital signs and a range of respiratory symptoms (Kugler et al., 2009; Kugler et al., 2010; Lindgren, Snyder, Sabati, Adam, & Finkelstein, 2002; Sabati, Snyder, Edin-Stibbe, Lindgren, & Finkelstein, 2001; Yoon et al., 2008). Adhering to these self-monitoring activities helps LTRs detect early signs and symptoms of rejection or infection and seek prompt treatment thereby minimizing if not preventing poor health outcomes (DeVito Dabbs et al., 2009; Finkelstein et al., 1999; Finkelstein et al., 2012; Kugler et al., 2009; Yoon et al., 2008). Despite evidence that rates of nonadherence to self-monitoring of lung-function are high, reaching up to 62.0% at 2-years post-transplant (Dew, DiMartini, et al., 2008; Kugler et al., 2010; Lindgren et al., 2002; Morlion, Knoop, Paiva, & Estenne, 2002; Sabati et al., 2001; Teichman, Burker, Weiner, & Egan, 2000), little is known about the patterns and correlates of adherence to self-monitoring among LTRs over time.

Therefore, the third aim of this dissertation study was to 1) describe distinct patterns of adherence to self-monitoring and 2) identify correlates of adherence to self-monitoring among LTRs over the first 12-months post-hospital discharge after transplant. We analyzed the same dataset as Study 2 and reported corresponding findings in the third manuscript of this dissertation (see Chapter 4).

The direct contribution of this dissertation project is to 1) provide an overview of current state of science regarding the adherence behaviors among LTRs and 2) expand the field's understanding of patterns and correlates of SCA and adherence to self-monitoring after lung transplantation. The knowledge gained in this study could be used to inform the development of behavioral interventions aimed at promoting self-monitoring behaviors after lung transplantation. The evidence obtained in this dissertation may also contribute to the growing body of literature on adherence to self-monitoring more generally among patients with chronic illnesses since self-monitoring is an essential component of self-management across a broad range of lung and other diseases. In line with recent calls at the national level (Ohno-Machado, 2014), this dissertation also served as an exemplar of using advanced statistical techniques to make full use of an existing dataset. Such approaches hold the potential to clarify some of the most challenging questions faced by behavioral researchers in nursing science.

The methods (including study design, sample and setting, measures, statistical analysis) for each study are described in details in each manuscript (see Chapter 2, 3, and 4). Following the three manuscripts, an integrative summary of dissertation findings is provided.

# 2.0 MANUSCRIPT 1: NONADHERENCE TO THE MEDICAL REGIMEN AFTER LUNG TRANSPLANTATION: A SYSTEMATIC REVIEW

## INTRODUCTION TO MANUSCRIPT 1

This chapter reports findings regarding the first specific aim of the dissertation work:

**Aim 1:** Systematically review the evidence regarding the 1) prevalence of nonadherence; 2) risk factors for nonadherence; 3) impact of interventions for promoting adherence; and 4) outcomes of nonadherence, among LTRs.

While the science of adherence to the medical regimen in LTRs has continuously expanded over the last few years, there is a lack of a systematic examination of published evidence on adherence after lung transplant. Without a systematic review, it is challenging for clinicians to translate evidence into their care of LTRs. Therefore, the first study of this dissertation aimed to provide an overview of the current state of science on adherence to the medical regimen in LTRs. Instead of focusing on one particular element of post-transplant medical regimen, this review examined the broad landscape of the LTR adherence literature by including reports on adherence to any element of the medical regimen among LTRs. Following on this brief introduction is the full report of manuscript 1, titled “Nonadherence to the Medical Regimen after Lung Transplantation: A Systematic Review”.

## 2.1 ABSTRACT

**Background:** Lung transplant recipients (LTRs) are required to adhere to a lifelong complex medical regimen post-transplant. While a growing number of studies have explored adherence behaviors among LTRs, translating this body of research to practice requires a systematic examination of the evidence. This study aims to systematically review evidence regarding 1) the prevalence of post-transplant regimen nonadherence (NA); 2) risk factors for NA; 3) impact of interventions for promoting adherence; and 4) transplant-related clinical outcomes of NA among LTRs.

**Method:** Following the PRISMA guideline, a literature search in 5 medical databases was conducted using key terms focusing on elements of medical regimen after lung transplant. We calculated the NA person-time incidence rates to account for different follow-up durations across studies. The effects of interventions and associations between NA and clinical outcomes were calculated.

**Results:** Thirty articles were included in this review. Together, these articles suggest that NA to the medical regimen is prevalent, varies by elements of the regimen, and is not consistently associated with any single risk factor. Intervention studies yielded a wide range of effect sizes for impact on adherence (correlation coefficients: 0.05-0.45). Articles examining the relationship between NA and patient mortality found weak correlations ranging from 0.03-0.08. Major limitations across studies were weaknesses in the methodologies for measuring NA, varying definitions of NA, lack of a theoretical basis for interventions, small sample sizes, and limited follow-up periods.

**Conclusion:** This review underscores the need for rigorous studies of risk factors and clinical outcomes of NA in LTRs and for large-scaled randomized controlled trials to examine the effects of interventions on adherence in LTRs.

## 2.2 INTRODUCTION

Lung transplantation is one of the most effective treatments for improving quality of life for persons with end-stage lung disease (Finlen Copeland, Vock, Pieper, Mark, & Palmer, 2013; Kugler et al., 2005; Kugler, Tegtbur, et al., 2010; Ortega et al., 2009; Rodrigue et al., 2005; Santana, Feeny, Jackson, Weinkauf, & Lien, 2009; Vasiliadis et al., 2006). While great success has been made in terms of short-term survival, the long-term survival rate for LTRs is less optimal (Lund et al., 2014; Yusen et al., 2014). One reason is that LTRs are at a higher risk of developing transplant-related complications (Demeo & Ginns, 2001; Studer et al., 2004).

To allow for early detection and intervention on post-transplant complications, LTRs are expected to actively engage in self-management behaviors (De Geest et al., 2005; DeVito Dabbs et al., 2009; Dew et al., 2007; Dew, DiMartini, DeVito Dabbs, et al., 2008; Finkelstein et al., 1993, 1999). These self-management behaviors include adhering to a lifelong medical regimen involving: 1) medication-taking, 2) self-monitoring of both lung function and signs and symptoms of complications, and 3) lifestyle recommendations like tobacco abstinence. Adhering to these elements of medical regimen has been widely recognized to have the potential to maximize the health outcomes among LTRs (De Geest

et al., 2005; DeVito Dabbs et al., 2009; Dew et al., 2007; Dew, DiMartini, DeVito Dabbs, et al., 2008; Finkelstein et al., 1993, 1999).

While there is a growing body of literature on adherence behaviors among LTRs, translating this body of research to practice requires a systematic examination of the evidence. To date, one meta-analysis and two reviews have examined prevalence and risk factors of nonadherence among heart transplant recipients, LTRs and heart-lung transplant recipients (De Geest et al., 2005; Dew et al., 2007; Korb-Savoldelli et al., 2010). However, most of the conclusions from those reviews pertained to heart transplant recipients as very few conclusions could be drawn regarding the LTRs population due to a limited number of published articles on LTRs at the time of those reviews. For example, in the meta-analysis by Dew and colleagues (Dew et al., 2007), only 5 articles including LTRs were identified for inclusion. This resulted in very few conclusions regarding adherence in this population.

Although LTRs may share some similarities with heart transplant recipients as both are cardiothoracic transplant groups, there are unique characteristics and challenges for LTRs to adhere to the post-transplant regimen. For example, while both groups are at risk for infection due to immunosuppression, LTRs are at particularly high risk for developing life-threatening pneumonia infections due to the direct exposure of the pulmonary graft to infectious pathogens and post-transplantation physiologic changes in mucous clearance (Remund, Best, & Egan, 2012). Thus, in addition to adhering to medication regimen, LTRs must adhere to recommendations for daily self-monitoring of pulmonary function. In order to maximize their effectiveness in educating and supporting LTRs, nurses and other

clinicians must be up to date on the scientific literature on adherence after lung transplantation.

Without a systematic review of the current evidence, it is challenging for clinicians to apply research evidence into their care for LTRs. Therefore, our goal was to systematically review the evidence regarding the 1) prevalence of nonadherence; 2) risk factors for nonadherence; 3) impact of interventions for promoting adherence; and 4) outcomes of nonadherence, among LTRs. Our rationale for including articles on outcomes of nonadherence was that although there is no doubt that post-transplant medication regimen is effective for preventing complications (Taylor, Watson, & Bradley, 2005), less is known about the strength of the relationship between nonadherence and outcomes such as mortality and morbidity.

## 2.3 METHODS

### 2.3.1 Search strategies

An electronic literature search was conducted in PubMed MEDLINE, EBSCOhost CINAHL, Ovid PsycINFO, Ovid Global Health, and EMBASE. The keywords of “lung transplant” or “lung transplantation” were paired with combinations of the terms “(non)adherence”, “(non)compliance”, “medication”, “monitoring”, “diet”, “exercise”, “alcohol drinking”, “smoking”, “tobacco use”, “substance use” and “spirometry”.

Truncation was used to ensure that both noun and verb forms of each word were captured. Databases were searched from the earliest available dates through April 1, 2015.

### 2.3.2 Inclusion and exclusion criteria

Articles included in this review met the following criteria: 1) reported LTRs' post-transplant nonadherence to any element of the medical regimen, 2) focused on adults (≥ 18 years old), 3) quantitative research study, and 4) English language. Articles were excluded if they met any of the following criteria: 1) did not report post-transplant nonadherence for adult LTRs, 2) case study, 3) clinical guideline, 4) conference abstract or proceeding, 5) commentary or qualitative study, and 6) review article.

### 2.3.3 Data extraction for review

This project was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009). Each article was screened by at least two independent reviewers and if any discrepancies occurred, two reviewers discussed and reached an agreement on whether to include the article or not. If no agreement was reached, further consultation was sought from the content experts on the team (M.A.D., A.D.D.). The screening processes are reported in Figure 1. Key information from each article was extracted, including the first author, year, sample size, definitions and measures of adherence and findings. We assessed the quality of each article using the level of evidence by the Agency for Healthcare Research and Quality (West et al., 2002). A summary of key

characteristics for each article, organized by the aims of this review, is displayed in Tables 1, 2, and 3.

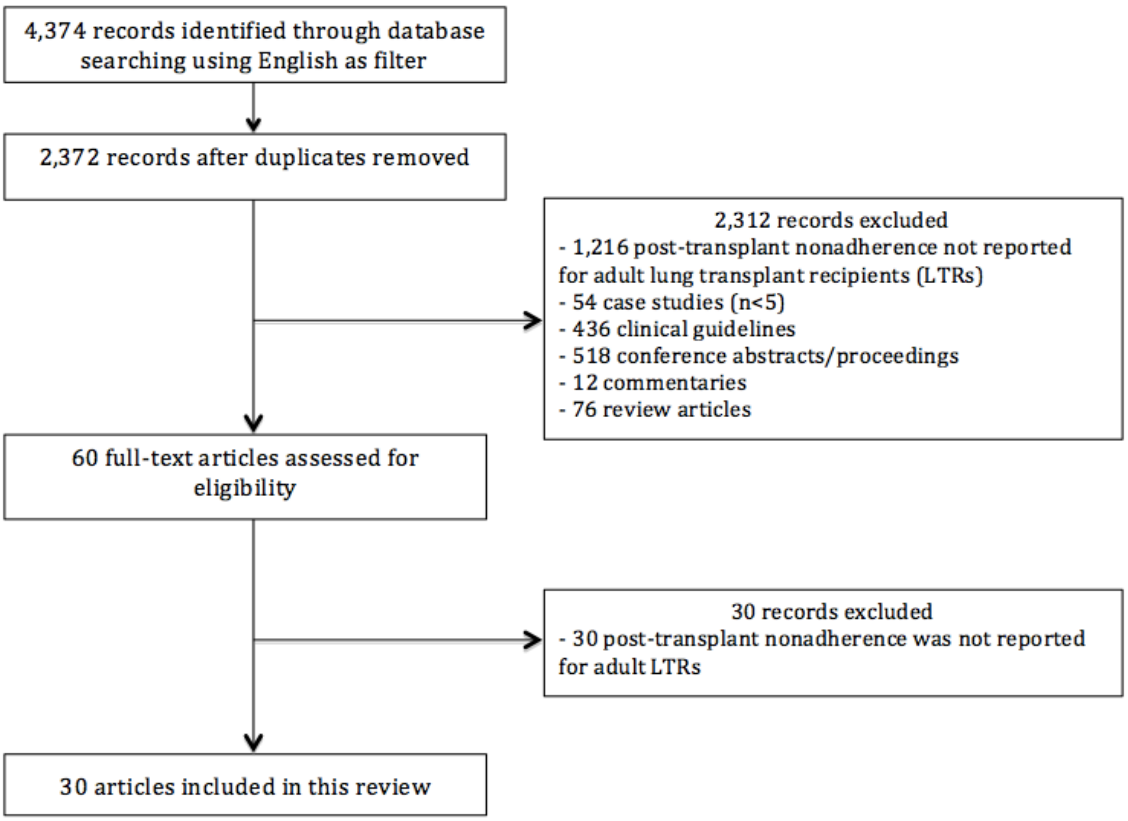



**Figure 1 Study Flow Chart**

**Table 1 Articles on Prevalence and Risk Factors of Nonadherence to Medical Regimen among Lung Transplant Recipients (LTRs)**

| First Author (Year) Country Level of Evidence | N | Measurement | Area of adherence and definition | Findings |
|---|---|---|---|---|
| | | | ***Medication Adherence*** | |
| Bosma (2011) The Netherlands Level 4 | 91 | Medication Electronic Event Monitoring (EEM) | Nonadherence (NA): taking both daily doses of tacrolimus at around the recommended time-points on < 80% days or missing >=1 doses per month, following Dew et al. (2008)'s criteria | Median observation time: 95 days (50-124 days)<br>Using 80% criteria, NA rate is 7.7%<br>Using Dew's criteria, NA rate is 15.4%<br>Sig. predictors: younger age and lower self-care ability |
| Dew (2008) United States Level 3 | 178 | Health Habits Assessment (LTRs and caregivers version) | NA: missed >= once a month<br>Report from either LTRs or caregivers as evidence of NA | NA rates are 9.6%, 8.3%, 14.3%, 14.5%, and 19.7% for baseline-2 months, 2-7 months, 7-12 months, 12-18 months, and 18-24 months respectively.<br>Sig. predictors: relying on public health insurance; poor CG and friends' support. |
| De Bleser (2011) Belgium Level 3 | 104 | 1. Self-report<br>2. Collateral report<br>3. Blood Assay of Immunosuppressant (IS)<br>4. EEM<br>5. Composite adherence (AD) score (CAS) | 1. BAASIS: NA on any items<br>2. VAS: 0 (NA)-100 (perfect adherence (AD))<br>3. Collateral report: either physician or nurse rated patients (pts) as less than 'good' is NA<br>4. Assay: Sub-therapeutic values as NA<br>5. EEM: (i) taking AD (% of blister removals) (ii) dosing AD (% days with correct doses), (iii) timing AD (% days with correct dosing intervals), (iv) drug holidays (no blister removals > 24 hours)<br>6. CAS-1: either (self-report or collateral report) showed NA; CAS-2: either (self-report or collateral report or assay) showed NA | NA at baseline (NA at 3-months)<br>1. BAASIS – Overall 40.4% (35.9%); Taking NA: 12.6% (10.8%), Timing NA: 36.5% (27.9%)<br>2. VAS- Median 95 (95)<br>3. Collateral-Physician: 31.4% (33.3%)<br>4. Collateral-Nurse: 32.7% (39.3%)<br>5. Assay: 30.4% (32.1%)<br>6. CAS-1: 63.1% (63.3%); CAS-2: 71.8% (72.2%)<br>8. EEM: 13% taking NA; 22.6% timing NA 14.8% dosing NA; 1.39 % drug holidays |

| First Author (Year) Country Level of Evidence | N | Measurement | Area of adherence and definition | Findings |
|---|---|---|---|---|
| De Geest (2014) Switzerland Level 3 | 181 | BAASIS | NA: any missing dose | 6-months: 2.3% (taking NA); 0 (drug holidays);<br>12-months: 9.6% (taking NA); 1.3% (drug holidays);<br>24-months: 13% (taking NA); 2.3% (drug holidays);<br>36-months: 7.3% (taking NA); 0 (drug holidays) |
| Goetzmann (2009) Switzerland Level 4 | 76 | TxEQ-D | No definition for NA because they reported adherence subscale score as a continuous variable | Observation time: mean 48 months (3-133 months)<br>Sig predictors: poor organ integration (meaning perceived closeness of transplanted organ to self) |
| Hugon (2014) France Level 3 | 33 | Morisky-Green scale and plasma level of IS | NA: self-reported adherence score was $\leqslant 4$ and/or had a ratio of inadequate trough concentrations (# of assays with less than targeted concentrations divided by total # of assays) > 0.2 | Observation time: 6 months<br>NA rate: 48.5% |
| Kugler (2007) Germany Level 4 | 287 | subscale of investigator - developed scale | NA: self-report of a at least one drug holiday within the past 14 days | Observation time: over past 14 days<br>NA rate to IS and corticosteroids: 4.5%<br>Sig predictors: adverse effects |
| Kung (2012) New Zealand Level 3 | 46 | Immunosuppressant therapy adherence scale (ITAS) | NA (ITAS score < 12) | Observation time: 3 months<br>NA rate: 56%;<br>Sig. predictors: younger age, completed postsecondary education, less convinced that IS would prevent organ rejection, and had higher symptom distress |
| Matthees (2001) United States Level 4 | 99 | 4-item scale | High AD: score of 4;<br>Moderate AD: score of 3;<br>Low AD: < = 2 | Observation time: median 49.9 months (9-123 months)<br>63% high, 28% moderate, 9% low AD; |
| O'Brien (2008) Australia Level 4 | 33 | Investigator-developed scale | Missed one dose since transplant | Observation time: mean 51.5 months (0.8-142 months)<br>NA: 48.5% |

| First Author (Year) Country Level of Evidence | N | Measurement | Area of adherence and definition | Findings |
|---|---|---|---|---|
| Santana (2009) Canada Level 4 | 43 | Morisky scale | Ever forgot to take medication over past 6-months | Observation time: 6 months<br>NA: 9% |
| Su (2013) Canada Level 3 | 65 | Pharmacy dispensing record | NA: medication possession ratio (MPR, days of medication supplied/actual days) < 80% | Observation time: 2 years<br>NA rate: 8% |
| Teichman (2000) United States Level 4 | 31 | self-report demographic questionnaire and compliance questionnaire by subjects, CG, and Tx coordinator | Forgot once monthly | Observation time: mean 24 months (3-57 months)<br>NA rate: 19.5% |
| ***Adherence to Self-Monitoring of Lung Function*** | | | | |
| Dew (2008) United States Level 3 | 178 | collateral report from patients and caregivers using Health Habits Assessment | Performed spirometry less than several times a week<br><br>Report from either LTR or caregivers as evidence of NA | NA rates are 24.2%, 47.1%, 54.6%, 64.5%, and 65.9% for baseline-2mons, 2-7mos, 7-12mos, 12-18mos, and 18-24mos respectively.<br>Sig. predictors: relying on public health insurance; poor CG and friends' support; lower internal locus of control; female gender |
| Kugler (2010) Germany Level 4 | 269 | Electronic monitoring (EM); Hannover Treatment Adherence Questionnaire | Self-monitoring of lung function (SMLF) adherence: one measurement/day<br>Adherent: >=90 measurements for the last three months | Observation time: EM: 3 months; self-report: over past 14 days<br>59.4% NA based on EM vs. 42.6% NA based on self-report<br>Sig. factors: age, higher education, not member in patient organization, belief that SMLF difficult to manage, had SMLF deviation, developed bronchiolitis obliterans syndrome (BOS), history of infections, and had support from Tx center |

| First Author (Year) Country Level of Evidence | N | Measurement | Area of adherence and definition | Findings |
|---|---|---|---|---|
| Lindgren (2002) United States Level 4 | 139 | EM | # of days with measurement divided by the total adjusted possible days.<br>Poor adherence: weekly adherence <70% | Observation time: 6 months<br>18% were poor adherers |
| Morlion (2002) Belgium Level 4 | 22 | EM | # of days with measurement sessions divided by the total adjusted possible days. | Observation time: median 473 days (60-822 days)<br>NA rate: 16% |
| Teichman (2000) United States Level 4 | 31 | self-report demographic questionnaire and compliance questionnaire by subjects, CG, and Tx coordinator | One measurement per day | Observation time: mean 24 months (3-57 months)<br>NA rate: 16.7%<br>Sig factors: CF patients; patients received Tx more recently |
| ***Adherence to Other Aspects of Medical Regimen*** | | | | |
| Bauldoff (2015) United States Level 4 | 34 | Serum cotinine and self-report | Self-report smoking behaviors after the Tx and confirmatory findings of serum cotinine | Observation time: 223-3160 days<br>NA rate: 14.7% |
| DeVito Dabbs (2003) United States Level 4 | 249 | Bronchi-alveolar lavage specimens | Smoking behaviors based on evidence of kaolinate accumulation in macrophages | Observation time: 1 year<br>NA rate: 45% |

| First Author (Year) Country Level of Evidence | N | Measurement | Area of adherence and definition | Findings |
|---|---|---|---|---|
| Dew (2008)<br>United States<br>Level 3 | 178 | patients and caregivers collateral report of Health Habits Assessment survey | Clinic appointments (missed >=1 visit);<br>Blood work (missed>=1 appointment);<br>Blood pressure monitoring (less than several times a week);<br>Exercise (less than several times a week);<br>Diet (went off diet at least weekly);<br>Used tobacco (any use);<br>Excessive alcohol use (>=2 drink/day);<br><br>They took report from either patient or CG, as evidence of NA. | *NA rates are for baseline-2mons, 2-7mos, 7-12mos, 12-18mos, and 18-24mos respectively.*<br>**tobacco use:** 0.0% 0.6% 1.3% 0.7% 1.6%<br>**alcohol use:** 3.9% 4.1% 9.1% 10.9% 10.2%<br>**clinic appt:** 11.8% 22.0% 22.2% 33.3% 27.8%<br>**blood work:** 15.3% 24.3% 24.8% 25.4% 28.3%<br>**exercise:** 31.5% 29.4% 38.3% 35.8% 41.3%<br>**diet:** 28.1% 33.3% 31.2% 30.4% 36.5%<br>**BP monitor:** 42.1% 55.9% 59.2% 67.4% 68.5%<br><br>**Sig. factors** in all domains: relying on public health insurance; poor CG and friends' support.<br>Lower internal locus of control and female gender predicted increased risks to NA to home self-care (BP monitoring, diet or exercise). |
| Evon (2005)<br>United States<br>Level 3 | 45 | Patient and Tx coordinator report | **Adherence** to Tobacco use: No use at all<br>**Adherence** to Alcohol use: < 2 drinks/day | Observation time: 1-7 years<br>NA to tobacco: 0; NA to alcohol: <40%<br>**Sig. factors:** lower levels of social support. |
| McDonald (1998)<br>United States<br>Level 4 | 29 | Serum cotinine and self-report | NA to tobacco: self-report smoking after Tx and confirmatory serum cotinine | Observation time: 4 years<br>NA rate: 13.8% |
| Ruttens (2014)<br>Belgium<br>Level 4 | 331 | Smoking<br>-questionnaire<br>-cotinine<br>-eCO | cotinine (>75 ng/ml as positive), eCO (>= 10ppm as positive) | Observation time: 1 year<br>Overall NA rate: 12%<br>**Sig. factors:** underlying disease, shorter abstinence period before Tx, prevalence of solid organ cancer, lung cancer |

| First Author (Year) Country Level of Evidence | N | Measurement | Area of adherence and definition | Findings |
|---|---|---|---|---|
| Teichman (2000) United States Level 4 | 31 | self-report demographic questionnaire and compliance questionnaire by subjects, CG, and Tx coordinator | No definition | Observation time: mean 24 months (3-57 months)<br>**Fevers**: Sig factors: number of months since Tx; social support; health locus of control related to powerful others;<br>**Time in the Sun**: A) Strength of sunscreen: Sig. factors: younger age; social support; |
| Vos (2010) Belgium Level 4 | 267 | Smoking<br>-questionnaire<br>-cotinine<br>-eCO | cotinine (>75 ng/ml as positive), eCO (>= 10ppm as positive) | Observation time: median 3.4 years (1.5-6.0 years)<br>Overall: 15.7% smoked after Tx<br>**Sig factors**: having the diagnosis of emphysema, years of Tx, SES, abstinence period, post-Tx second hand tobacco exposure |

AD: adherence; NA: Nonadherence; BAASIS: Basel Assessment of Adherence with Immunosuppressant Medication Scales; VAS: visual analog scale; Sig.: significant; TxEQ-D: Transplant Effects Questionnaire; pt: patient; Tx: transplant; BP: blood pressure; CG: caregiver; CF: cystic fibrosis; eCO: exhaled carbon monoxide; SES: socioeconomic status

**Table 2 Articles on Interventions to Promote Adherence among Lung Transplant Recipients (LTRs)**

| First Author (year)<br>Country<br>Study Design<br>Level of Evidence | N | Description of Intervention | Target area of regimen and definition | Findings |
|---|---|---|---|---|
| Chlan (1998)<br>United States<br>Pre-post test<br>Level 3 | 43 | HS system and research nurse tracked pts' progress and contacted pts when needed | HS measured by electronic spirometer<br>Adherent: >= one record/week | Pre-test: 83.3% (n=29);<br>Post-test: 88.5% (n=14)<br>(effect size (ES) =.37) |
| DeVito Dabbs (2009)<br>United States<br>Pilot RCT<br>Level 1 | 30 | Smartphone assists LTR to track their self-monitoring data with decision support to report to worrisome values to clinical team | 10 areas measured by Health Habit Assessment by caregivers and LTRs<br>Overall adherent: adherent to >= 9 areas<br>Self-monitoring adherent: > 80%<br>HS adherent: ≥ 3 times/week | Intervention group had a sig. higher rate of adherence to daily monitoring and performing HS than control group (ESs are .46, .45, respectively). I group also has a higher rate of overall adherent (ES=.47). |
| Sengpiel (2010)<br>Germany<br>Pilot RCT<br>Level 1 | 56 | Using Bluetooth, HS data will be automatically sent to a database, which can generate alarm messages | HS measured by electronic spirometer<br>Good adherence: ≥ 80%;<br>Moderate adherence: 50%-79%;<br>NA: <50% | Intervention group had an adherent rate of 97.2% while the control group had 95.2% (ES=.05). |
| Goldstein (1996)<br>United States<br>Quasi-experiment<br>Level 2 | 23 | Clinic: rushed education about HS, self-monitoring<br>PLC: tailored education | HS measured by electronic spirometer<br>No definition | # of records<br>Clinic 3mos(6mos): 46.8 (84.1)<br>PLC 3mos(6mos): 62.4 (108.2)<br>ES=.28 |
| LaVelle (2010)<br>United States<br>Correlational<br>Level 3 | 48 | All pts received a HS system, education about HS, a quarterly educational newsletter | HS measured by electronic spirometer<br>Adherent: > 1 blow a week, adjusted for special occasions. | Increased perceived worthwhileness of the newsletter was correlated with higher percentage of weeks the subjects were adherent to HS (ES=.36). |
| Suhling (2014)<br>Germany<br>RCT<br>Level 1 | 64 | iPad-based education vs. paper-based education on medication adherence | Medication adherence:<br>- physician rating: good, moderate, bad adherence<br>- surveys: BAASIS, VAS, Morisky (no definition was provided) | No difference in physician rating or surveys assessments of adherence between two groups (ES=.11). |

HS: home spirometry; pts: patients; PLC: problem-based learning center; BAASIS: Basel Assessment of Adherence with Immunosuppressant Medication Scales; VAS: visual analog scale; ES: effect size; I: Intervention; C: Control; NA: nonadherence; sig.: significant;

**Table 3 Articles on Clinical Outcomes of Nonadherence among Lung Transplant Recipients**

| First Author (year)<br>Country<br>Level of Evidence | N | Area of regimen and definition | Outcome measures | Findings |
|---|---|---|---|---|
| Yoon (2008)<br>United States<br>Level 4 | 246 | Home spirometry<br>Adherent: ≥ once/week<br>High adherence: > 75%<br>Low adherence: ≤ 75% | Survival time<br>Mortality | High adherence group had better survival but not significant (effect size, ES=.08)<br>Cumulative incidence of pulmonary-related death is reduced with better adherence to home spirometry, but not significant (ES=.09)<br>Cumulative incidence of non-pulmonary death was similar for two groups (ES=.02) |
| Kugler (2009)<br>Germany<br>Level 4 | 226 | Home spirometry<br>Adherent: ≥ once/day<br>Good adherer: ≥ 80%<br>Moderate adherer: 50%-79%<br>Nonadherer: < 50% | Graft loss<br>Incidence of BOS<br>Re-transplantation | No significant impact of adherence on patient survival (ES=.03)<br>Significant shorter time free from BOS in nonadherers compared with good or moderate adherers (ES=.16)<br>Tendency toward lower re-transplantation rates for good adherers (ES=.12) |

BOS: bronchiolitis obliterans syndrome

### 2.3.4 Data Analysis

To address the fact that LTR participants had different follow-up duration across studies, we calculated the person-time incidence nonadherence rates. Specifically, we calculated the number of cases of nonadherence per 100 person-years for each study in each element of medical regimen. The effect sizes of intervention impact on promoting adherence and relationships between nonadherence and clinical outcomes were examined by extracting or calculating correlation coefficients.

## 2.4 RESULTS

As shown in Figure 1, 30 articles were included in this review: 22 (73.3%) focused on prevalence and/or risk factors of nonadherence (see Table 1), 6 (20.0%) articles examined the effects of interventions to promote adherence (see Table 2), and 2 (6.7%) articles explored outcomes related to nonadherence (see Table 3). The sample sizes ranged from 22 to 331 with a pooled total sample size of 3,388. The samples were predominantly comprised of individuals who were white, middle aged, married or living with partners, and carried a diagnosis of obstructive disease or cystic fibrosis. These sample characteristics are consistent with the characteristics of the worldwide LTRs population (Yusen et al., 2014).

### 2.4.1 Prevalence and Risk Factors of Nonadherence to the Medical Regimen

***Nonadherence to medication-taking***

Medication nonadherence was examined in thirteen articles (Bosma et al., 2011; De Bleser et al., 2011; Sabina De Geest et al., 2014; Dew, DiMartini, DeVito Dabbs, et al., 2008; Goetzmann et al., 2009; Hugon et al., 2014; Kugler et al., 2007; Kung, Koschwanez, Painter, Honeyman, & Broadbent, 2012; Matthees et al., 2001; O'Brien, Aslani, Ciccia, & Brien, 2008; Santana et al., 2009; Su et al., 2013; Teichman et al., 2000), with rates ranging from 2.3% to 72.2%. When taking different follow-up time in consideration, the medication nonadherence rates ranged from 4 to 100 cases for every 100 persons in a given observation year. Approaches to defining and measuring medication nonadherence varied within this set of articles. Some articles (De Bleser et al., 2011; Dew, DiMartini, De Vito Dabbs, et al., 2008; Kugler et al., 2007) defined medication nonadherence as any missing dose over a month or between study follow-ups, while others defined medication nonadherence as following the medication instructions less than 80% of the days over 3 months (Bosma et al., 2011; Su et al., 2013). Across articles, self-report approaches (with or without collateral report) to measure medication nonadherence were the most common, with fewer articles incorporating measures like electronic medication event monitoring (Bosma et al., 2011; De Bleser et al., 2011) or records of pharmacy dispensing (Su et al., 2013). One article used a combined approach of self-report and plasma concentration of immunosuppressant (Hugon et al., 2014). Notably, among the articles using self-report measures, a variety of the scales were used with most of scales being validated in other chronic diseases or other solid transplant recipients, and their reliability and validity among LTRs was generally unreported (De Bleser et al., 2011; Sabina De Geest et al., 2014;

Hugon et al., 2014; Kugler et al., 2007; O'Brien et al., 2008; Santana et al., 2009; Teichman et al., 2000).

Among those 13 articles on medication nonadherence, 6 reported associated risk factors among LTR participants (Bosma et al., 2011; Dew, DiMartini, DeVito Dabbs, et al., 2008; Goetzmann et al., 2009; Kugler et al., 2007; Kung et al., 2012; Matthees et al., 2001). None of the factors were examined in a sufficient number of articles (i.e., >5) to allow for a meta-analysis. Of the factors that were examined in more than one article, our synthesis revealed conflicting results. For example, one article (Kung et al., 2012) found that higher educational level was a significant predictor of nonadherence to medication while two other articles (Bosma et al., 2011; Dew, DiMartini, DeVito Dabbs, et al., 2008) reported that level of education was not significantly related to medication nonadherence.

***Nonadherence to self-monitoring of lung function***

Five articles examined nonadherence to self-monitoring of lung function with rates ranging from 16% to 65.9% (Dew, DiMartini, DeVito Dabbs, et al., 2008; Kugler, Gottlieb, et al., 2010; Lindgren et al., 2002; Morlion et al., 2002; Teichman et al., 2000). When the follow-up duration was considered, the calculated rates ranged from 8.3 to 100 cases per 100 person-years. No standard definition was found across articles. For example, one article (Kugler, Gottlieb, et al., 2010) defined adherence to self-monitoring of lung function as performing home spirometry once daily while another article (Lindgren et al., 2002) classified poor adherers as weekly adherence of less than 70%. Three articles used electronic monitoring (Kugler, Gottlieb, et al., 2010; Lindgren et al., 2002; Morlion et al., 2002) while the other two articles (Dew, DiMartini, et al., 2008; Teichman et al., 2000)

used a combination of sources, including collateral reports from family caregivers or transplant coordinators to validate patients' self-reports. Similar to the results of nonadherence to medication-taking, no conclusive risk factors for nonadherence to performing spirometry were identified due to limited evidence and/or inconsistent findings across the articles.

***Nonadherence to other aspects of the post-transplant medical regimen***

Nonadherence to other aspects of the post-transplant medical regimen was also examined in several articles, including tobacco use, alcohol use, and having blood work performed as prescribed. Seven articles (Bauldoff, Holloman, Carter, Pope-Harman, & Nunley, 2015; DeVito Dabbs et al., 2003; Dew, DiMartini, DeVito Dabbs, et al., 2008; Evon et al., 2005; McDonald, Keller, Ramos, & Brunt, 1998; Ruttens et al., 2014; Vos et al., 2010) examined nonadherence to tobacco use. While two articles (Dew, DiMartini, et al., 2008; Evon et al., 2005) found low nonadherence rates (less than 2%), other articles (Bauldoff et al., 2015; DeVito Dabbs et al., 2003; McDonald et al., 1998; Ruttens et al., 2014; Vos et al., 2010) reported higher nonadherence rates, ranging from 12% (Ruttens et al., 2014) to 45% (DeVito Dabbs et al., 2003). When translating these rates to the person-time incidence rate, nonadherence to tobacco ranged from 0 to 52.3 cases/100 person-years. Each of these articles treated any tobacco use after the transplantation as nonadherent. Two articles (Dew, DiMartini, et al., 2008; Evon et al., 2005) used patients' reports and collateral reports from family caregivers, and/or transplant coordinators, while the others used a combination of self-report and/or a physiologic measure like urine test of cotinine

(McDonald et al., 1998; Ruttens et al., 2014; Vos et al., 2010) serum cotinine (Bauldoff et al., 2015) or biopsy data (DeVito Dabbs et al., 2003).

### 2.4.2 Interventions for Promoting Adherence

Six articles reported on the effects of interventions to promote adherence (Chlan et al., 1998; DeVito Dabbs et al., 2009; Goldstein et al., 1996; Lavelle et al., 2010; Sengpiel et al., 2010; Suhling et al., 2014), four of which focused on adherence to performing home spirometry (Chlan et al., 1998; Goldstein et al., 1996; Lavelle et al., 2010; Sengpiel et al., 2010), one on adherence to medication-taking (Suhling et al., 2014) and one on adherence to the overall medical regimen (DeVito Dabbs et al., 2009). All of these studies had a relatively small sample size, ranging from 23 to 64. Many of them failed to describe the theoretical basis for the design of the interventions (Chlan et al., 1998; Goldstein, Snyder, Edin, Lindgren, & Finkelstein, 1996; Lavelle et al., 2010; Sengpiel et al., 2010; Suhling et al., 2014). In addition, the interventions focused exclusively on patient level factors despite increasing awareness that adherence is a multidimensional issue including patient, condition, treatment and health system factors (De Geest et al., 2005; Dew et al., 2007; Dew, DiMartini, DeVito Dabbs, et al., 2008; World Health Organization, 2003). Lastly, these studies followed participants for limited periods, typically 2 months. This relatively brief period of follow-up precludes determining patterns of adherence over an extended period when adherence is likely to decline.

The interventions designed to promote adherence to home spirometry shared common features (Chlan et al., 1998; DeVito Dabbs et al., 2009; Goldstein et al., 1996; Lavelle et al., 2010; Sengpiel et al., 2010). First, all of these interventions included an

educational component. Participants were instructed regarding the purpose, importance of, and skills needed to perform home spirometry. Second, they all used some form of technology to assist participants to better track their lung function at home. Third, the spirometry data were usually date-stamped, transmitted to the study center, and reviewed by the study team. Fourth, all of the studies provided some automatic decision support feedback; sent either to participants to report changes to their care team (DeVito Dabbs et al., 2009; Sengpiel et al., 2010) or sent directly to a member of the care team, typically the transplant coordinator (Chlan et al., 1998; Goldstein et al., 1996; Lavelle et al., 2010). With regard to the effects of interventions on promoting adherence, the calculated effect sizes using correlation coefficients ranged from 0.05 (Sengpiel et al., 2010) to 0.45 (DeVito Dabbs et al., 2009).

Two articles examined interventions to promote adherence to medication-taking (DeVito Dabbs et al., 2009; Suhling et al., 2014). Both studies were randomized controlled trials and used mobile technology as an interventional tool. In one study (Suhling et al., 2014), a nurse interventionist used an iPad at the time of hospital discharge to provide a single educational session about medication adherence, while the other study (DeVito Dabbs et al., 2009) provided smartphones to participants for 2 months. Compared to the conventional paper-based education, the one-time iPad-based patient education at discharge did not show a significant improvement in adherence to medication-taking (effect size r=0.11) (Suhling et al., 2014); however, LTRs who were randomized to the smartphone intervention reported a significantly higher overall adherence (including 10 elements of post-transplant medical regimen, one of which is medication adherence)

compared to patients in the usual care group (effect size r=0.47) (DeVito Dabbs et al., 2009).

### 2.4.3 Outcomes of Nonadherence

Two articles examined clinical outcomes of nonadherence to home spirometry among LTRs (Kugler et al., 2009; Yoon et al., 2008). One study (Kugler et al., 2009) used a prospective design while the other (Yoon et al., 2008) used a retrospective design. Both articles used electronic spirometers, which stored measurements in the device and transmitted the data to the study center. These articles adopted different criteria to define adherence. Yoon and colleagues (2008) considered *once per week* as adherent. However, Kugler et al. (2009) defined adherence as *once per day* and classified participants into 3 groups: good adherers (>=80%), moderate adherers (50%-79%), and nonadherers (<50%). Both found weak correlations (0.03-0.08) between adherence and patient survival. In addition, Kugler et al. (2009) reported correlations between nonadherence and other clinical outcomes such as time free from bronchiolitis obliterans syndrome (BOS), a form of the chronic graft rejection, and re-transplantation rates (correlation coefficients: 0.12-0.16).

### 2.4.4 Strength of the Evidence

According to the Agency for Healthcare Research and Quality (West et al., 2002), strength of evidence for articles included in this review can be categorized as the following (see Table 1, 2, and 3 for details): the majority (n=17, 56.7%) were level 4 (descriptive articles

without any control group); nine were level 3 (observational articles with controls), including either other solid organ transplant recipients or lung transplant candidates as comparison groups; one was level 2 (non-randomized controlled trials) and three were level 1 (randomized controlled trials).

## 2.5 DISCUSSION

To the best of our knowledge, this is the most recent systematic review of evidence regarding nonadherence to the medical regimen among LTRs. We included 30 articles, 22 of which focused on prevalence and/or risk factors of nonadherence, a number greatly increased since the last review in this area, which found only 5 articles focusing on prevalence and/or risk factors of nonadherence among LTRs (vs. 72 for kidney and 34 for heart recipients) (Dew et al., 2007). This increase in the volume of published articles indicates that progress has been made over the last few years in the field of adherence among LTRs. Yet, compared to the study of kidney or heart transplantation, the body of available evidence is still relatively small.

In the current review, nonadherence rates to different elements of the medical regimen for LTRs varied greatly and could not be consistently attributed to any specific factor, which is consistent with findings for other solid organ transplant recipients (De Geest et al., 2005; Dew et al., 2007). This may be due to the methodological heterogeneity of each study (i.e., different study design, sample size, settings, measures, and rigor) (Gagnier, Moher, Boon, Beyene, & Bombardier, 2012) or could be attributed to the

complexity of nonadherence behaviors (WHO, 2003). More exploratory studies are needed in LTRs population to better inform the content and targets of interventions going forward.

It is acknowledged that in the field of transplantation there is a push for more interventional studies to promote medical regimen adherence (Cupples et al., 2006). Examination of effect sizes across the 6 intervention studies included in this review showed that the impact of interventions on promoting adherence to performing home spirometry ranged from 0.05 (Sengpiel et al., 2010) to 0.45 (DeVito Dabbs et al., 2009). The variations in the effect sizes might be explained by the methodological issues mentioned in the results section, including relatively small sample sizes, lack of theoretical basis for intervention, an exclusive focus on patient-level factors and limited follow-up times (i.e., 2 months). These issues are consistent with problems identified in another review of interventions studies on promoting medication adherence (De Bleser, Matteson, Dobbels, Russell, & De Geest, 2009). More large-scale studies are needed to test theory-driven and evidence-based interventions in LTRs for an extended follow-up time.

Our review found that better adherence to home spriometry was significantly associated with prolonged time free from BOS and a tendency toward lower need for re-transplantation (Kugler et al., 2009; Yoon et al., 2008). Yet, neither study found a significant impact of nonadherence on patient survival. Studies in other solid organ transplant recipients have also failed to demonstrate such significance (De Geest et al., 1995; Denhaerynck et al., 2009). This suggests that other mechanisms may also contribute to patient survival and need to be further explored to promote transplant health outcomes.

A pervasive issue impacting this body of literature is the varying definitions of nonadherence. For example, one study defined adherence to home spirometry as one

measurement per day (Kugler et al., 2009) while another study defined it as one measurement per week (Yoon et al., 2008). The variations in the definitions may be driven by the varying recommendations provided at each transplant center, which presents a challenge to the process of aggregating findings across the studies. In addition, there was a notable variation in the self-report measures employed and limited discussion of the reliability and validity of the measures among LTRs. These weaknesses underscore the importance of clearly defining and striving for consistency in measuring nonadherence through combined approaches.

An emerging trend of using technology-based interventions to promote adherence was observed in this review, especially in those interventional studies where mobile technology or home telemonitoring system was used to assist participants to adhere to self-monitoring with or without decision-support (Chlan et al., 1998; DeVito Dabbs et al., 2009; Goldstein et al., 1996; Lavelle et al., 2010; Sengpiel et al., 2010; Suhling et al., 2014)**.** The use of technologies to measure nonadherence (i.e., electronic medication monitoring) (Bosma et al., 2011; De Bleser et al., 2011) was also noted in this review. These trends are likely reflective of the rapidly growing roles of information technology in the field of health care (Free et al., 2013). Future studies could further explore how to maximize the use of technologies to better measure and promote adherence among LTRs (DeVito Dabbs, Song, Myers, et al., 2013).

While this review pointed out several problems in the adherence literature among LTRs population, we also noted several encouraging indicators of progress in the field. First, our review found that several recent studies acknowledged nonadherence as a complex and multidimensional problem (WHO, 2003) and explored system-related risk

factors (Dew et al., 2008; Kugler et al, 2010). For example, Dew et al. (2008) reported that relying exclusively on public health insurance was a significant risk factor for nonadherence to all domains of medical regimen among 178 LTRs, which provided an important implication for healthcare policy and pointed to the need of involving multidisciplinary stakeholders to address this challenging issue. This is a remarkable paradigm shift as compared to previous studies mostly focused on patient-related factors (i.e., patients' beliefs and attitudes). Second, a growing number of studies have started to use multiple strategies and combined approaches to measure adherence, which aligns well with the current recommendations of adherence literature (Dew et al., 2007; Dew, DiMartini, et al., 2008; DiMatteo, 2004). Lastly, while the conclusive evidence on risk factors is lacking in LTRs population, researchers are still actively designing and conducting pilot interventions studies based on clinical observation and evidence from other fields (i.e., non-transplant chronic disease). Some pilot work has even demonstrated promising results in promoting adherence among LTRs (DeVito Dabbs et al., 2009).

There are several limitations to acknowledge for this review. First, qualitative research, grey literature such as conference abstracts, and literature in other than English language were not reviewed, which might limit our knowledge in this area. Second, studies regarding pediatric LTRs were excluded, which limited the generalizability of our findings. Lastly, as is true in other reviews, our findings might be biased due to the fact that researchers are more likely to publish studies with positive results (Easterbrook, Berlin, Gopalan, & Matthews, 1991; Olson, 2008).

## 2.6 CONCLUSIONS

This review provides an overview of the evidence in nonadherence to the post-transplant medical regimen among adult LTRs over the past 20 years. While encouraging progress has been made, we identified several implications and knowledge gaps in the field. Future research should consider: (1) applying more rigorous and standard methodologies to define and measure adherence, while accounting for clinical variations in patient instructions; (2) conducting more large-scale randomized trials to test theory-driven and evidence-based interventions; and (3) exploring ways to better utilize the currently available information technology to promote medical regimen adherence and ultimately achieve better health outcomes among LTRs.

# 3.0 MANUSCRIPT 2: PATTERNS AND CORRELATES OF SELF-CARE AGENCY IN LUNG TRANSPLANT RECIPIENTS OVER THE FIRST 12-MONTHS POST-HOSPITAL DISCHARGE AFTER TRANSPLANT

## INTRODUCTION TO MANUSCRIPT 2

This chapter includes manuscript 2, which addresses the second specific aim of the dissertation study: **Aim 2:** Identify distinct patterns and correlates of self-care agency (SCA) among LTRs over the first 12-months post-hospital discharge after transplant.

One of the limitations identified in the systematic review (manuscript 1) is that there is a general lack of theoretical basis for adherence research among LTRs. This chapter focuses on a critical theoretical construct in self-care theory (Orem, 2001), self-care agency, which is defined as one's willingness and ability to perform self-care behaviors. While a prior report found that the majority of LTRs perceived high SCA prior to discharge (DeVito Dabbs et al., 2013), it is unclear whether and how SCA changes over time after transplantation. Understanding the longitudinal patterns and correlates of this potentially important theoretical concept may help inform the design of future self-care promotion interventions among LTRs. In this study, we took advantage of an existing dataset, employed an advanced statistical technique, group-based trajectory modeling, and identified distinct patterns of SCA among LTRs over the first 12-months post-discharge from transplant hospitalization. Based on the identified patterns, we examined both baseline and longitudinal correlates of SCA patterns.

## 3.1 ABSTRACT

**Background:** Actively engaging in post-transplant self-care may help to maximize health outcomes for lung transplant recipients (LTRs). Self-care agency (SCA), defined as one's ability and willingness to perform self-care, has been identified as a key factor influencing one's performance of self-care behaviors. Understanding patterns and correlates of SCA over time may inform the design of self-care promotion interventions in LTRs. Therefore, we sought to identify patterns and correlates of SCA among LTRs over the first 12-months post-hospital discharge after transplant.

**Methods:** This correlational secondary analysis used data from the usual care group (N=102) of a completed randomized controlled trial. Group-based trajectory modeling was used to identify distinct patterns of SCA (as measured by Perception of Self-Care Agency) over the first 12-months post-hospital discharge after transplant. Baseline (meaning prior to discharge) measures of sociodemographic, clinical, and psychosocial factors, as well as longitudinally assessed psychological distress were examined for their associations with predicted trajectory group membership using ordinal logistical regression and linear mixed modeling, respectively.

**Results:** Three distinct stable (zero-slope) SCA trajectories were identified: *persistently low, persistently moderate,* and *persistently high*. Based on the final parsimonious multivariate model, having been re-intubated during the transplant hospitalization (p=.043), discharged to a facility rather than home (p=.048), and endorsing a higher baseline anxiety level (p=.001) were significantly associated with membership in the *persistently low SCA* group. Linear mixed models revealed that higher anxiety and depression levels were associated with lower SCA in the *persistently moderate and low SCA* groups over 12-months (*p*s<.05).

**Conclusions:** Given the negative relationship between psychological distress and SCA, future interventions to promote SCA should consider assessing and reducing psychological distress among LTRs.

## 3.2 INTRODUCTION

Over the last few decades, lung transplantation has been increasingly performed for individuals with end-stage lung diseases (Yusen et al., 2014) and has led to markedly improved quality of life (Kugler et al., 2005; Rodrigue, Baz, Kanasky, & MacNaughton, 2005; Vasiliadis, Collet, & Poirier, 2006). As a medically complex and chronically ill population, lung transplant recipients (LTRs) are prescribed a lifelong medical regimen to follow after the transplantation. LTRs are expected to perform a variety of self-care behaviors such as adhering to medication taking, self-monitoring of their lung functions, vital signs and symptoms, and communicating critical changes to their transplant coordinators in a timely manner (De Geest, Dobbels, Fluri, Paris, & Troosters, 2005; DeVito Dabbs et al., 2009; Dew et al., 2007, 2008). Despite the widely agreed importance of these self-care behaviors, accumulating evidence shows that LTRs' actual performance of these behaviors is suboptimal and far below the recommended levels (DeVito Dabbs et al., 2003; Dew et al., 2007; Hugon et al., 2014; Kugler, Gottlieb, et al., 2010; Kung et al., 2012).

Orem's theory of self-care (Orem, 2001) purports that self-care agency (SCA), defined as one's ability and willingness to engage in self-care behaviors, influences how well an individual performs a wide variety of self-care behaviors across many chronic illness populations (Baker & Denyes, 2008; Bosma et al., 2011; Callaghan, 2003, 2006; Dale et al., 2012; Drevenhorn et al., 2015; Hu et al., 2014; Ovayolu et al., 2012; Wang et al., 2014; Wong et al., 2015). Furthermore,

the self-care theory posits that SCA is influenced by sociodemographic, clinical, and psychosocial characteristics of an individual (Callaghan, 2006; Orem, 2001; Sousa, Hartman, Miller, & Carroll, 2009).

Although SCA has gained much attention in individuals with chronic conditions such as diabetes, hypertension, and arthritis, research regarding SCA after lung transplantation is limited. To date, only one study has described levels of SCA and examined its correlates among LTRs prior to discharge from their transplant surgery (DeVito Dabbs et al., 2013). DeVito Dabbs and colleagues (2013) found that LTRs reported higher levels of SCA than patients with other chronic diseases and suggested one possible explanation was that prior to discharge when SCA was assessed, LTRs might be overly confident about their capability to perform self-care behaviors at home. Thus, DeVito Dabbs and colleagues (2013) called for future work to explore the longitudinal patterns of SCA among LTRs.

Given the key role that self-care behaviors play in promoting health outcomes after lung transplantation, it is important to more fully understand the longitudinal patterns and correlates of SCA to guide the development of interventions to promote SCA or prevent a decline in SCA among LTRs. Therefore, the purposes of this study were to: 1) explore the distinct patterns of SCA and 2) examine correlates of SCA among LTRs over the first 12-months post-hospital discharge after transplant.

## 3.3 METHODS

### 3.3.1 Study design

This study was a correlational secondary analysis of data collected during a randomized controlled trial (NR107011, PI: DeVito Dabbs) (DeVito Dabbs, Song, Myers, et al., 2013). The aims of the parent study were to examine the efficacy of the Pocket PATH®, a mobile health intervention, compared to usual care for promoting self-care behaviors (primary outcomes), self-care agency and transplant-related health (secondary outcomes) among LTRs over the first 12-months post-hospital discharge after transplant (DeVito Dabbs, Song, Myers, et al., 2013).

### 3.3.2 Sample and setting

Eligibility for this study was identical to that of the parent study. Inclusion criteria included LTR who should be: 1) > 18 years of age; 2) stable enough to be transferred from the cardiothoracic ICU to the acute care unit; and 3) able to speak and read English; LTRs who: 1) had received any prior transplant or 2) were unable to perform their self-care were excluded. All LTRs were recruited from the Cardiothoracic Transplant Program of the University of Pittsburgh Medical Center.

The sample for this study was comprised of the 102 LTRs who were randomized to the usual care arm. The rationale to focus only on this usual care group is to avoid the possible intervention effect on SCA. The sample used for this secondary analysis partially overlapped with the sample reported in DeVito Dabbs et al. (2013), which focused on baseline data (prior to

randomization) for 111 LTRs, whereas this longitudinal investigation included all LTRs in the usual care arm.

### 3.3.3 Procedures

We obtained IRB approval for both parent study and the current study. As part of the usual care, all LTRs were prepared to perform self-care behaviors during a one-on-one education session with a transplant coordinator who provided written materials and a spirometer for LTRs to monitor lung function at home (DeVito Dabbs, Song, Myers, et al., 2013). LTRs were instructed to self-monitor changes in health parameters such as temperature, spirometry readings, and symptoms for possible complications and to record these data on paper and pencil logs (DeVito Dabbs, Song, Myers, et al., 2013). Prior to hospital discharge, all potential eligible LTRs were approached and asked to sign written informed consent to participate in the parent RCT. Baseline data were collected by trained interviewers after the standard discharge education but prior to discharge and the randomization. All participants were re-assessed at 2, 6, and 12-months post-hospital discharge after transplant.

### 3.3.4 Measures

**Dependent Variable - Self-care agency (SCA):** We used the 53-item, self-report instrument, Perception of Self-Care Agency (Hanson & Bickel, 1985), to measure LTRs' perceptions of their level of SCA. The survey uses a 5-point Likert scale with higher scores indicating higher perceived SCA (possible score range, 53 to 265). A sample item is "*I can choose what is important and least important when taking care of myself*" with the responses ranging from never like me (1) to always

like me (5). The reliability of this scale based on Cronbach's alpha has been established in prior studies (Gast et al., 1989; Hanson & Bickel, 1985; DeVito Dabbs et al., 2013). Cronbach's alpha was 0.94 in this current sample. This scale was completed at baseline (meaning post-transplant but immediately prior to discharge) and at 2, 6, and 12-months post-hospital discharge after transplant.

**Potential Correlates of SCA:** The following potential correlates were selected to be consistent with the factors outlined by Orem's self-care theory (2001) and prior research in LTRs and other chronic illness populations (Akyol et al., 2007; Bağ & Mollaoğlu, 2010; Callaghan, 2003; Callaghan, 2006; Dale et al., 2012; DeVito Dabbs et al., 2013; Fex et al., 2012; Karagozoglu et al., 2012; Lauck et al., 2009; Yildirim et al., 2013)

**Socio-demographic Correlates:** Characteristics, such as age, gender, race, employment status, marital status, education, and whether respondents felt that their income met their needs were collected at baseline using a Socio-demographic Profile. Given the small number of non-white participants, race was excluded as an analysis variable in the model building processes.

**Clinical Correlates**: Data for factors including type of lung transplant (single vs. double), underlying lung disease (obstructive vs. non-obstructive), and need for re-intubation (yes vs. no), duration of ventilation (< 48 hours vs. ≥ 48 hours), number of days in ICU, number of days with chest drain, length of hospital stay (days), and discharge destination (home vs. other facilities) during the transplant hospitalization were abstracted from the medical record.

**Psychosocial Correlates**

**Quality of recipient-caregiver relationship:** The quality of the relationship between LTRs and their caregivers was assessed at baseline using a 15-item, self-report questionnaire

adapted from the Dyadic Adjustment Scale (DAS) (Spanier, 1976); higher scores indicate higher relationship quality (Cronbach's alpha = 0.80 in the present sample).

**Health locus of control:** The Multi-Dimensional Health Locus of Control Scale (B. S. Wallston & Wallston, 1978; K. A. Wallston, Wallston, & DeVellis, 1978) was used to measure LTRs' beliefs about responsibility for control over health outcomes at baseline. LTRs rated the extent to which they believed their health outcomes were: 1) their own responsibility (Internality) 2) due to chance (Chance subscale) or 3) their health care professionals' responsibilities (Externality subscale) (Cronbach's alpha in the present sample was 0.78, 0.77 and 0.43, respectively). Higher subscale scores indicate stronger control beliefs. We omitted externality subscale from our analysis because the Cronbach's alpha for this subscale was low.

**Psychological distress:** The Anxiety and Depression subscales of the Symptom Checklist 90-Revised (SCL-90-R) (Derogatis, 1994) was used to measure psychological distress at all four time points, baseline, 2-, 6-, 12-months post-hospital discharge after transplant. The subscales focus on the past two weeks and use a 5-point rating scale (0=not at all to 4=extremely distressed). Higher scores indicate higher levels of distress. The subscale scores were obtained by averaging item scores. Cronbach's alpha in the current sample was 0.86 for the anxiety and 0.82 for depression subscale.

### 3.3.5 Statistical analysis

Descriptive analyses were performed using IBM® SPSS® Statistics for Windows (version 23, IBM, Corp., Armonk, NY). The significance level was set to .05 for two-tailed hypothesis testing. For continuous variables without outliers, we reported means and standard deviations. For continuous

variables with outliers, we reported medians and inter-quartile ranges. Categorical variables were summarized using frequency counts and percentages. Outliers for each variable were examined and replaced with the next highest/lowest values that are not outliers (Hastings, Mosteller, Tukey, & Winsor, 1947). We did not impute any missing data given that the missingness was found to be missing completely at random (MCAR) (SPSS MCAR test p=.53), which can be handled directly by the trajectory modeling (Jones, Nagin, & Roeder, 2001; Jones & Nagin, 2007; Nagin, 2005).

The TRAJ procedure (PROC TRAJ) in SAS (version 9.4, SAS Institute, Cary, NC) was used to perform group-based trajectory modeling (Jones et al., 2001; Jones & Nagin, 2007; Nagin, 2005) to identify distinct trajectories of SCA over the first 12 months post-hospital discharge after transplant. Censored normal model was chosen because the dependent variable, SCA, is a continuous variable. We determined the appropriate number of groups and the shapes of trajectories by comparing Bayesian Information Criteria (BIC) and Bayes factor for competing models (Jones et al., 2001; Jones & Nagin, 2007; Nagin, 2005).

We applied ordinal logistic regression (using PLUM routine in SPSS) to examine the baseline correlates of predicted membership by the trajectory modeling. In order to maximize the ratio of sample size to number of variables, we first performed univariate ordinal logistic regression considering each variable singly to screen for candidate variables for the multivariate modeling. Only those with p-values equal or less than 0.30 from the univariate modeling were considered as candidate variables for the multivariate modeling (Babyak, 2004; Steyerberg, Eijkemans, Harrell, & Habbema, 2001). Given the relatively small sample size for this investigation, we used a liberal 0.30 p-value cutoff for univariate screening in order to retain likely important variables in the final model (Babyak, 2004; Steyerberg et al., 2001). Using a backward elimination approach, a final parsimonious multivariate model was determined where all retained

variables were statistically significant ($p<0.05$). The proportional odds assumption was tested and met for all ordinal logistical regressions. For the longitudinally measured psychosocial correlates (anxiety and depression), we applied linear mixed modeling to examine the associations between these time-dependent covariates (dependent variable, DV) and the predicted group membership for SCA (independent variable, IV) over the first 12-months post-hospital discharge after transplant.

## 3.4 RESULTS

### Sample Characteristics

We excluded 8 participants who died during the study, leading to a final sample of 94 LTRs. There was no difference between these 8 participants and the rest of the sample, except that those 8 LTRs were more likely to be discharged to facilities other than home. Table 4 summarizes the sociodemographic, clinical and psychosocial characteristics of the sample. These characteristics were representative of the lung transplant population in the United States (Organ Procurement and Transplantation Network, 2012).

**Table 4 Sample Characteristics at Baseline (N=94)**

| | Baseline Characteristics | Mean±SD or n(%) |
|---|---|---|
| **Sociodemographics** | Age (Years) | 57.20 (13.58) |
| | Male | 56 (59.6%) |
| | White | 83 (88.3%) |
| | > High School | 63 (67.0%) |
| | Not currently working | 86 (91.5%) |

| | | |
|---|---|---|
| | Income met needs | 75 (79.6%) |
| | Currently married | 67 (71.3%) |
| **Clinical Correlates** | Obstructive lung disease | 40 (42.6%) |
| | Re-intubated post-transplant (No) | 67 (71.3%) |
| | Bilateral lung transplant | 78 (83.0%) |
| | < 2 days on ventilator | 59 (62.8%) |
| | Discharge to home | 81 (86.2%) |
| | Length of ICU stay (days)* | 7 (11.25) |
| | Chest drain (days)* | 12 (10.00) |
| | Length of hospital stay (days)* | 33 (28.00) |
| **Psychosocial Correlates** | DAS-Quality of recipient-caregiver relationship* (possible score range: 0-75) | 67.00 (7.75) |
| | MHLC-Internal subscale (possible score range: 6-36) | 23.71 (6.59) |
| | MHLC-Chance subscale (possible score range: 6-36) | 18.26 (7.10) |
| | SCL-90 Anxiety* (possible score range: 0-4) | 0.40 (0.65) |
| | SCL-90 Depression* (possible score range: 0-4) | 0.50 (0.51) |

Note: *Median and interquartile range was used to describe those variables given there are outliers for those variables.
SD: Standard Deviation; DAS: Dyadic Adjustment Scale; MHLC: Multidimensional Health Locus of Control; SCL: Symptom Checklist

**Trajectories of Self-Care Agency**

Based on the group-based trajectory modeling, a model with three distinct stable (i.e., zero slope) trajectory groups provided best fit to the data (BIC=-1573.58). As shown in Figure 2, group 1 (*persistently low SCA*) consisting of 21.34% of the sample (n=20) was characterized by a flat trajectory (zero slope) with an intercept of 199.65 ($p<.001$). This group had a relatively low SCA (199.65 out of 265) at baseline that persisted throughout the 12 months of follow-up. Group 2 (*persistently moderate SCA*, n=46, 48.64%), also had a flat trajectory (zero slope) but with a relatively higher intercept (intercept, $b_0=223.32$, $p<.001$). This trajectory was characterized by a moderate level of SCA (223.32 out of 265) at baseline that persisted at this level over 12 months of follow-up. Group 3 (*persistently high SCA*, n=28, 30.01%) with a flat zero-slope trajectory ($b_0=247.26$, $p<.001$). These participants started at a relatively high level of SCA (247.26 out of 265) compared to the other two groups and stayed at this level over 12 months of follow-up.

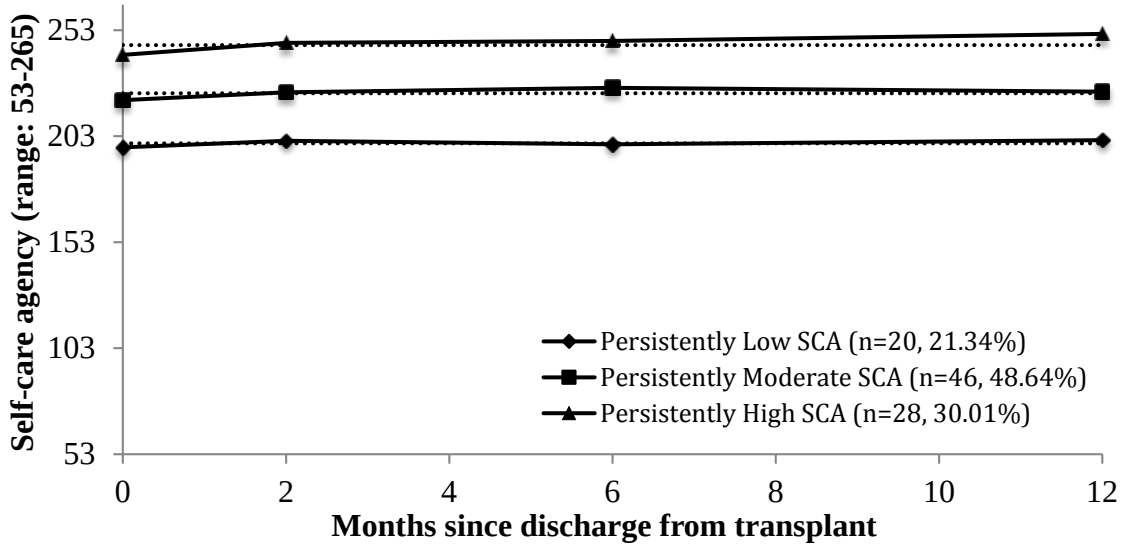



**Figure 2 Trajectory Groups for Self-Care Agency (SCA) over the First 12-months after Discharge from Lung Transplant***

*Note: Solid lines are based on actual SCA scores and dashed lines are based on predicted values from group-based trajectory modeling.

**Baseline Correlates of Membership in the Persistently Low SCA Group**

As reported in Table 5, 7 candidate correlates met the threshold of p<.30 based on the univariate analyses and were included in the full multivariate model for membership in the persistently low SCA group: age, need for re-intubation, discharge destination, length of stay, pre-discharge anxiety, pre-discharge depression, and quality of recipient-caregiver relationship. Using a backward elimination approach, we obtained the most parsimonious model with only 3 correlates retained, including requiring a re-intubation during hospital stay (OR=2.61, 95% CI: 1.03-6.55, p=.043), discharged to a facility other than home (OR=3.53, 95% CI: 1.01-12.30, p=.048), and higher baseline level of anxiety (OR=4.06, 95% CI: 1.79-9.21, p=.001).

**Table 5 Baseline Correlates of Membership in the Persistently Low Self-Care Agency (SCA) Group**

| Baseline Correlates | Univariate Model for 7 Candidate Correlates | | | Parsimonious Multivariate Model after Backward Elimination at p (removal) ≥.05 | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p | OR | 95% CI | p |
| Age (years)* | 1.02 | 0.99, 1.05 | .15 | | | |
| Discharged to any facility other than home | 4.76 | 1.49, 14.29 | .01 | 3.53 | 1.01, 12.30 | .048 |
| Re-intubated during hospital stay | 2.56 | 1.08, 6.25 | .03 | 2.61 | 1.03, 6.55 | .043 |
| Length of hospital stay (days)* | 1.02 | 1.00, 1.04 | .07 | | | |
| Quality of caregiver-recipient relationship | 0.92 | 0.86, 0.97 | .004 | | | |
| SCL-90 Anxiety | 4.35 | 1.92, 9.09 | <.001 | 4.06 | 1.79, 9.21 | .001 |
| SCL-90 Depression* | 4.17 | 1.92, 1.85 | .001 | | | |

Notes: *These correlates were dropped in the final parsimonious model when using backward elimination approach.
b: regression coefficient; OR: Odds Ratio; CI: Confidence Interval; p: p-value; SCL: Symptom Checklist

**Longitudinal Correlates of SCA**

Table 6 shows the descriptive statistics (means and standard deviations) and the linear mixed modeling results for longitudinal correlates of SCA. There was a significant group effect ($p=0.002$) for anxiety, suggesting that the changes in anxiety score over the 12 months were distinctly different among the three SCA groups such that the *persistently high SCA* group had significantly lower anxiety levels than both the *persistently low SCA* group ($p=0.03$) and the *persistently moderate SCA* group ($p=0.049$) (Figure 3). There was a significant group effect ($p<0.001$) and group by time interaction effect ($p=0.01$) for depression, suggesting that the changes in depression among the three SCA groups differed over time (Figure 4). Specifically, significantly lower levels of depression were observed in the *persistently high SCA* group relative to those observed in both the *persistently low SCA* group ($p=0.002$) and the *persistently moderate SCA* group ($p<0.001$). This suggests that higher depression levels were associated with relatively lower SCA levels in *persistently moderate and low SCA* groups. These overall patterns of differing depression levels across the three groups held up even though there were within group changes in depression levels at varying time points (Figure 4). Specifically, depression levels decreased at the 6-month interval within the *moderate SCA* group and increased within the *low SCA* group but neither of these changes were of a magnitude large enough to match the depression levels observed within the other groups.

**Table 6 Descriptive Statistics (mean and standard deviation) and Linear Mixed Modeling Results for Longitudinally Assessed Correlates by Predicted Self-Care Agency (SCA) Trajectory Groups**

| | Persistently Low SCA | Persistently Moderate SCA | Persistently High SCA | p-values | | |
|---|---|---|---|---|---|---|
| | | | | Group | Time | Group by Time Interaction |
| SCL-90 Anxiety | | | | | | |
| 2 months | 0.80 (0.61) | 0.55 (0.50) | 0.22 (0.26) | .002 | .08 | .16 |
| 6 months | 0.72 (0.54) | 0.44 (0.39) | 0.33 (0.42) | | | |
| 12 months | 0.48 (0.38) | 0.41 (0.40) | 0.22 (0.28) | | | |
| SCL-90 Depression | | | | | | |
| 2 months | 1.03 (0.72) | 0.66 (0.56) | 0.29 (0.27) | <.001 | .09 | .01 |
| 6 months | 1.06 (0.61) | 0.55 (0.34) | 0.44 (0.40) | | | |
| 12 months | 0.70 (0.44) | 0.65 (0.36) | 0.27 (0.25) | | | |

SCA: Self-Care Agency; SCL: Symptom Checklist

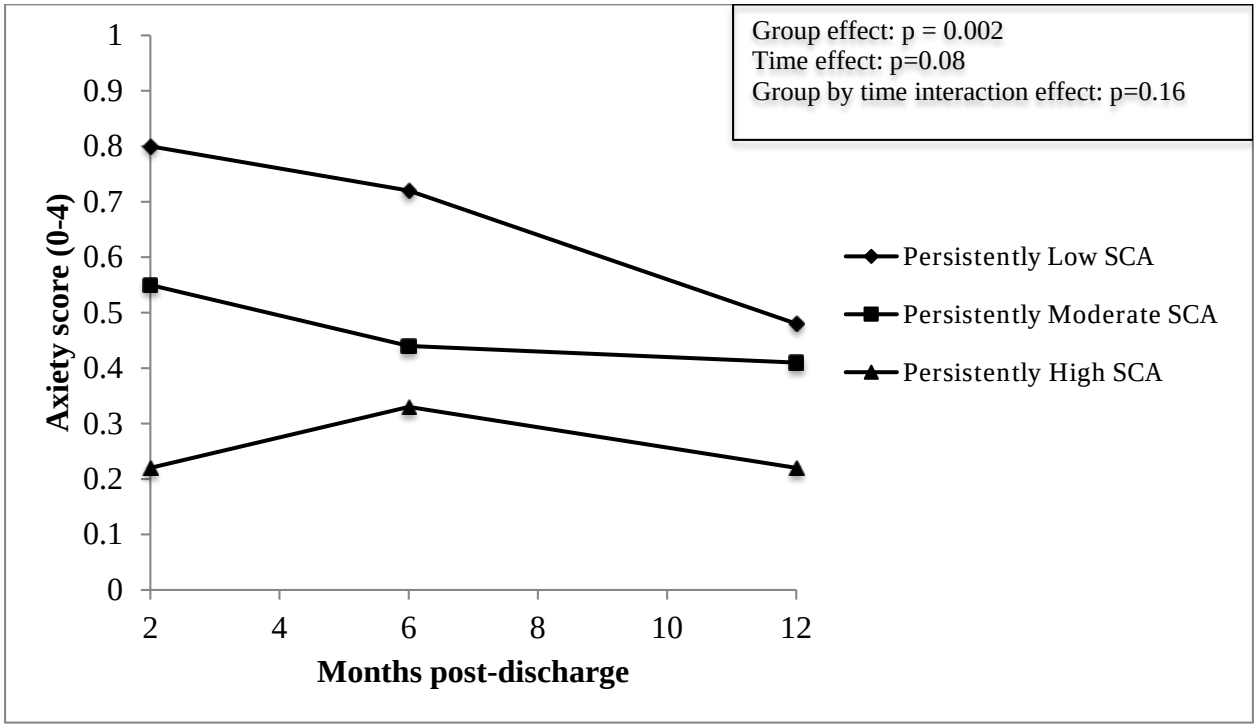



**Figure 3 Levels of Anxiety over 12-months by Three Self-Care Agency (SCA) Trajectory Groups**

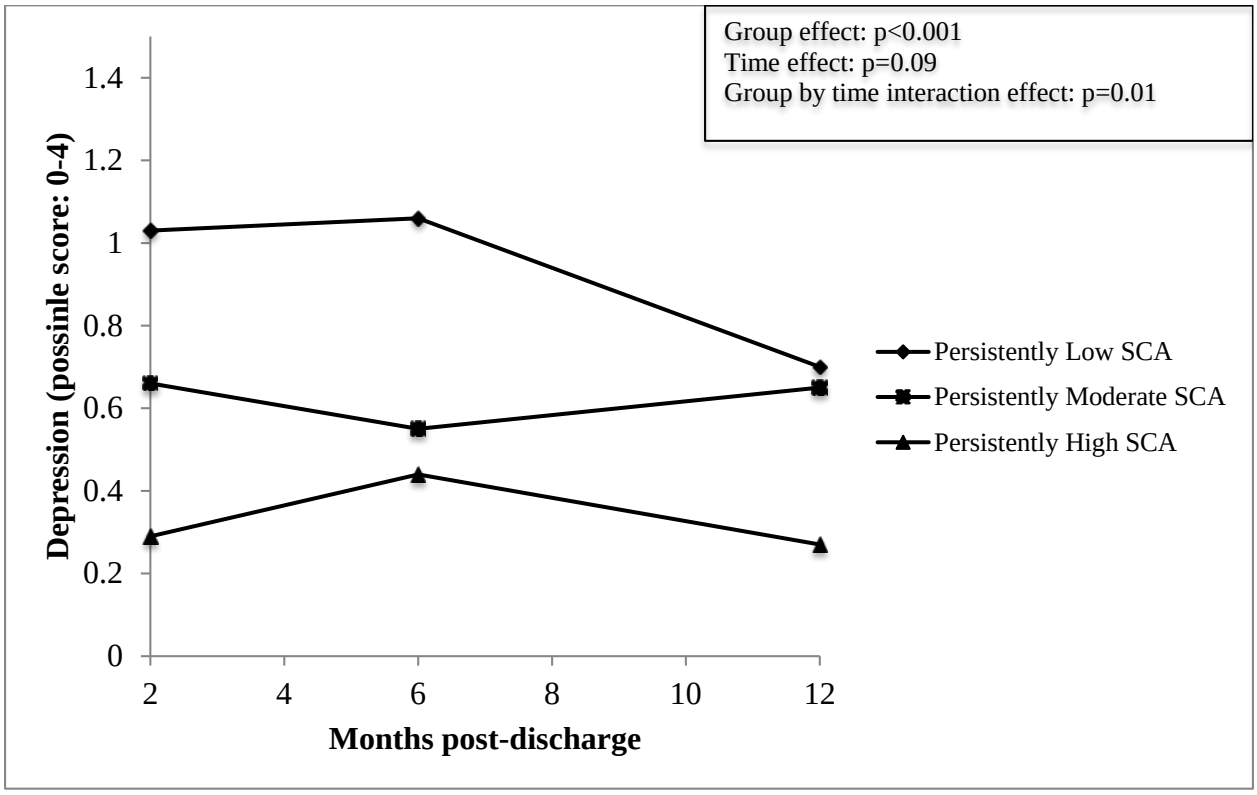



**Figure 4 Levels of Depression over 12-months by Three Self-Care Agency (SCA) Trajectory Groups**

## 3.5 DISCUSSION

This study examined patterns of SCA over the first 12-months post-hospital discharge after transplant. Three patterns of SCA were identified: a *persistently low SCA group, a persistently moderate SCA group and a persistently high SCA group*. This suggests that SCA levels remained relatively stable within each group over time. Of particular note, there were approximately 20 points differences in SCA levels among the three trajectory groups. While higher scores indicate higher perceived SCA, it is unclear whether these 20 points reflect clinically meaningful differences.

While we found that under a usual care condition SCA levels were stable, others have demonstrated that SCA is responsive to interventions and can improve over time (DeVito Dabbs et al., 2009; Drevenhorn et al., 2015). For example, DeVito Dabbs and colleagues (2009) demonstrated that a mobile health intervention significantly increased SCA and overall adherence among LTRs compared to the usual care group. These findings suggest the importance of assessing LTRs' SCA prior to discharge and intervening early to reinforce and/or strengthen LTRs' SCA (Cebeci & Çelik, 2007), and ultimately to promote better health outcomes over time.

This study also examined correlates associated with patterns of SCA. We found that LTRs who required re-intubation during the transplant hospitalization or were discharged to care facilities other than home, were more likely to report a lower level of SCA. Requiring a re-intubation or discharged to care facilities may indicate the poor physical health status of LTRs. The relationship between poorer physical health and lower SCA has been reported in other chronic diseases population (Lukkarinen & Hentinen, 1997; Ovayolu et al., 2012). It is possible that poor physical health status diminishes one's confidence in ability to perform self-care behaviors (Sabati, Snyder, Edin-Stibbe, et al., 2001). In cases where SCA is likely to be significantly compromised by poor health over time, it may be important to engage family caregivers as co-managers of the LTRs' health post-transplant (DeVito Dabbs, Song, De Geest, & Davidson, 2013; Dew et al., 2008; Rosenberger, Dew, DiMartini, DeVito Dabbs, & Yusen, 2012).

The current study revealed a significant negative correlation between psychological distress and SCA level with higher levels of baseline anxiety associated with lower SCA. This finding is consistent with the earlier report (DeVito Dabbs et al., 2013) which found that LTRs with higher psychological distress level prior to discharge were more likely to report lower SCA. This negative relationship has also been reported in other populations, such as patients with chronic

obstructive pulmonary diseases (Yildirim et al., 2013), coronary heart disease (Lukkarinen & Hentinen, 1997), and patients receiving percutaneous coronary intervention (Lauck et al., 2009). The current study confirms that baseline distress levels are inversely related to baseline SCA levels, and that this association persists over time. Psychological distress has been shown to negatively influence a person's motivation, self-concept and ability to problem solve and cope (Coleman & Newton, 2005). This may explain why LTRs with higher distress report lower SCA, highlighting the importance of monitoring psychological distress over time and intervening to reduce the distress among LTRs following transplantation when needed.

Several limitations were noted in this study. As a secondary data analysis, the study is limited to the data collected for the parent study, which precludes the possibility of including other potential associated factors noted in the literature such as sense of coherence (defined as ability to deal with stressors) (Dale et al., 2012; Fex, Flensner, Ek, & Söderhamn, 2012). The sample was recruited from a single transplant program, which may limit the generalizability of our research findings, although the sample was representative of LTRs population in the United States (Organ Procurement and Transplantation Network, 2012). We only focused on the group who were randomized to the usual care group, which limited our sample size. However, we employed several strategies (i.e., univariate screening and backward elimination) and ensured that the respondent-to-variable ratio met the suggested target of 10:1 (Tabachnick & Fidell, 2007). Lastly, some of the correlates, such as the quality of recipient-caregiver relationship, were only measured at baseline, limiting our ability to explore how these correlates may be associated with SCA over time.

## 3.6 CONCLUSIONS

In conclusion, this is the first study to examine longitudinal patterns of SCA and its associated correlates over the first 12-months after discharge from transplant hospitalization. Three stable patterns of SCA were identified, indicating that under usual care conditions, over the first 12-months post-hospital discharge after transplant, SCA is a relatively stable phenomenon. The negative association between psychological distress and SCA points to important targets for strengthening SCA, promoting self-care, and ultimately optimizing health outcomes after lung transplantation.

# 4.0 MANUSCRIPT 3: PATTERNS AND CORRELATES OF ADHERENCE TO SELF-MONITORING IN LUNG TRANSPLANT RECIPIENTS DURING THE FIRST 12-MONTHS AFTER DISCHARGE FROM TRANSPLANT

## INTRODUCTION TO MANUSCRIPT 3

This chapter reports findings regarding the third aim of this dissertation, that is, **Aim 3:** Identify distinct patterns and correlates of adherence to self-monitoring in LTRs over the first 12-months post-hospital discharge after transplant.

Among the elements of post-transplant medical regimen, we specifically focused on adherence to self-monitoring among LTRs because adherence to this element is particularly difficult for LTRs (DeVito Dabbs et al., 2009; Dew, DiMartini, et al., 2008) and the cumulative incidence rate for nonadherence to self-monitoring was unacceptably high (i.e., more than 62.0% nonadherence rate by the end of 2 year post-transplant) (Dew, DiMartini, et al., 2008). Despite the prevalence of this issue, limited evidence is available regarding the longitudinal patterns and correlates of adherence to self-monitoring among LTRs. Therefore, to address this gap, we examined longitudinal patterns and correlates of adherence to self-monitoring among LTRs during the first 12-months post-discharge from transplant hospitalization.

## 4.1 ABSTRACT

**Background:** Lung transplant recipients (LTRs) often experience complications such as graft rejection and infection. Daily self-monitoring of lung function, vital signs and symptoms is crucial to ensure early detection of complications and prompt intervention. Yet, nonadherence to self-monitoring among LTRs is high and little is known regarding the patterns and correlates of adherence to self-monitoring among LTRs. This study sought to explore patterns and correlates of adherence to self-monitoring among LTRs over the first year post-discharge from transplant.

**Methods:** This correlational secondary analysis used data from participants assigned to the usual care arm of a randomized clinical trial who tracked self-monitoring activities using paper-and-pencil logs. Adherence was calculated as the percent of days LTRs recorded any self-monitoring data per interval: hospital discharge to ≤2 months, > 2 to ≤6 months, and >6 to ≤12 months. Group-based trajectory modeling was used to identify trajectory patterns of adherence to self-monitoring. Binary logistic regression and linear mixed modeling were used to examine baseline and longitudinal correlates of predicted group membership.

**Results:** The sample (N=91) was mostly white (87.9%), male (61.5%), with a mean age of 57.19 (SD=13.76) years. Group-based trajectory analyses revealed 2 groups: 1) *moderately adherent with slow decline* (n=29, 31.9%) and 2) *persistently nonadherent* (n=62, 68.1%). Multivariate binary logistic regression revealed the following baseline correlates of membership in the *persistently nonadherent* group: female (p=.035), higher baseline anxiety (p=.008), and weaker sense of personal control over health (p=.005). Poorer physical health over 12-months were associated with the membership in the *persistently nonadherent* group ($p$<.05).

**Conclusions:** This study revealed two adherence patterns and highlighted several modifiable factors for the membership in the *persistently nonadherent* to self-monitoring group, suggesting

future interventions should aim to reduce post-transplant anxiety, and strengthen sense of control for one's own health in LTRs.

## 4.2 INTRODUCTION

To date, more than 47,000 persons have undergone lung transplantation worldwide, a number largely limited by the scarcity of organ donors (International Society for Heart and Lung Transplant, 2015). Despite improved physical functioning and quality of life, lung transplant recipients' survival is often compromised by the high susceptibility to infections and graft rejection (Demeo & Ginns, 2001; DeVito Dabbs et al., 2003; Trulock et al., 2007; Yusen et al., 2014) with approximately 75% of LTRs developing infection and 50% developing acute rejection during the first year post-transplantation (Burguete, Maselli, Fernandez, & Levine, 2013). Thus, there is a pressing need to detect complications early and intervene promptly to maximize outcomes in LTRs. Frequent self-monitoring of health conditions at home has been shown as a reliable and valid approach for early detection and prompt treatment-seeking to reduce morbidity and mortality (Finkelstein et al., 1993; Morlion et al., 2002; Otulana et al., 1990).

Prior to discharge, LTRs are instructed to perform self-monitoring activities including daily assessment of lung function using a home spirometer, vital signs, and common symptoms of post-transplant complications (Chhajed, Tamm, Malouf, & Glanville, 2002; Chlan et al., 1998; Finkelstein et al., 1996, 1999; Goldstein, Snyder, Edin, Lindgren, & Finkelstein, 1996; Kugler et al., 2009, 2010; Kukafka, O'Brien, Furukawa, & Criner, 1997; Yoon et al., 2008). One study showed that 100% adherence to home self-monitoring reduced total post-transplant medical costs by more than 50% (Adam, Finkelstein, Parente, & Hertz, 2007). Despite the well-recognized

importance of self-monitoring, adherence to self-monitoring among LTRs is less than ideal (Dew, DiMartini, DeVito Dabbs, et al., 2008; Kugler et al., 2009, 2010; Lindgren et al., 2002; Morlion, Knoop, Paiva, & Estenne, 2002; Teichman, Burker, Weiner, & Egan, 2000; Yoon et al., 2008) with nonadherence rates for performing spirometry reportedly as high as 54.6% and 65.9% at 12 and 24 months post-transplant, respectively (Dew, DiMartini, et al., 2008). Without a clear understanding of the patterns and correlates of adherence to self-monitoring, it is difficult to design, implement, and evaluate interventions to address this problem.

According to the World Health Organization (WHO) (World Health Organization, 2003), there are five major dimensions affecting adherence behaviors: 1) social/economic factors; 2) patient-related factors; 3) condition-related factors; 4) therapy-related factors; and 5) health system-related factors. Factors in each of the five dimensions have been examined in the context of adherence to self-monitoring after lung transplantation (Dew, DiMartini, DeVito Dabbs, et al., 2008; Kugler, Gottlieb, et al., 2010; Lindgren et al., 2002; Teichman et al., 2000). Yet, the published evidence regarding the correlates of adherence to self-monitoring has been limited in several ways. First, the evidence to date is limited in quantity. Our recent literature search of five large medical and nursing databases yielded only four published studies that examined the correlates of adherence to self-monitoring among LTRs (Dew, DiMartini, DeVito Dabbs, et al., 2008; Kugler, Gottlieb, et al., 2010; Lindgren et al., 2002; Teichman et al., 2000). Second, results from these four studies were inconsistent, limiting the conclusions that can be drawn about the correlates of adherence to self-monitoring. For example, age was not a significant correlate of adherence to self-monitoring of lung function in Dew et al. (2008) and Teichman et al. (2000), while Kugler and colleagues (2010) found that younger age (<40 years old) was significantly correlated with poorer adherence to home spirometry. Third, several methodological issues limit

the strength of the evidence, including small sample sizes (Teichman et al., 2000), reliance on cross-sectional study designs (Kugler, Gottlieb, et al., 2010; Lindgren et al., 2002; Teichman et al., 2000), and varying definitions of adherence to self-monitoring of lung function (Dew, DiMartini, et al., 2008; Kugler, Gottlieb, et al., 2010; Lindgren et al., 2002; Teichman et al., 2000). Finally, little is known about patterns of adherence to self-monitoring over time. To address this gap and identify distinct groups of individuals who demonstrate similar adherence patterns over time, in this study we used group-based trajectory modeling (Jones et al., 2001; Jones & Nagin, 2007). The aims of this study were to: 1) describe distinct patterns of adherence to self-monitoring and 2) identify correlates (representing each dimension of the WHO model) associated with patterns of adherence to self-monitoring during the first year after discharge from transplantation.

## 4.3 METHODS

### 4.3.1 Study design

This study was a correlational secondary analysis of data from a completed randomized controlled trial, Phase III Trial of Pocket PATH: A Computerized Intervention to Promote Self-Care (NR107011, PI: DeVito Dabbs) (DeVito Dabbs, Song, Myers, et al., 2013). The primary aim of the parent study was to test the efficacy of the Pocket PATH®, a mobile health intervention, relative to usual care to promote self-care behaviors (including adherence to daily self-monitoring) during the first year following discharge from the transplant hospitalization (DeVito Dabbs, Song, Myers, et al., 2013).

### 4.3.2 Sample and setting

We examined only the usual care group of the parent study for this investigation. This decision was made for the reason that our aim was to describe underlying patterns of adherence to self-monitoring but the Pocket PATH intervention might influence adherence to self-monitoring. Eligibility criteria for this current study were: 1) lung transplant recipient; 2) > 18 years of age; 3) be stable enough to be transferred from the cardiothoracic intensive care unit (ICU) to the acute care unit; 4) be able to speak and read English, 5) no previous organ transplantation, 6) expected to be involved in post-transplant care, and 7) randomized to the control condition (usual care). All participants were recruited from the Cardiothoracic Transplant Program of the University of Pittsburgh Medical Center prior to hospital discharge. IRB approval was obtained for the parent and current study.

### 4.3.3 Measures

**Outcome Variable: Adherence to Self-Monitoring.** Prior to discharge, participants in the usual care group were instructed to daily self-monitor a variety of health indicators on paper logs, including lung function using home spirometry, vital signs and symptoms. Adherence was calculated as the percent of days LTRs recorded data for any health indicator on the paper logs and this was calculated for each of the three intervals (hospital discharge to ≤2 months, > 2 to ≤6 months, and >6 to ≤12 months). These intervals were informed by the time intervals used in previous research (Dew, DiMartini, et al., 2008) and were also selected to be consistent with the measurement time points in the parent study (DeVito Dabbs, Song, Myers, et al., 2013) and to reflect typical intervals for follow up visits in clinical care. Total days per interval were adjusted

for any days that LTRs were re-hospitalized and therefore not expected to perform self-monitoring. The decision to count monitoring in any of these areas rather than analyzing the data for each type of self-monitoring activity was based on the following reasons. First, there is precedence for this approach in the literature, with at least 6 recent publications treating self-monitoring as a global concept (Adam et al., 2007; DeVito Dabbs et al., 2009, 2016; Finkelstein et al., 2013; Mullan et al., 2003; Wang et al., 2013). Second, from a clinical perspective, the instruction to self-monitor is typically delivered as one recommendation to perform self-monitoring behaviors for a related set of health indicators (vital signs, spirometer readings, and symptoms). Third, review of the descriptive data (i.e., frequency distribution) for each area of self-monitoring in our dataset revealed a similar degree of recording for vitals signs and spirometer readings.

**Potential Correlates of Adherence to Self-Monitoring**. The identification of the potential correlates of adherence that were examined in our analyses was informed by prior studies (Dew, DiMartini, De Vito Dabbs, et al., 2008; Kugler, Gottlieb, et al., 2010; Lindgren et al., 2002; Teichman et al., 2000) and based on the five dimensions of the WHO adherence model: social/economic, patient-related, condition-related, therapy-related, and healthcare system factors (World Health Organization, 2003).

**Social/Economic factors** included *socio-demographic characteristics* and the *quality of the patient's relationship with his/her family caregiver*. *Socio-demographic characteristics* were collected at baseline and included age, education, gender, race, employment status, marital status, and whether the respondents felt that their income met their household needs. Given that there was limited number of non-white or currently employed LTRs or LTRs who felt their income did not meet needs in this study, we omitted these variables for model building processes. *The quality of*

*the patient's relationship with his/her family caregiver* was measured at baseline using the 15-item adapted Dyadic Adjustment Scale (DAS) (Spanier, 1976). Higher scores indicate better relationship quality. Cronbach's alpha was 0.80 for this current sample.

**Patient-related factors** included *self-care agency* and the *patient's health locus of control*. *Self-care agency*, defined as ones' willingness and ability to perform self-care, was assessed using a 53-item scale, Perception of Self-Care Agency (Hanson & Bickel, 1985), at baseline, 2-, 6-, and 12-month post-discharge. Higher scores indicate higher levels of perceived self-care agency. Cronbach's alpha was 0.94 for our present sample. *The 18-item Multi-Dimensional Health Locus of Control Scale* (B. S. Wallston & Wallston, 1978; K. A. Wallston et al., 1978) (MHLC) was administered at baseline to measure the extent to which LTRs believed that health outcomes were 1) their own responsibility (internality) (Cronbach's alpha = 0.78 for this current sample), 2) their health professionals' responsibility (externality) (Cronbach's alpha = 0.43 for this current sample), or 3) determined by chance alone (chance) (Cronbach's alpha = 0.77 for this current sample). Higher scores reflect stronger beliefs in each of the three domains. Given that Cronbach's alpha was relatively low (0.43) for the externality subscale, we dropped it from our analysis.

**Condition-related factors** included the *underlying lung disease, levels of anxiety and depression, and physical and mental health-related quality of life*. The *underlying lung disease* (obstructive vs. non-obstructive) was collected from the medical record. The *anxiety and depression* subscales of the Symptom Checklist-90 (SCL-90) (Derogatis & Unger, 2009; Rodin & Voshart, 1986) were administered at baseline, 2-, 6-, and 12-month post-hospital discharge to assess symptoms of psychological distress during the past two weeks. Items were formatted using a 5-point Likert scale (0 "not at all" to 4 "extremely distressed"). The subscale scores were calculated by averaging the score for each item (Derogatis & Unger, 2009; Rodin & Voshart,

1986). Higher scores indicate greater levels of psychological distress (anxiety or depression). Cronbach's alpha was 0.86 and 0.82 for anxiety and depression subscales, respectively, in our current sample. The *physical component and mental component summary scores*, calculated based on the 8 subscales of the Medical Outcomes Study Short Form-36 (MOS SF-36) (Ware & Gandek, 1998; Ware & Sherbourne, 1992), were used to assess LTRs' health-related quality of life at 2-, 6-, and 12-month post-discharge. In this current sample, the Cronbach's alpha for the 8 subscales ranged from 0.79 to 0.96. Higher scores reflect better health-related quality of life.

**Therapy-related factors** included the *type of transplant, whether re-intubated or not post-transplant, days requiring chest tubes, and whether post-operation ventilator needs exceeded 48 hours.* Data for each of these variables were abstracted from medical record review at baseline.

**Health system-related factors** included *length of hospital stay, number of days in ICU,* and *discharge destination.* We abstracted these data from medical record review.

### 4.3.4 Statistical analysis

Descriptive analyses were conducted using IBM® SPSS® Statistics (Version 23, IBM Corp., Armonk, NY). The level of statistical significance was set at 0.05 for two-tailed hypothesis testing. Data were screened for data anomalies (e.g., nonnormality, outliers, multicollinearity) and the amount and patterns of missing data. We calculated means and standard deviations for continuous variables without outliers and frequencies and percentages for categorical variables. For continuous variables with outliers, we reported median and interquartile ranges. We replaced outliers for each variable with the next highest/lowest values that are not outliers (Hastings et al., 1947).

We used PROC TRAJ in SAS (Version 9.4, SAS Institute Inc., Cary, NC) to perform the

group-based trajectory modeling (Jones et al., 2001; Jones & Nagin, 2007; Nagin, 2005) to identify distinct patterns of adherence to self-monitoring in LTRs during the first 12 months after discharge from transplant hospitalization. Based on Bayesian Information Criteria (BIC) values for competing models, the model with smallest BIC based on Bayes factor was chosen as having the best fit. Given that our data were found to be missing completely at random (MCAR) (SPSS MCAR test p=.96) and trajectory modeling is able to handle this type of missingness, imputation for missing data was not applied.

For baseline correlates, we applied univariate logistic regression analyses to examine the association between each correlate and the predicted group membership. Baseline correlates with p-values less than 0.30 in the univariate models were considered as candidates for the multivariate logistic regression models. We chose this liberal p-value cutoff as this approach is more likely to retain important factors in the final model given a small sample size (Babyak, 2004; Steyerberg et al., 2001). A backward elimination approach using likelihood ratio Chi-squared test statistic (Babyak, 2004; Steyerberg et al., 2001) was used to identify the final most multivariate parsimonious model retaining candidate factors significant at $p<0.05$. We calculated crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

For longitudinal correlates, we conducted linear mixed modeling to examine their associations with predicted group membership. These longitudinal correlates included self-care agency, SF-36 physical component summary (PCS), SF-36 mental component summary (MCS), and SCL-90 Anxiety and Depression subscales. We reported group effect, time effect and group by time interaction effect for each longitudinal correlate.

## 4.4 RESULTS

**Sample.** Individuals who did not provide any adherence data (n=3) and those who died during the study (n=8) were excluded from the analysis, which yielded a final sample of 91 LTRs for analysis. The excluded individuals were more likely to be female, have a diagnosis of obstructive lung disease, and report poorer quality of relationship with their caregivers.

Baseline characteristics of the total sample are displayed in Table 7. The total sample was predominantly white (87.9%), male (61.5%), and currently married (70.3%), with a mean age of 57.19 (SD=13.76) years. Most participants had above a high school education (68.1%) and reported having incomes that met their needs (80.0%).

**Table 7 Sample Characteristics and Baseline Correlates of Membership in the Persistently Nonadherent to Self-Monitoring Group Based on Univariate Logistic Regression Analyses**

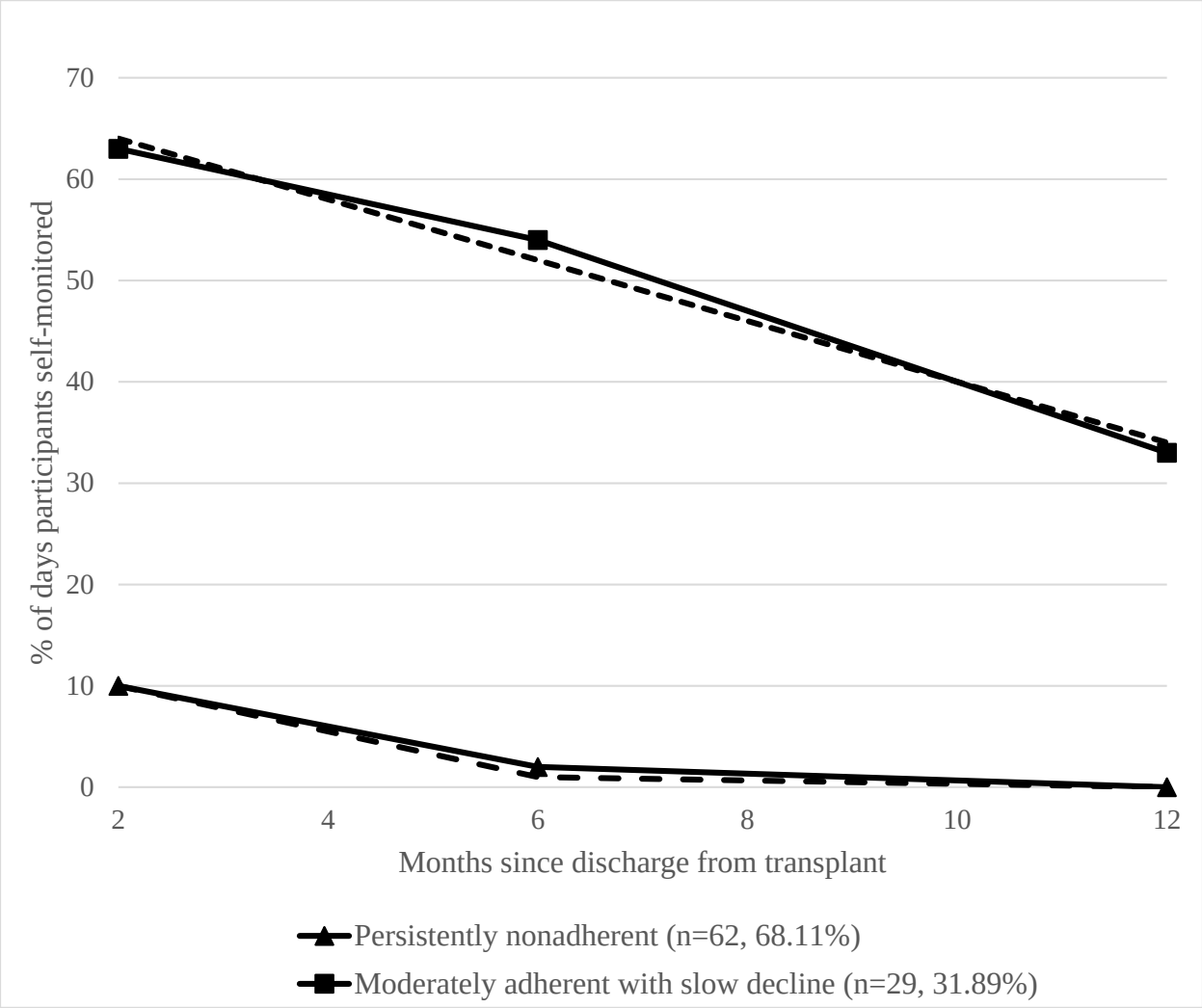
| | | Adherence to Self-Monitoring | | | |
|---|---|---|---|---|---|
| **Correlates** | **Total Sample (N=91) M±SD or n (%)** | **Moderately adherent with slow decline group (n=29) M±SD or n (%)** | **Persistently nonadherent group (n=62) M±SD or n (%)** | **Unadjusted Odd Ratio** | **95% CI** |
| **Social/Economic** | | | | | |
| Age (years) | 57.19±13.76 | 58.62±15.47 | 56.52±12.97 | 0.99 | 0.96, 1.02 |
| > High school education | 62 (68.1%) | 20 (69.0%) | 42 (67.7%) | 0.95 | 0.37, 2.44 |
| Currently employed | 7 (7.7%) | 3 (10.3%) | 4 (6.5%) | n/a | n/a |
| Non-white | 11 (12.1%) | 1 (3.4%) | 10 (16.1%) | n/a | n/a |
| Female | 35 (38.5%) | 6 (20.7%) | 29 (46.8%) | 3.37 | 1.21, 9.41 |
| Income met needs: No | 18 (20%) | 2 (6.9%) | 16 (26.2%) | n/a | n/a |
| Currently married or living with a partner | 64 (70.3%) | 23(79.3%) | 41 (66.1%) | 0.51 | 0.18, 1.44 |
| Quality of dyadic relationship* | 68.00±7.00 | 68.00±9.75 | 67.00±5.50 | 0.98 | 0.92, 1.06 |
| **Patient-related** | | | | | |
| MHLC internal subscale | 23.96±6.48 | 26.72±6.27 | 22.66±6.21 | 0.90 | 0.83, 0.97 |
| MHLC chance subscale | 18.29±7.02 | 17.80±6.43 | 18.52±7.32 | 1.02 | 0.95, 1.08 |
| Self-care agency | 222.24±23.90 | 224.14±20.78 | 221.35±25.3 | 1.00 | 0.98, 1.01 |
| **Condition-related** | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Obstructive lung disease | 37 (40.7%) | 10 (34.5%) | 27 (43.5%) | 1.47 | 0.59, 3.66 |
| SCL-90 anxiety score* | 0.40±0.73 | 0.30±0.30 | 0.50±0.95 | 4.26 | 1.37, 13.28 |
| SCL-90 depression score | 0.62±0.55 | 0.44±0.34 | 0.70±0.61 | 3.15 | 1.05, 9.42 |
| **Treatment-related** | | | | | |
| Single lung transplant | 16 (17.6%) | 7 (24.1%) | 9 (14.5%) | 0.53 | 0.18, 1.61 |
| Re-intubated | 26 (28.6%) | 6 (20.7%) | 20 (32.3%) | 1.83 | 0.64, 5.19 |
| Post-op ventilator needs ≥48 hours | 35 (38.5%) | 7 (24.1%) | 28 (45.2%) | 2.59 | 0.97, 6.94 |
| Days with chest drain* | 12.00±8.75 | 12.50±10.25 | 12.00±8.00 | 1.00 | 0.95, 1.06 |
| **Healthcare system-related** | | | | | |
| Length of hospital stay (days)* | 31.00±27.00 | 27.00±25.00 | 33.00±28.25 | 1.01 | 0.99, 1.03 |
| Days in ICU* | 6.00±10.00 | 4.00±5.00 | 7.00±11.50 | 1.01 | 0.97, 1.05 |
| Discharge to any home setting | 78 (85.7%) | 24 (82.8%) | 54 (87.1%) | 0.71 | 0.21, 2.40 |

Note: *Medians and inter-quartile ranges were reported for those variables with outliers.
M: Mean; SD: Standard deviation; CI: Confidence Interval; MHLC: Multidimensional Health Locus of Control; ICU: Intensive Care Unit; SCL-90: Symptom Checklist 90.

**Patterns of Adherence to Self-Monitoring.** Group-based trajectory modeling revealed that there were 2 adherence trajectory patterns: 1) *moderately adherent with slow decline* and *2) persistently nonadherent*. As shown in Figure 5, the *moderately adherent with slow decline* group (n=29, 31.89%) started with 63.84% adherence to self-monitoring and linearly declined at a small slope ($b_1$=-4.03, p=0.002) over time. The *persistently nonadherent* group (n=62, 68.11%) started at a low percent of adherence (10.02%) at 2 months and declined to 1% adherence at 6-months and 0% at 12 months, meaning they performed minimal self-monitoring over 12 months. This group declined at a much greater slope ($b_1$=-12.34, p=0.007).

**Figure 5 Estimated Trajectory Groups of Adherence to Self-Monitoring**




Note: Solid lines are mean percent adherence based on raw data and dashed lines are predicted mean percent adherence based on trajectory modeling.

**Baseline Correlates of Adherence to Self-Monitoring.** As displayed in Table 8 (Model 1), 8 candidate correlates met the threshold of $p<0.30$ based on the univariate analyses, including: gender, marital status, internal health locus of control, anxiety, depression, type of transplant, whether re-intubated post-transplant, and post-operation ventilator needs. Using a backward elimination approach, we obtained the most parsimonious model with only 3 correlates retained,

including gender, internal health locus of control, and anxiety (See Model 2 in Table 8). More specifically, the adjusted odds of being in the *persistently nonadherent* group (as opposed to the *moderately adherent with slow decline* group) was 3.39 (95% CI, 1.09-10.53) for females, 1.14 (95% CI: 1.04-1.26) for every one unit decrease in internal health locus of control, and 6.08 (95% CI, 1.60-23.07) for every one unit increase in anxiety.

**Table 8 Adjusted Odds Ratios for Membership in the Persistently Nonadherent Group Based on Multivariate Logistic Regression**

| Baseline Correlates | Adjusted OR (95% CI) in Model 1[a] | Adjusted OR (95% CI) in Model 2[b] |
|---|---|---|
| **Social/Economic** | | |
| Female | 2.54 (0.66, 9.76) | 3.39 (1.09, 10.53) |
| Currently married | 0.82 (0.21, 3.28) | |
| **Patient-related** | | |
| MHLC Internal subscale score | 1.14 (1.03, 1.25) | 1.14 (1.04, 1.26) |
| **Condition-related** | | |
| SCL-90 anxiety score | 7.41 (0.95,57.69) | 6.08 (1.60, 23.07) |
| SCL-90 depression score | 0.75 (0.11, 5.12) | |
| **Treatment-related** | | |
| Single lung transplant | 0.76 (0.20, 2.91) | |
| Re-intubated: Yes | 1.27 (0.36, 4.45) | |
| Post-op ventilator needs >=48 hours | 1.80 (0.52, 6.24) | |

[a] Model 1: represents the multivariate model with all possible candidate correlates ($p < 0.30$) identified from univariate logistic regression analyses

[b] Model 2: represents the most parsimonious model with all correlates in the model significant at $p < 0.05$ after applying backward elimination to Model 1

OR: Odds Ratio; CI: Confidence Interval; MHLC: Multidimensional Health Locus of Control; SCL-90: Symptom Checklist 90.

**Longitudinal Correlates of Adherence to Self-Monitoring**

Table 9 summarizes the descriptive statistics (means and standard deviations) and the linear mixed modeling results for longitudinal correlates of adherence to any self-monitoring including, self-care agency, physical component summary score, mental component summary score, anxiety and depression subscales. Given that our aim was to examine whether these longitudinal correlates were associated with the predicted membership, we mainly focused on identifying group effects or group by time interaction effects. There was a significant group effect for the physical component summary score (p=0.004), suggesting that lower physical component summary scores of the quality of life measure were associated with the membership in the *persistently nonadherent group* over the 12 month of observation. All the other longitudinal correlates were not significant.

**Table 9 Descriptive Statistics (mean and standard deviations) and Linear Mixed Modeling Results for Longitudinal Correlates by Predicted Trajectory Group Membership**

| Correlates | Moderately adherent with slow decline group (n=29) | Persistently nonadherent group (n=62) | p-values | | |
|---|---|---|---|---|---|
| | | | Group | Time | Group*Time Interaction |
| Self-Care Agency | | | | | |
| 2 months | 227.21 (26.94) | 226.03 (22.50) | 0.13 | 0.52 | 0.05 |
| 6 months | 235.28 (21.06) | 223.25 (23.18) | | | |
| 12 months | 232.71 (24.17) | 225.29 (23.85) | | | |
| SF-36 PCS | | | | | |
| 2 months | 41.58 (7.85) | 36.99 (9.30) | 0.004 | <0.001 | 0.47 |
| 6 months | 45.59 (9.33) | 38.91 (10.93) | | | |
| 12 months | 46.11 (8.80) | 41.52 (10.51) | | | |
| SF-36 MCS | | | | | |
| 2 months | 51.65 (11.99) | 51.44 (10.78) | 0.58 | 0.13 | 0.56 |
| 6 months | 52.17 (10.21) | 52.46 (9.54) | | | |
| 12 months | 55.63 (5.89) | 53.06 (8.74) | | | |
| SCL-90 Anxiety | | | | | |
| 2 months | 0.38 (0.34) | 0.57 (0.62) | 0.11 | 0.06 | 0.51 |
| 6 months | 0.40 (0.37) | 0.49 (0.49) | | | |
| 12 months | 0.31 (0.34) | 0.39 (0.39) | | | |
| SCL-90 Depression | | | | | |
| 2 months | 0.55 (0.51) | 0.67 (0.65) | 0.24 | 0.23 | 0.85 |
| 6 months | 0.58 (0.60) | 0.66 (0.48) | | | |
| 12 months | 0.45 (0.30) | 0.59 (0.42) | | | |

Note: SF-36: Short Form-36; PCS: Physical Component Summary; MCS: Mental Component Summary; SCL-90: Symptom Checklist-90.

## 4.5 DISCUSSION

This study employed trajectory modeling to examine patterns and correlates of adherence to self-monitoring over the first year after discharge from transplant hospitalization. Findings revealed two distinct patterns of adherence to self-monitoring, namely *persistently nonadherent* and *moderately adherent with slow decline* and identified several baseline and longitudinal correlates associated with predicted trajectory group membership.

Having lower internal health locus of control beliefs at baseline was a significant correlate of membership in the *persistently nonadherent* group, which is consistent with findings of Dew et al. (2008) that having a weaker belief that one's own actions influenced health outcomes increased the odds of being persistently nonadherent to performing spirometry. While the mean score of internal health locus of control for our overall sample is comparable to that in previous reports (DeVito Dabbs, Kim, Hamdan-Mansour, Thibodeau, & McCurry, 2006; Lindgren et al., 2002), our results showed that the *persistently nonadherent* group possessed a significantly lower internal health locus of control than the *moderately adherent* group, suggesting that clinicians should encourage LTRs to play an active role and reinforce the importance of taking personal responsibility in post-transplant care management.

Our results demonstrated that poorer ratings of the physical health component of quality of life were associated with the membership in the *persistently nonadherent* group over the 12-months post-discharge. This is consistent with findings of previous qualitative evidence that reported LTRs' views that their perceived poor physical health is a major barrier for adherence to self-monitoring of lung function (Kugler, Gottlieb, et al., 2010; Sabati, Snyder, Edin-Stibbe, et al., 2001). We also found that endorsing a higher anxiety level was associated with being persistently nonadherent. The negative association between psychological distress and 1) self-care agency, 2)

adherence behaviors and 3) transplant-related health outcomes among LTRs and other solid organ recipients has been well-established (Barbour, Blumenthal, & Palmer, 2006; DeVito Dabbs, Terhorst, Song, et al., 2013; Dew & DiMartini, 2005; Dew et al., 2012, 2015; Rosenberger et al., 2012). Clinicians can apply this evidence to identify LTRs with higher physical and psychological burden and intervene to directly address these perceptions and potentially promote better self-monitoring and better outcomes.

We found that female LTRs were at increased risk of being in the persistently nonadherent group. Being female has also been found to be a significant predictor of nonadherence to home spirometry by Dew and colleagues (2008). While the reason for this finding has not been well examined, it is possible that female LTRs may have more competing priorities with self-management (Manteuffel et al., 2014), which lead to limited attention to their own health issues, and thus, lower adherence. These findings suggest that clinicians may need to identify unique barriers to adherence among female LTRs and monitor their adherence more closely after discharge.

Two distinct adherence patterns were identified in this current study, *moderately adherent with slow decline* and *persistently nonadherent*. Although the *moderately adherent group* demonstrated better adherence to self-monitoring than *the persistently nonadherent* group, the adherence level declined over time in both groups. This decline in adherence behavior has been repeatedly observed in prior studies (De Geest et al., 2014; Dew, DiMartini, et al., 2008). In addition, our results showed that even with the better adherence group, they only started with moderate level of 63.84% adherence to self-monitoring at 2-months post-discharge. This together suggests that adherence to self-monitoring is a problematic issue and continues to be challenging in LTRs. Clinicians may need to reinforce the importance of self-monitoring and regularly check

LTRs' adherence to self-monitoring during their clinical follow up visits. This also points to a pressing need for more intervention studies to explore effective strategies to promote and sustain adherence to self-monitoring in LTRs.

**Limitations**

This study has several limitations. As a secondary analysis of data from a completed study, we were unable to collect data for additional variables that may have influenced adherence to self-monitoring, such as patient's beliefs about self-monitoring. Also, some variables, such as the quality of the relationship with caregiver and health locus of control beliefs were only measured at baseline, limiting our ability to examine them as longitudinal correlates of adherence to self-monitoring. Because our aim was to describe the natural course of adherence to self-monitoring over the first year post-transplant, we only studied LTRs randomized to the usual care arm of the parent study, which provided a relatively small sample size for this analysis. However, we did employ several approaches (e.g., we screened univariate relationships first to identify candidate correlates ($p<0.30$) in the multivariate models, and used backward elimination to reach a most parsimonious model) which permitted us to meet the recommended case-to-variable ratio of 10:1 (Tabachnick & Fidell, 2007). Also, we relied on paper logs as a proxy measure of self-monitoring, which may have underestimated adherence because participants may have performed self-monitoring but not necessarily documented on the paper log. In addition, we used a global measure of self-monitoring, that is self-monitoring of any health indicator (i.e., lung function, vital signs, symptoms), yet this global measure of self-monitoring has been reported and used often in the literature (Adam et al., 2007; DeVito Dabbs et al., 2009; Finkelstein et al., 2013; Mullan et al., 2003; Wang et al., 2013). This study was conducted at only one transplant center which may have

limited the generalizability; however, the characteristics of our sample were representative of the United States samples (Organ Procurement and Transplantation Network, 2012). Despite its limitations, this study demonstrated the application of group-based trajectory modeling to the study of adherence behaviors in LTRs and is among the first study to explore the associations between longitudinal covariates and adherence behaviors over time, which could inform the design of future interventions.

## 4.6 CONCLUSIONS

Promoting adherence to self-monitoring could improve early detection and treatment of complications and thus optimize health outcomes for LTRs. Our findings suggested two distinct patterns of adherence to self-monitoring and pointed to several modifiable targets for interventions to promote adherence to self-monitoring among LTRs, such as reducing post-transplant anxiety, and strengthening the sense of personal control over health. Findings also suggest clinicians should target LTR who is female or has poor physical health as high-risk population for poor adherence to self-monitoring.

# 5.0 SUMMARY OF DISSERTATION FINDINGS

This dissertation project consists of 3 complementary studies to address several gaps in the scientific literature on adherence to the medical regimen following lung transplantation. Findings are documented in the following three manuscripts:

**Manuscript #1**: Nonadherence to the Medical Regimen after Lung Transplantation: A Systematic Review;

**Manuscript #2**: Patterns and Correlates of Self-Care Agency in Lung Transplant Recipients over the First 12-months Post-Hospital Discharge Following Transplantation; and

**Manuscript #3**: Patterns and Correlates of Adherence to Self-Monitoring in Lung Transplant Recipients over the First 12-months Post-Hospital Discharge Following Transplantation.

Although each of these three manuscripts had a distinct purpose, viewing their findings together reveals several key messages. **First, nonadherence to post-transplant medical regimen is a complex and prevalent issue among LTRs.** The complex nature of nonadherence was reflected in our systematic review (manuscript 1), which revealed that nonadherence rates varied greatly across studies and between different elements of the post-transplant medical regimen and could not be attributed to any specific factor. Findings of manuscript 3 confirmed that adherence to self-monitoring, in particular, was challenging and less than ideal among LTRs. Although the use of trajectory modeling helped to identify two distinct trajectory groups for adherence to self-monitoring, with one group maintaining a relatively higher level of adherence than the other group, adherence declined in both groups over the first 12-months post-discharge following transplant.

Indeed, the moderately adherent group maintained only 32% adherence to self-monitoring at the end of first-year. Taken together, these alarming findings affirm previous reports that nonadherence continues to be a challenging and prevalent issue among LTRs.

Evidence suggests that LTRs may stop self-monitoring because they failed to perceive a need to do so when their transplant care providers stopped reviewing the logs of their self-monitoring readings after the first few follow up visits (Dew et al., 2008). This highlights the critical role that clinicians play in promoting adherence to self-monitoring and the importance of empowering LTRs. Some examples of patient empowerment for clinicians to consider include: helping LTRs to establish the habits of self-monitoring during transplant hospitalization, reinforcing the importance of the patient's important role in ongoing self-monitoring, reviewing self-monitoring logs at follow up visits to emphasize the value of self-monitoring, and asking about and addressing barriers LTRs face in performing self-monitoring.

**Another key message from this dissertation work is that psychological distress is an important factor in post-transplant care of LTRs.** Our findings showed that higher levels of psychological distress were associated with both lower self-care agency (SCA) (manuscript 2) and being persistently nonadherent to self-monitoring (manuscript 3). It must be acknowledged that these are associations and not causal relationships. Specifically, it is plausible that psychological distress leads to lower SCA, but it is also plausible that individuals with lower SCA are more susceptible to psychological distress. While sychological distress may contribute to poorer adherence behaviors, the demands of adherence to a complex medical regimen may also lead to psychological distress. Regardless of the direction of these relationships, there is a case to be made for identifying and addressing psychological distress among LTRs. Given the clinical importance and high incidence rate of psychiatric disorders (reaching up to 30% in LTRs) (Dew et al., 2012),

transplant care teams should consider screening and treating psychological distress as one of major priorities in post-transplant care. Clinicians should identify those high-risk populations and intervene to help psychologically distressed individuals, which may include exploring and addressing the role of SCA or demands of the medical regimen, with the goal of ultimately positively impacting health outcomes among LTRs.

**Lastly, our findings revealed several other targets for promoting SCA and adherence behaviors among LTRs.** Findings from manuscript 3 suggested that having a weaker sense of control over one's own health (internality health locus of control) significantly increased the odds of being in the persistently nonadherent group. This points to the need to educate, encourage, and empower LTRs to take a more active role in their post-transplant care. Some strategies for patient empowerment have been mentioned above. In addition, we also found that poorer physical health status was associated with lower SCA (manuscript 2) and being persistently nonadherent to self-monitoring (manuscript 3). Given that poor physical health status may pose a health threat to LTRs, it is important for clinicians and researchers to engage family members more in the post-transplant care for LTRs who are struggling with poor health.

In conclusion, this dissertation provided an overview of the current state of science regarding adherence behaviors among LTRs and specifically explored adherence to self-monitoring and self-care agency among LTRs over the first 12-months post-discharge from transplantation. Knowledge obtained from this dissertation work suggests future research studies should explore the following issues:

1) Descriptive studies are needed to explore the clinically meaningful level of adherence to self-monitoring after lung transplantation.
2) Future intervention research on promoting adherence among LTRs should test theory-

driven strategies and consider assessing and reducing distress, and reinforcing sense of control over one's own health as components of their interventions. In addition, future interventions should also explore how to leverage current technologies to better measure and promote adherence among LTRs.

## APPENDIX A IRB APPROVAL LETTER FOR THIS DISSERTATION STUDY

**University of Pittsburgh**
***Institutional Review Board***

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

**Memorandum**

To: Lu Hu
From: IRB Office
Date: 2/27/2015
IRB#: PRO15020553
Subject: Trajectory Analysis of Adherence to Self-Monitoring in Lung Transplant Recipients

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The above-referenced project has been reviewed by the Institutional Review Board. Based on the information provided, this project meets all the necessary criteria for an exemption, and is hereby designated as "exempt" under section
45 CFR 46.101(b)(4).

Please note the following information:

- Investigators should consult with the IRB whenever questions arise about whether planned changes to an exempt study might alter the exempt status. Use the "**Send Comments to IRB Staff**" link displayed on study workspace to request a review to ensure it continues to meet the exempt category.
- It is important to close your study when finished by using the "**Study Completed**" link displayed on the study workspace.
- Exempt studies will be archived after 3 years unless you choose to extend the study. If your study is archived, you can continue conducting research activities as the IRB has made the determination that your project met one of the required exempt categories. The only caveat is that no changes can be made to the application. If a change is needed, you will need to submit a NEW Exempt application.

**Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.**

## APPENDIX B IRB APPROVAL LETTER FOR THE PARENT STUDY

**University of Pittsburgh**
***Institutional Review Board***

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

**Memorandum**

| | |
|---|---|
| To: | Dr. Annette De Vito Dabbs |
| From: | IRB Office |
| Date: | 4/7/2015 |
| IRB#: | REN15030291 / PRO08070401 |
| Subject: | Comparing Methods for Tracking Health Information at Home after Lung Transplant |

Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:

45 CFR 46.110.(5)
45 CFR 46.110.(6)
45 CFR 46.110.(7)

Please note the following information:

| | |
|---|---|
| Approval Date: | 4/7/2015 |
| Expiration Date: | 4/6/2016 |

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

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