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Feasibility and Acceptability of Integrative Therapy in Symptom Management for Persons with Pulmonary Hypertension

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Research Protocol

I. Introduction

Patients with severe, life-limiting cardiopulmonary (CP) conditions face particularly difficult symptom management challenges and poor health-related quality of life (HRQoL) (Ståhl et al., 2005; Taichman et al., 2005). Interventions are desperately needed to ameliorate symptom burden and promote quality of life in persons with severe and debilitating chronic CP conditions. Fifteen million Americans reported that they have been told by their healthcare providers that they have Chronic Obstructive Pulmonary Disease (COPD) and among these, 64.2% reported that shortness of breath interferes with their quality of life (Kosacz et al., 2012). Patients with heart failure experience high symptom prevalence (shortness of breath, lack of energy, and insomnia) and high symptom burden (difficulty sleeping) (Zambroski, Moser, Bhat, & Ziegler, 2005). Patients with pulmonary hypertension (PH) reported at least 17 bothersome symptoms with shortness of breath and fatigue to be the most prevalent with high intensity score (Matura, McDonough, & Carroll, 2014).There is a gap in scientific knowledge about the therapeutic effectiveness of non-pharmacologic, integrative approaches to symptom management in adults with chronic cardiopulmonary disease. Urban Zen Integrative Therapy (UZIT) is a tailored, multicomponent therapy featuring a combination of integrative modalities including 1) essential oils, 2) gentle movement/restorative poses, 3) body-awareness meditation, and 4) Reiki. UZIT is designed to target symptoms associated with complex chronic illness. The UZIT program is currently being implemented in a variety of health care settings (i.e., intensive care, inpatient, hospice and palliative care). However, feasibility and acceptability have not been evaluated in community-dwelling persons with chronic, life-limiting cardiopulmonary disease as an integrative approach to reducing symptom presence and severity.

II. Objectives

The primary goal of this study is to determine the feasibility and acceptability of a 6-week (Freedenberg, Thomas, & Friedmann, 2015) multi-component integrative therapy program, UZIT, for adults with chronic, life-limiting cardiopulmonary disease. The secondary goal is to explore the preliminary efficacy of UZIT in symptom management. Pulmonary hypertension (PH) presents an excellent model of a severe, life-limiting cardiopulmonary condition with high symptom burden and poor outcomes suitable for this scientific inquiry.

This study will use a single group repeated-measures design to address the following Specific Aims:

Aim #1: To determine the feasibility of a 6-week UZIT intervention in community-dwelling adults with PH. Feasibility will be determined by 1) recruitment rate (>40% recruited from those approached), 2) enrollment ($\geq$two participants /month) (Carter et al., 2013; Uebelacker et al., 2010), 3) home practice ($\geq$ 1/week), and 4) retention rate ($\geq$70% of participants remaining at study completion). We will also explore UZIT interventionists' perception about study feasibility.

Hypothesis 1: UZIT will meet feasibility targets for community-dwelling adults with PH.

Aim #2: To determine the acceptability of UZIT among community-dwelling adults with PH for symptom management. Acceptability will be determined by participants' evaluation of the UZIT program (composite mean System Usability Scale score > 5, scale 1-7),(Brooke, 1986) and session completion rate (at least 5 of 6 sessions [83% attendance] (Campo et al., 2013; Cohen et al., 2007; Lee et al., 2010; Lengacher et al., 2011; Palumbo, Wu, Shaner-McRae, Rambur, & McIntosh, 2012) by the participants retained at the study end. An exploratory sub-aim (Aim 2-A) is to determine what components of the UZIT program are preferred by adults with PH. We will also explore UZIT interventionists' perception about participants' acceptability of the UZIT intervention.

Hypothesis 2: UZIT will meet acceptability standards among community-dwelling adults with PH.

Aim #3: To explore the preliminary efficacy of UZIT intervention.

Aim #3a: To explore the preliminary efficacy of weekly UZIT sessions on dyspnea, pain, fatigue and anxiety.

Aim #3b: To explore the preliminary efficacy of a 6-week UZIT program on PH-related symptoms and HrQoL.

Hypothesis 3a: Patients will report reduced presence and intensity of dyspnea, pain, fatigue and anxiety after each UZIT session.

Hypothesis 3b: Patients will report a decrease in the presence, severity, and activity interference for PH-related symptoms and improvement in HrQoL after UZIT program compared to baseline.

III. Background and Rationale

Despite medical and pharmacological advances in treatment, 50-55% of persons with PH will die within three years after diagnosis (Benza et al., 2010). Medical management often involves life-long complex pharmacological treatment requiring high levels of skill, knowledge, and social support. Clusters of bothersome symptoms such as chest pain, anxiety, insomnia, dyspnea, and fatigue can overwhelm patients' ability to manage daily activities and medication treatment regimens. Side effects of treatment induce additional noxious symptoms (Mathier, McDevitt, & Saggar, 2010). The high prevalence of physical symptoms, depression, and anxiety among adults with PH (McCollister et al., 2010) was confirmed in my prior work. There is also a positive correlation between reported symptoms and reduction in health-related quality of life (HRQoL) (Von Visger, T., Kuntz, K., Phillips, G., Happ, MB., Sood, N, 2014). A literature review of PubMed and CINAHL databases using the terms "integrative therapy", "complementary therapy" AND "pulmonary hypertension" found no published report of complementary, integrative therapy interventions to alleviate symptoms in adults with PH.

This study will fill a gap in symptom science by exploring an integrative therapy approach to treating significant and burdensome disease-related and medication-related symptoms commonly experienced by persons with chronic, life-limiting CP disease. The individual therapies within the UZIT program are supported by a body of evidence documenting efficacy in reducing symptoms of stress, anxiety, depression, insomnia, pain, fatigue in persons with cancer, diabetes, cardiac, renal, inflammatory, neurological, and pulmonary chronic conditions (Ayan et al., 2013; Bagheri-Nesami, Espahbodi, Nikkhah,

Shorofi, & Charati, 2014; Baldwin, Fullmer, & Schwartz, 2013; Bernardi, Amorim, Zandonade, Santaella, & Barbosa Jde, 2013; Boehm, Bussing, & Ostermann, 2012; Hofmann, Sawyer, Witt, & Oh, 2010; Lavretsky et al., 2013; Lytle, Mwatha, & Davis, 2014; Newham, Wittkowski, Hurley, Aplin, & Westwood, 2014; S. E. Thrane, Maurer, Ren, Danford, & Cohen, 2016; Wurtzen et al., 2013). There is currently an absence of evidence investigating these integrative therapies in persons with CP conditions or studies that investigate combination therapies, such as the UZIT program, in an outpatient setting. This study is designed to address this gap by measuring immediate change in symptoms after each UZIT session as well as a change over time in symptoms and HrQoL. Pulmonary hypertension (PH) is the chronic condition selected for UZIT testing because it represents the most rapidly progressive CP disease with many severe symptoms and high mortality.

Patients with chronic, life-limiting cardiopulmonary (CP) conditions face difficult symptom management challenges. Pulmonary hypertension (PH), a CP condition with high symptom burden, serves as an excellent model for symptom management intervention development and testing. Characterized by high mean pulmonary arterial pressures, PH affects an estimated 15,000 Americans and shares symptom characteristics common to several life-limiting chronic conditions (McLaughlin et al., 2009). Despite medical advancements, the average 3-year mortality rate for pulmonary arterial hypertension (an important PH subtype) continues to be high, above 50% (Badagliacca et al., 2012; Benza et al., 2010). Patients with PH require complex management (Hoeper et al., 2013; Keogh et al., 2011; Krasuski et al., 2011) and experience frequent hospitalizations, overwhelmed by a cluster of symptoms such as, pain, anxiety, insomnia, dyspnea, dizziness, and fatigue (Matura et al., 2012). Moreover, bothersome medication-related side effects include nausea, cough, dry mouth, and jaw pain, adding to the disease-related symptoms (Mathier, McDevitt, & Saggar, 2010). The combination of these symptoms makes effective self-management of PH extremely challenging for patients and caregivers. High PH-related symptom burden is correlated with worse health-related quality of life (HRQoL) (Matura et al., 2014). Evidence-based non-pharmacological symptom treatments are desperately needed to improve HRQoL for these patients.

Approximately 36% of adults in the United States use integrative therapies for symptom management (Clarke, Black, Stussman, Barnes, & Nahin, 2015), and some approaches have shown benefit in the reduction of symptom intensity in other disease populations (Asmaee Majid, Seghatoleslam, Homan, Akhvast, & Habil, 2012; Birocco et al., 2012; Conrad & Adams, 2012; Hoffman, 2012; Igarashi, 2013; Klainin-Yobas, Cho, & Creedy, 2012; Newham et al., 2014; S. Thrane, 2013; S. Thrane & Cohen, 2014). In a systematic review of 25 randomized controlled trials published in peer-reviewed journals, integrative therapy demonstrated a dramatic reduction (moderate to large effect sizes) in pain and anxiety in children and adolescents with cancer (S. Thrane, 2013). Although integrative therapy use is common worldwide, Thrane's analysis was limited by the small number of studies that met the inclusion criteria. Individual integrative therapy modalities have been studied for therapeutic response (Andersen et al., 2013; Baldwin et al., 2013; Fung, Tsang, & Chung, 2012; Gross et al., 2009; Lytle et al., 2014; Nyklicek, Dijksman, Lenders, Fonteijn, & Koolen, 2014; Sharma, Robbins, Wagner, & Colgrove, 2015; Yadav, Magan, Mehta, Sharma, & Mahapatra, 2012a), however, combination therapy may provide benefits superior to a single approach. In a retrospective chart review of 6,587 hospitalized cardiovascular patients who received integrative therapy, the application of two or more integrative therapies was associated with significant reductions in anxiety compared to one treatment (Johnson et al., 2014). Two combination approaches of

1) mind-body therapy with energy therapy and 2) Traditional Chinese medicine reduced patients' anxiety scores significantly when compared to a single therapy (massage) (Johnson et al., 2014). While this study included a large sample size, it did not take into account the pharmacological effects on pain and anxiety nor evaluate/ monitor intervention fidelity. There is relatively little research testing combination therapy on symptom outcomes. However, combination integrative therapies such as Traditional Chinese Medicine and Ayurvedic Medicine have been used for centuries (A. Burke, Kaptchuk, Lao, Weber, & Killen, 2016; Weber & Killen, 2015), and combination approaches are currently gaining popularity in community and in-patient settings. Co-application of 4 integrative therapies, as in Urban Zen Integrative Therapy (UZIT), may have synergistic effects on symptom management and warrants examination.

To obtain additional information pertaining to the study aims of UZIT feasibility and acceptability, we plan to conduct a focus interview with UZIT interventionists after all UZIT sessions are delivered to study participants. Exploring interventionists' overall impressions about the study conduct using complex intervention such as UZIT is important in future refinement of the intervention in a larger scale research. Because UZIT is a multi-component complementary health intervention, intervention fidelity assurance is critical to the internal validity. Prior research demonstrated the importance of obtaining interventionists' perception in a complex intervention such as Motivational Interviewing research (Kimber et al, 2017), and behavioral health research (Wyatt, 2010 & Carpenter et al, 2013). The questionnaire will also solicit interventionists' perception about patients' acceptability of UZIT intervention. Because interventionists had close therapeutic relationship with study participants throughout the course of study period, their perception is invaluable to the overall determination of UZIT acceptability. Interventionists' audio recorded comments will be transcribed verbatim, coded and categorized for common themes using NViVo qualitative data analysis program.

Urban Zen Integrative Therapy (UZIT)

UZIT is a multi-modal integrative therapy that includes: 1) essential oils, 2) gentle movement/ restorative poses, 3) body-awareness meditation, and 4) Reiki therapy tailored to individual patients' symptoms (Kligler et al., 2011). The basis from which these therapies are applied stems from mindfulness training and yoga practices. UZIT is designed to address the classic symptoms associated with chronic illness: exhaustion, pain, anxiety, nausea, insomnia, and constipation. Through the targeted application of a chosen essential oil, patients practice awareness in recognizing body sensations through relaxation and calmness. Restorative yoga poses (such as side-lying child's pose and supported relaxation pose) are used to enhance relaxation and release tension. Each session is provided by the UZIT therapist in a synergistic and collaborative approach with strong emphasis on patients' input about bothersome symptoms. At present, more than 900 UZIT sessions are already documented at OSUWMC.

A quasi-experimental study comparing two independent patient groups before (n = 89) and after (n= 74) UZIT implementation in an oncology unit showed improvements in patient mood and health state (Kligler et al., 2011). Patients who received UZIT reported significantly less tension, depression, fatigue, increased mobility, and less overall mood disturbance (Kligler et al., 2011). Although there were no between-group differences in pain, a statistically

significant decrease in pain was observed in the UZIT group after vs. before therapy. While UZIT is available in some inpatient and hospice settings, application of this therapy among community-dwelling adults with chronic conditions is lacking. **Formal scientific evaluation of this integrative approach for symptom self-management in patients with chronic life-limiting cardiopulmonary conditions, such as PH, is urgently needed**. Evidence for each component of UZIT is reviewed below.

Essential Oil.

Application of lavender, citrus, and peppermint essential oils demonstrated therapeutic benefits of symptom alleviation for insomnia, pain, stress, anxiety, and nausea respectively in a variety of adult populations (Ayan et al., 2013; Bagheri-Nesami et al., 2014; Hirokawa, Nishimoto, & Taniguchi, 2012; Igarashi, 2013; Lytle et al., 2014; Matsumoto, Asakura, & Hayashi, 2014). Across most studies, 5-10 minutes inhalation of essential oil was adequate to achieve immediate symptom improvement. In a study of patients undergoing routine hemodialysis needle insertion, procedural pain severity was significantly improved at the end of three treatments among those who received 5-minutes inhalation of lavender oil before the procedure as compared to a non-treatment control group (Bagheri-Nesami et al., 2014). In another study, pregnant women assigned to receive 5-minute inhalation of lavender or citrus essential oils showed a similar statistically significant reduction in tension and anxiety compared to before treatment (Igarashi, 2013). A reduction in acute stress biomarker (salivary chromogranin) and improved mood states were observed among healthy college students after 10-minute inhalation of Japanese Citrus Yuzu essential oil (Matsumoto et al., 2014). Improved sleep quality was reported by college student volunteers exposed to lavender oil throughout the night during sleep for five consecutive nights (Hirokawa et al., 2012). A systematic review demonstrated a reduction in anxiety, depression, and improved sleep in cancer patients (Boehm et al., 2012). Taken together, reduction in pain, tension, and anxiety and improved sleep quality were reported with lavender oil (Bagheri-Nesami et al., 2014); reductions in stress and anxiety were observed with citrus essential oil (Goes, Antunes, Alves, & Teixeira-Silva, 2012; Matsumoto et al., 2014); reduction in nausea was shown with peppermint oil (Ferruggiari, Ragione, Rich, & Lock, 2012). Evidence from these studies, however, is limited due to the lack of randomized controlled trial (RCT) study design, small sample sizes, and varied dose delivery. Demonstrated benefits in symptom reduction justify more rigorous testing of essential oils to address similar symptoms in adults with PH.

Gentle movement/Restorative Poses.

Derived from yoga practice, gentle movement/restorative poses included supported recumbent positions meant to induce deep relaxation. There is limited evidence available specifically regarding gentle movement/restorative poses. However, evidence for the therapeutic benefits of yoga practice is substantive. Yoga practice (60-minutes, once a week for 6-12 weeks) among persons with chronic illnesses demonstrated improvement in anxiety, depression, and quality of life (Bernardi et al., 2013; Lavretsky et al., 2013; Newham et al., 2014; Siddarth, Siddarth, & Lavretsky, 2014; Vadiraja et al., 2009; Yadav, Magan, Mehta, Sharma, & Mahapatra, 2012b). Reduction in disease-specific symptoms and serum cortisol were observed among patients with chronic illnesses (diabetes, hypertension, mental stress, and musculoskeletal pain) (Yadav et al., 2012b). Reductions in fatigue and insomnia were

demonstrated among community-dwelling patients with stage III and IV breast cancer (Vadiraja et al., 2009). While these studies reported the therapeutic benefit of yoga, their results are limited by small sample size, lack of randomization, and inconsistent intervention dose. Reported improvements in stress, anxiety, depression, mood, insomnia, and fatigue as a result of yoga practice among chronically ill adults (Sharma et al., 2015; Yeung et al., 2014) support testing gentle movement/restorative poses in controlled trials of symptom management and quality of life improvement.

Body-awareness meditation.

Body-awareness meditation is a type of mindfulness practice that focuses on one's awareness of the present bodily state. From the perspective of psychological well-being, mindfulness is a state of present-centered, attention-awareness, and open receptivity to the present (Brown & Ryan, 2003). Mindfulness is a process of bringing a certain quality of attention to moment-by-moment experience (Kabat-Zinn, 2005), and is defined as "a process that leads to a mental state characterized by nonjudgmental awareness of the present experience, including one's sensations, thoughts, bodily states, consciousness, and the environment, while encouraging openness, curiosity, and acceptance"(p. 169) (Hofmann et al., 2010). Recent meta-analyses using this definition of mindfulness indicate that mindfulness-based therapy (MBT) is effective in treating depression and anxiety among patients with chronic conditions (Azulay, Smart, Mott, & Cicerone, 2013; Hofmann et al., 2010; S. Jain et al., 2012) and those with psychiatric illness.(Klainin-Yobas et al., 2012). Reduction in anxiety and depression among patients with cancer were observed using MBT (Hofmann et al., 2010; Wurtzen et al., 2013). MBT showed reduction in anxiety, depression, and suicidal ideation among veterans (Serpa, Taylor, & Tillisch, 2014), reduction in stress, insomnia and fatigue among patients with fibromyalgia (Cash et al., 2014), reduction in stress among caregivers (Hou et al., 2014; F. A. Jain, Nazarian, & Lavretsky, 2014; Whitebird et al., 2013), and reduction in anxiety and depression among solid organ transplant recipients (Gross et al., 2010). MBT intervention among patients with generalized anxiety disorder showed statistically significant reductions in anxiety, depression, and worry (Asmaee Majid et al., 2012). Anxiety, depression, and stress improved in cardiac patients undergoing percutaneous intervention who received MBT compared to a control group (Nyklicek et al., 2014). MBT is acceptable and feasible to patients with diabetes (van Son et al., 2013) and coronary heart disease for improved sleep, increased relaxation, and acceptance of illness (Keyworth et al., 2014). Evidence supporting the use of MBT is substantive with several RCTs using large sample sizes across multiple populations. In this proposed study, mindfulness is defined as present-centered, attention-awareness (Brown & Ryan, 2003) of symptoms using body-awareness meditation technique.

Reiki.

Reiki is an energy healing technique performed by systematic hand placement over specific body areas to facilitate energy flow for healing. A systematic review of RCTs showed that Reiki had moderate effects on pain among cancer patients and large effects among older adults (S. Thrane & Cohen, 2014). Reiki reduces pain and anxiety (medium to large effect

sizes) in children in palliative care (S. E. Thrane et al., 2016). An RCT among 80 participants with limited shoulder movement showed that energy healing techniques (Reconnective Healing and Reiki) were as effective as physical therapy in improving range of motion and pain (Baldwin et al., 2013). Given that Reiki demonstrated therapeutic benefit in symptom management with no reported side effects in multiple studies (Marcus, Blazek-O'Neill, & Kopar, 2013; Post-White et al., 2003; S. E. Thrane et al., 2016) and systematic reviews, it is included as a component of UZIT in this proposal. While the therapeutic benefit of Reiki is documented, Reiki application standardization is a challenge, and nonrandom selection of participants in these studies may limit the generalizability of the results.

Essential oils, gentle movement/restorative poses, mindfulness, and Reiki, individually have demonstrated positive clinical outcomes. In two studies with non-significant results, intervention failures were attributed to challenges in treatment acceptance, adherence, or both (Kubo, Hung, & Ritterman, 2011; Ussher et al., 2014). Clearly, careful evaluation of treatment acceptance and adherence are critical in studies of mind-body integrative therapy. The unique contribution of the UZIT intervention to symptom science in chronic, debilitating illness is the potential synergy of combined modalities. To date, there have been no studies evaluating the 4-component UZIT intervention in a systematic scientific approach. The only published study testing UZIT omitted the essential component of Reiki while introducing additional variables (e.g., remodeled environment and an audiovisual yoga education) that are not part of UZIT into the implementation (Kligler et al., 2011).

This is an important foundational study to establish feasibility and acceptability and, potentially, to identify needed refinements, in integrative therapies for symptom management in complex chronic, life-limiting cardio-pulmonary disease. Once UZIT is established as feasible and acceptable for PH patients, future research will focus on testing the efficacy and effectiveness of UZIT to reduce symptom burden and promote HRQOL for persons with complex chronic, life-limiting cardio-pulmonary disease. Additional studies will include analysis of cost and health care utilization outcomes. The long-term goal of this program of research is to advance knowledge and evidence-based application of integrative therapies to manage symptoms and promote quality of life for persons with complex chronic, life-limiting cardiopulmonary conditions.

III. Procedures

A. Research Design

This feasibility and acceptability study will use a pre/post intervention (6-weeks UZIT program) mixed-method design with repeated (weekly) measures of a single cohort of patients with PH. We will also explore preliminary efficacy testing to construct sample size estimates for future randomized control trials. Patients will serve as their controls.

B. Sample

We will enroll 20 patients from two PH clinics within the Ohio State University Wexner Medical Center (OSUWMC). Patients with PH condition related to the cardiac cause are managed at the OSU Cardiology clinic located at the Ross Heart Hospital. Patients with PH condition related to other causes are managed at the OSU Pulmonary clinic at Martha Morehouse. These inter-professional clinics provide access to a patient population with diverse race/ ethnicity, sex, and age. Overall, the OSUWMC PH Program manages approximately 350 PH patients each year and receives referrals for 50 new patients per year. PH patients' characteristics are similar to the U.S. data registry with a mean age of 55.8 years, 75% female, and 79% Caucasian. Patients at all stages of PH disease are followed for routine clinic appointments at 6-month intervals or more frequently if clinically indicated. Newly diagnosed patients are seen by PH specialists at 2-4 weeks interval for the first six months due to frequent monitoring and medication adjustments. All eligible patients managed at both PH clinics at OSUWMC will be invited to participate. Patients in both clinics receive standard medical treatments according to institutional and national clinical practice guidelines (McLaughlin et al., 2009; The Ohio State University Wexner Medical Center, 2014).

Sample.

Twenty convenience sample of community-dwelling adults with PH will be recruited for this study. *Inclusion criteria* are: 1) confirmed diagnosis of PH in the past, 2) age ≥ 18 years, (children typically have different etiologies, and often require parent involvement in symptom management), 3) ability to ambulate independently, 4) New York Heart Association functional classification II/III, and 5) willingness to participate in the entire 6-8 weeks study. *Exclusion criteria* are 1) known allergies to essential oils (lavender, lemon, or peppermint), 2) Asthma condition, 3) psychiatric illness requiring hospitalization within the last year per self-report or medical record, 4) self-reported pregnancy, 5) on-going participation in mind-body integrative therapy, and 6) inability to read/write English (to complete questionnaires).

Sample Size and Statistical Power.

The primary purposes of this study are to establish feasibility and acceptability of the UZIT intervention. A descriptive analysis will be applied. Pilot feasibility and acceptability studies of integrative behavioral approaches similar to the one proposed here generally include 6-19 participants (Cohen et al., 2007; Freedenberg, Thomas, & Friedmann, 2015; Lengacher et al., 2011; Palumbo, Wu, Shaner-McRae, Rambur, & McIntosh, 2012; Uebelacker et al., 2010; Yeh et al., 2010). With regards to preliminary efficacy outcomes of PH-related symptoms and PH-related HRQoL, we estimated statistical power. Power analysis using two-sided paired tests (*t*-tests for continuous and McNemar test for dichotomous/categorical outcomes) indicates that a sample size of 15 has sufficient power (≥0.8) to detect large effect size (standardized mean difference of 0.78 or greater for continuous outcomes; odds ratio of 7 or greater for dichotomous/categorical outcomes, assuming that proportion of discordant pairs is o.6) with a significance level of 0.05. Therefore, small to medium effect sizes will not be detected as statistically significant in this study. As a pilot study to generate information on preliminary efficacy, we will not rely on statistical significance, but rather on clinical differences. Anticipating 10-15% attrition rate over a 6-8 week behavioral intervention study (Carter et al., 2013; Grossman et al., 2010), we will enroll 20 participants to achieve a final minimum sample of 15.

C. Measurement / Instrumentation

Table 1 outlines the data collection timeline. Participants will provide demographic data at enrollment. The PI's preliminary work demonstrated that PH patients were able to complete four questionnaires in outpatient clinic settings within 15-minutes without undue burden. One hundred and eleven participants of 115 enrolled (96.5%) completed all four questionnaires without difficulty.

***Table 1*: Data Collection Timeline**

Measurement	Study AIMS	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Consent		X						
Demographics		X						
UZIT Intervention			X	X	X	X	X	X
Phone Call			X	X	X	X	X	X
Diary Record	2, 3b		X	X	X	X	X	X
Field Notes	2		X	X	X	X	X	X
Debriefing (P)	2				X			X
Debriefing (I)	2, F		X	X		X	X	
Session Video Recording	2, F		X	X	X	X	X	X
Acceptability Survey	2							X
PAHSS	3b		X					X
Dyspnea, Pain, Fatigue, Anxiety	3a		X	X	X	X	X	X
Manipulation Check	F						X	
Enactment Check	F						X	
CAMPHOR	3b		X					X

Data Collection Instruments

System Usability Scale (SUS, modified).

This tool is comprised of 13 Likert Scale questions (1-7) capturing generic constructs about ease of use of a program (Table 8). Seven questions are positively worded, and six are negatively worded. Originally developed for assessment of new technologies (Brooke, 1986; Mc Lellan, Muddimer, & Peres, 2012), this tool was adapted to assess the acceptability of the UZIT program. Higher scores (7) indicate greater user ease and acceptability. Since this tool is modified for assessment of UZIT program, psychometric properties (internal consistency)

will be assessed in this study population. Additionally, content validity will be determined to ensure that the measure represents all facets of acceptability construct. Two experts will judge each item regarding relevance, sufficiency, and clarity in representing the concepts underlying the measurement's development using a list of behavioral objectives and definition of terms. Content validity index (CVI) will be calculated to represent an interrater agreement between experts. They will be asked to judge each item in Likert Scale of (1) not relevant, (2) somewhat relevant, (3) quite relevant, and (4) very relevant. CVI is equivalent to the proportion of items given a rating of 3 or 4 by both judges, which we expect to be 80% agreement or higher (Waltz, Strickland, & Lenz, 2010). This tool takes approximately 3 minutes to complete.

Video-Recording.

The study PI will set up the video recording equipment to capture therapeutic actions, verbal and non-verbal communications, and patient response during the UZIT session. Because some components are applied simultaneously (e.g. essential oil inhalation and gentle movement/restorative pose), video-recordings will provide comprehensive documentation of UZIT for fidelity monitoring and future detailed descriptive analysis.

UZIT Session Field Notes & Debriefing.

The study PI will observe and describe any relevant impressions during the UZIT session; and document semi-structured debriefing interviews at the end of the session with patients or therapist independently. Post session debriefing will be conducted with participants at the end of week #3 and week #6 and with interventionist at the end of other sessions (#1, #2, #4, and #5) to ensure adherence to the research protocol. Patients will be asked to rate their preference for each UZIT component ("like" most to least). Exit interview questions will be included at the end of UZIT program.

Home Practice Diary.

Participants will rate the intensity of dyspnea, pain, fatigue, and anxiety and record each UZIT modality used (Table 10). They will describe how they manage other symptoms and the amount of time (minutes) spent each day practicing each component. Participants will be reminded to complete diary entries using paper format prior to each UZIT session.

Pulmonary Arterial Hypertension Symptoms Severity Scale (PAHSS).

PAHSS is specifically designed to assess presence and intensity of 17 common symptoms identified from a sample of PAH patients (Matura et al., 2014), which respondents rate in severity from "0" to "10" (Table 11). This tool demonstrated construct validity with SF-36 (α= .84) and the Profile of Mood States (α= .70).

Cambridge Pulmonary Outcome Review (CAMPHOR).

CAMPHOR is a 45 item, PH-specific quality of life tool that measures everyday experiences of PH patients. It measures multiple elements of each domain (symptoms, functional activities, and QOL perception) with simple and easy-to-understand phrasing (Table

12). The CAMPHOR demonstrated good internal consistency (Cronbach α= 0.90 – 0.92) and excellent test-retest correlation (r= 0.86-0.92) (McKenna et al., 2006), high sensitivity, specificity, and capacity to measure QOL change over time (Meads et al., 2008). Scores within each domain indicate patients' perception of symptoms, functional ability, and QOL. This questionnaire takes approximately 10 minutes to complete.

Modified Borg Dyspnea Scale (MBDS).

Modified Borg Dyspnea Scale is a valid and reliable tool use in the clinical assessment of dyspnea symptoms for patients with cardiopulmonary conditions. MBDS is presented to participants to rate in a vertical format which indicates the ordinal scale ranges from "0" to "10" and accompanied by written descriptors representing the intensity of breathlessness (Table 13). The tool captures twelve levels of dyspnea because of the addition of "0.5" scale distinguishing level "0" = "nothing at all" and level "1" = "very slight". Modified Borg Dyspnea Scale is valid and highly correlates with physiologic indices among normal subjects (Wilson & Jones, 1989), patients with COPD (r = .91) (Mador et al., 1995), and emergency patients with COPD and asthma (Kendrick, Baxi, & Smith, 2000). It is reproducible and reliable for the measurement of breathlessness during exercise over extended study period (Wilson & Jones, 1991). This tool takes approximately 1 minute to complete.

Visual Analog Scale-Pain (VAS-P).

Visual Analog Scale-Pain ranges from "0" = "no pain" to "10" = "worse pain possible", in a 100 mm scale, presented in a vertical format (Table 14). Visual Analog Scale-Pain has test-retest reliability among patients with acute pain in an emergency (r =.97) (Bijur, P et al, 2001), and among the general patient population (r = .94) (Hawker, Mian, Kendzerska, & French, 2011). The tool is valid and correlates well with numeric rating scale tested among immediate post-operative patients (Delock, L et al, 1998; Ahlers et al., 2008) and was simple to use by ICU patients (Ahlers et al., 2008). This tool takes approximately 1 minute to complete.

Visual Analog Scale-Anxiety (VAS-A).

Visual Analog Scale-Anxiety scale ranges from "0" = "not anxious at all" to "10" = "most anxious ever", in a 100 mm scale, presented in a vertical format (Table 15). Visual Analog Scale-Anxiety instrument correlate with the Spielberger State Anxiety Inventory (r = .50) (Chlan, L. 2004; Facco, E et al, 2015). It is less burdensome to complete and was shown to be an excellent tool for use among ICU patients (L. Chlan & Savik, 2011; L. L. Chlan, 2004; Elliott, 1993).

Visual Analog Scale-Fatigue (VAS-F).

Visual Analog Scale-Fatigue scale ranges from "0" = "not tire at all" to "100" = "the most tire I've ever been", in a 100 mm scale, presented in a vertical format (Table 15). The original 18-items (physical and emotional dimensions of fatigue) fatigue instrument has documented validity and reliability (K. A. Lee, Hicks, & Nino-Murcia, 1991). The single item VAS-F

instrument was shown to correlate well (r = .80) with the fatigue subscale of POMS among end-stage-renal disease patients (Brunier & Graydon, 1996). The VAS-F was compared to an 11-item numeric rating scales (NRS) among patients with idiopathic chronic fatigue and healthy adults and found capture the fatigue severity in similar manner; the NRS and VAS-F scores were approximately 2.7 time higher in patients compared to healthy adults (N. H. Lee & Son, 2012). The single item VAS-F instrument is demonstrated to be practical for use in critically ill mechanically ventilated patients in intensive care unit (L. L. Chlan & Savik, 2015).

Manipulation Check Questions.

As an important part of intervention fidelity check, manipulation check will be conducted to ensure that participants retain the knowledge and skills relevant to UZIT training. These 5 multiple choice questions will include the content regarding essential oil use, gentle body movement, body-guided meditation, and Reiki therapy. This manipulation check will be completed at the end of session #5.

Enactment Check Questions.

As an important part of intervention fidelity check, enactment check will be conducted to determine the concordance between participant's and interventionist's perception with regards to the knowledge and proficiency level about UZIT training. These 2 multiple choice questions ask both participant and interventionist to rate in a Likert scale from 0 to 7 to the level of competency and proficiency about UZIT practice. This enactment check will be completed at the end of session #5.

UZIT Interventionists Focus Interview Questionnaire.

The UZIT Interventionists questionnaire will also solicit interventionists' perception about UZIT feasibility, patients' acceptability of UZIT intervention, and UZIT fidelity. Because interventionists had been closely involved in the creation and refinement of the UZIT intervention protocol and fidelity training throughout the course of study period, series of questions in this questionnaire will include these 3 aspects of query (please see attached). Interventionists' audio recorded comments will be transcribed verbatim, coded and categorized for common themes using NViVo qualitative data analysis program.

D. Detailed study procedures

Intervention.

Individual, one-to-one UZIT sessions will be delivered by experienced therapists who are trained and certified in UZIT curriculum and training protocol (4 months coursework + 6-8 hours/week practice+50 hours clinical practicum). Individual rather than group intervention delivery reduces distractions and the social influences of a peer group. Private UZIT sessions are also more conducive to tailored treatment and allow for a more accurate symptoms query. A competency check-off list will be required of all UZIT interventionists before delivering study intervention. At least two experienced, UZIT-trained therapists will be trained in the study intervention delivery according to the research protocol. Sessions will be arranged at a convenient time for patient and therapist and conducted at the OSU Integrative Medicine outpatient facility in Columbus, Ohio. The facility is easily accessible and conveniently located close to the main medical facility; parking is free. Patients will participate in a total of 6 visits lasting approximately 1 to 1.5 hours per visit to be scheduled within an 8-week period. Participants will receive an incentive of $30.00 in gift certificates for the entire study, distributed in $5 increments at the end of each visit. This amount is considered reasonable because the study intervention (personal UZIT sessions) has an estimated market value of $100.00 per session and will be provided at no cost to participants.

We received UZIT therapist recommendations and rationale for proper intervention sequence. Our UZIT study session will include the following procedures. After a brief introduction, the therapist will inquire about bothersome symptoms. The session will include essential oil inhalation, gentle movements/restorative pose, body-awareness meditation, and Reiki. A guided breath awareness exercise will be synchronized with body movement. Participants will practice body-awareness meditation by focusing on the therapist's guided instruction on how to bring awareness to bodily sensation. Specific instruction and demonstration will be provided for an appropriate restorative pose using a yoga mat, bolster, blankets, and gentle weights (1-3 lbs) (Yee, 2004). The therapist may assist the participant in comfortable positioning and will apply each modality within a specified time frame. At the end of the session, participants will receive a personalized recommendation for appropriate gentle movement/restorative poses and samples of essential oil for home practice. Interventionist's behaviors will be monitored via direct observation, review of video and audio recordings to ensure intervention dose delivery (Wyatt, Sikorskii, Rahbar, Victorson, & Adams, 2010).

Study intervention fidelity will be ensured in the following ways: (1) therapists will achieve initial competency training in adherence to the research protocol at 80% compliance rate (Gearing et al., 2011); (2) intervention implementation adherence will be monitored via direct (but remote) video observation of each session with 25% of video recordings (n=30) receiving detailed review. Although the principal investigator *(*PI*)* will review each UZIT session, the Hawthorne effect will be minimized by the use of remote video recording. We will audit therapist's intervention delivery using a pre-determined checklist to validate dose delivery and detect any drift warranting therapist retraining. To enhance patient adherence, participants will receive weekly appointment and practice reminders via phone calls/text messages.

Recruitment.

Study participants will be recruited in the following ways: (1) patient response to a recommendation by their clinicians; (2) patient response to a posted study advertisement; (3) patient response through a secure NIH-sponsored volunteer registry (ResearchMatch)

available through the OSU Center for Clinical and Translational Science; or (4) patients with confirmed PH diagnosis will be screened by clinic staff during routine PH clinic visits for potential study eligibility. When PH clinic patients are identified as potentially eligible, clinic staff will provide a study brochure and inquire whether the patient would like to learn more about the study. If a patient indicates interest in the study, s/he will be approached by the study PI for consent. Clinic staff will follow a verbal script in seeking patients' interest. Research staff will follow a verbal script in describing general information about the study. The consenting process will include further discussion about the study protocol and participation including risks and benefits with sufficient time to address all questions. After consent, the initial study visit will be scheduled.

Potential Risks.

A foreseeable potential risk to research participants is a possible allergic reaction to inhalation of essential oil during the UZIT session, which is considered to be rare, a minimum risk. UZIT has been provided to more than 900 hospitalized patients at the OSUWMC without any demonstrated reactions to these three essential oils (Beth Steinberg, personal communication). There is no known evidence that essential oils interact with PH medications that participants may be taking. Using essential oil in patients with PH, we will take into consideration the following safety risks. PH patients with comorbidity of asthma condition may respond to essential oil inhalation with some airway reactivity. "Rarely, essential oils can cause respiratory irritation, rash, asthma, or headaches. People with severe asthma who are sensitive to aromatic triggers should be cautious about using aromatherapy. Some people are more sensitive to synthetic chemical fragrances than essential oils derived directly from plants."[98] In this study protocol, we will use high purity therapeutic grade essential oil derived directly from plants provided by Young Living, Inc., which is less likely to cause this reaction even among asthmatic patients. In adherence to the OSUWMC Aromatherapy Practice Protocol, the oil will be introduced slowly accompanied by continuous observation and monitoring of patient's response. We will place 1-3 drops of essential oil on a small cotton pad and put on the outside of patient's clothing not in direct contact with the skin in the upper chest area approximately 1 inch away from the nose. Patient's body heat and breath inhalation will facilitate the oil delivery slowly through the nose. Nursing staff or other licensed health professional staff who provide documentation of having completed an approved training on aromatherapy may supervise, use, or instruct staff/patient/family in the use of essential oils for increased comfort and symptom management. The study PI has completed this required educational training that included: 1) History/background of the use of essential oils in healthcare; 2) Clinical indications/research support for use of essential oils in healthcare 3) Proper application/controlled use of essential oils, and 4) Safety considerations, risks, allergic reactions, and contraindications associated with the use of essential oils. https://herbs-supplements.osu.edu/

Also, patients who require continuous oxygen use (with its associated airway "drying" effect) may report further discomfort to essential oil inhalation. For patients who currently use inhaled prostacyclin (Ventavis® or Tyvasso®), there is a potential risk that essential oil inhalation may have an added "drying" effect on the respiratory mucosa. Essential oil is non-

combustible and is safe for use while patients receiving oxygen. Furthermore, essential oil in this delivery method have been applied safely to ICU patients on mechanical ventilators.

We will limit the use of essential oil to the most frequently used and well-tolerated scents (Lavender, Lemon, and Peppermint) to reduce this likelihood. As a part of current practice, these three essential oils are being used in hospitalized patients at the OSUWMC with no adverse incidence to date after approximately 900 applications (Beth Steinberg, personal communication). Patients who have known allergy or reactions to essential oil will be excluded from this study.

There is an extremely unlikely possibility that persons with PH may experience some changes in hemodynamic status related to position change during UZIT practice. Although these changes have been documented during routine exercise, it is less likely to occur with UZIT practice. UZIT is not an exercise routine but rather a gentle, slow, and gradual position change that excludes any contraindicated positions. Despite the fact that yoga practice is encouraged for persons with PH, patients are cautioned not to assume “bending over” or “reaching overhead” postures due to the risk of a sudden drop in cardiac output. (“Exercise/Yoga/Tai Chi –What can be done & what to avoid”, 2012 Pulmonary Hypertension Association Conference Webinar) www.PHAasociation.org (Accessed, 1/13/16). A comparative study evaluating possible mechanism for hemodynamic changes during exercise between COPD patients with or without PH reveals the following differences. Because of existing high pulmonary pressure, stroke volume change (increase) as a response to exercise is compromised in patients with PH leading to reduced cardiac output.[2] Given this impaired compensating mechanism, we must take extra precaution when participants change position from lying down to sitting and to standing ***abruptly***. PH clinicians encourage patients to be active by participating in moderate exercise and integrative practice (yoga, Tai Chi, mindfulness practice). Strong emphasis is made to avoid bending over positions and the importance of “breathing through activities”, and “pay attention to your body” (“Breathing your way calm” and “Exercising mindfully with PH” www.PHAasociation.org (Accessed, 1/13/16). Therefore, UZIT can be an important adjunctive approach due to its incorporation of body-awareness meditation to ascertain the physical capability that is safe for patients.

We will provide all UZIT sessions at the CIHW outpatient clinic located at 2000 Kenny Road, Columbus, Ohio. As a part of the OSUWMC, this outpatient facility is equipped with quick access to emergency medical equipment (Resuscitation Cart).The applicant/PI is an experienced ICU nurse, trained in Advanced Cardiovascular Life Support (ACLS) protocol, and very familiar with emergency response system within the OSUWMC campus. The applicant/PI will be present at all visits to monitor study intervention, collect data, and assist UZIT therapist if an emergency situation were to occur. The CIHW is located close (< 5 min) to the OSUWMC emergency department.

There is also a potential risk of emotional distress to participants when answering survey questions about symptoms or feelings. Although unlikely, participants may experience feelings of anxiety, depression, and symptoms. In such a scenario, every attempt will be made to allow participants to rest and re-focus while providing emotional support. If needed, participants will be referred to psychologist/social work counselors available within the OSUWMC. In a situation of severe emotional distress, participants may be taken to an

emergency department through a 911 system. Questionnaires included in this research study are standardized tools that have been used in previous research conducted by the PI with 115 patients with PH without untoward effect on subjects' emotional state. Fatigue is possible when answering questions from a battery of questionnaires. We will provide rests or breaks if needed or will terminate a data collection session if the patient becomes too tired, upset or unable to continue. In a situation of minor physical distress/discomfort, we will provide continuous monitoring while allowing participant sufficient time to rest. If there is severe physical distress, participants may be taken to an emergency department through the 911 system. Appropriate Adverse Event reporting will be filed according to the IRB guideline and will be evaluated by the Data Safety and Monitoring Board of the study (below). As in all research, there is a potential for loss of confidentiality.

Protection against Risk (Confidentiality of Data and Computer Records).

Confidentiality will be protected through the use of study identification numbers that will be kept separate from personal identifiers. All study documents will be kept in designated locked file cabinets in the Center of Excellence in Critical and Complex Care Research Office at the College of Nursing. All study materials will identify participants solely by the assigned code numbers. The following steps will be taken to protect the confidentiality of all data and computer records:

- Identification codes rather than names will be used on all source documents
- The identifiers linking identification codes with individual names are only available to the project PI, and Primary Sponsor and stored in password-protected, encrypted file.
- Completed questionnaires will be collected by the researcher immediately in a sealed envelope for proper storage.
- Paper data collection forms will be stored in a locked file cabinet, and only researchers involved in the study have access.
- Electronic data files will be stored in a file folder that is dedicated to this project only and not linked to any public servers. Secured access to the research file folders will be limited to those study personnel directly responsible for analyzes and managing data. The computer and data files will be encrypted, and password protected. Participants' identification will be de-identified according to the College of Nursing de-identification standard using a study identification code for the subjects stored (keys) by encrypting them in a separate place/folder. All data will be housed on the College of Nursing's secure file storage server for research projects. The research server runs Windows Server 2012R2 Enterprise and is only used to host research files. No unnecessary services are running including no IIS, SQL, MS Office, and FTP. The Windows operating system is kept up to date by weekly, automatic updates from Microsoft. The physical server is housed in a secure room within Newton Hall. Only pertinent IT staff and the building coordinator have keys to access this room. The College's data center is also equipped with a video surveillance system that alerts IT personnel when someone accesses the room. Electronic access to the research server is restricted to the college LAN or VPN by a Cisco ASA firewall. Access from the Internet without VPN

is not allowed. Electronic access is further restricted by the on-host Windows Firewall, and User access is tightly controlled, by request only. Permissions are audited annually by IT in collaboration with the folder/study owner. All user accounts connecting to the server are domain accounts and are authenticated through a domain controller. User access and system information are also logged and exported to a central event logging server.

- For the video recording, a Foscam surveillance camera with a built-in microphone will be placed in a discrete location in the room. It will be connected to a computer directly with a network cable and will not be on the internet. The recording will be saved temporarily on the computer (encrypted and password-protected) and then deleted after being transferred to the secure research folder via a secure server within 24 hours after the recording session. The video recording data files will be uploaded to a secure access research file folder at the conclusion of each UZIT recording. The file folder is dedicated to this project and not linked to any public servers. Secured access to the temporary data file and video recording research data files will be limited to those study personnel directly responsible for analyzes and managing data. The computer and video data files will be encrypted, and password-protected. If/when participants withdraw from study participation, their video recording will be deleted. These procedures are consistent with methods previously used by the study Sponsor (Dr. Happ) and best practice in video recording for research.[99]

Potential Benefits of the Proposed Research to the Participants and Others.

Potential immediate benefits of participating in this research are the possible benefits of positive feelings and health benefits associated with relaxation and personal attention provided by therapist and research personnel. Additionally, learning how to be more aware of one's body sensation can have the potential benefit of effective physical tolerance and emotion regulation. However, no benefit to participants can be guaranteed. Knowledge gained from this study (acceptability of the treatment and its practical use) will extend its future application to larger patient population groups. Scientific evidence documenting UZIT's therapeutic impact on cardiopulmonary symptoms, and anxiety may provide valuable knowledge about patients' ability to self-manage and adhere to PH treatments. Furthermore, this early phase evidence can provide foundational data for future studies in identifying acceptability requirements and barriers of UZIT. Subsequently, efficacy testing can be carried out in patients with PH and other chronic disease conditions.

D. Internal Validity

The primary threat to internal validity is intervention fidelity which is a major concern in behavioral intervention research using multi-component mind-body integrative. As previously described, we identified specific ways to ensure intervention dose, intervention delivery, intervention receipt, and intervention enactment to avoid study bias. Study interventionists will be trained according to the intervention protocol and their competency will be checked at the initiation of the study as well as throughout the study period. Their delivery method and dose will be checked against a pre-defined fidelity checks through video recording review. Post-UZIT session debriefing with interventionists will provide an on-going quality assurance check

making sure that there is no drift in study implementation procedure. Intervention receipt and enactment will be checked by using manipulation checks and enactment checks questions.

E. Data Analysis

Descriptive statistics (mean and standard deviation (SD) for continuous variables and frequency and percentage for categorical variables) will be used to describe relevant demographics and clinical characteristics of the sample such as sex, gender, NYHA classification, and education level.

Aim 1: **To determine the feasibility of a 6-week UZIT intervention in community-dwelling adults with PH.**

Feasibility will be evaluated by recruitment and retention rates. *Recruitment rate* will be determined by 1) proportion of patients approached who consent to the study, and 2) length of time (months) required to recruit 20 subjects. *Retention rate* will be calculated as the proportion (completed/enrolled) of participants remaining to study completion. *UZIT Session Video Recording*: In addition to fidelity monitoring of initial 30 recordings, subsequent 30 recordings (total of 60 or 50%) will be randomly selected for quality/intervention fidelity audit using a checklist tool with the expected 80% protocol adherence level.

Aim 2: **To determine the acceptability of UZIT among community-dwelling adults with PH for symptom management. Sub-aim (2A): to determine what components of the UZIT program are preferred by adults with PH**.

Acceptability: Acceptability scores will be calculated from participants' responses to the SUS. Composite means and standard deviations will be computed for each item. An average of the total SUS scores for the sample (mean, SD) will be calculated. *Field Notes*: Semi-structured observation notes with free-text narrative will be transcribed, coded, formatted, and refined into qualitative themes regarding participant perceptions of the therapy, their practice of UZIT components, and symptom experience. Patients' preference rating of each UZIT component will be tabulated. *UZIT Attendance*: We will compute the number of sessions attended and completed per participant and for the total sample by range, median, mean and mean proportion. *Home Practice Diary*: Participants' written responses to questions on strategies for symptom self-management will be transcribed, coded, formatted, and refined into qualitative themes using basic qualitative description.(Miles, Miles, A Michael Matthew B, & Huberman, 1994). We will review the first participant's diary, develop a coding list and definitions, review and discuss with Sponsor in weekly analytic sessions using the constant comparison of subsequent diary entries. A stem-leaf diagram will be used to identify common themes. Participants' daily symptom ratings, the length of UZIT home practice time (minutes/day) will be analyzed descriptively (range, mean, SD, median, mode). Although self-reported health diary data collection method has potential limitations such as inaccurate and/or incomplete data (L. E. Burke et al., 2008; Stone, Shiffman, Schwartz, Broderick, & Hufford, 2003), it is suitable for use in this limited budget research proposal for the following reasons: ease of transport, ease of use, and is already a routine practice for patients with PH. Since this pilot study does not require precise time recording of certain activity (e.g., food intake time and amount), extensive data content entry, and does not extend beyond 6-8 weeks, we plan to use a simple paper and pencil health diary, rather than electronic data capture and to maintain participants' interest and motivation in this data collection with clear expectations and

emphasis of the importance of obtaining this data (Green, Rafaeli, Bolger, Shrout, & Reis, 2006).

Aim 3: To explore the preliminary efficacy of UZIT.

Aim 3A: To explore the preliminary efficacy of weekly UZIT sessions on dyspnea, pain, fatigue, and anxiety. Symptoms of dyspnea, pain, fatigue, and anxiety (symptom intensity) will be assessed in response to each UZIT session. We will plot the weekly visit rating of symptoms (dyspnea, pain, fatigue and anxiety) trajectory pattern from week 1 through week 6 for each participant and by biological variables (e.g. age groups, sex, and NYHA classification). Mixed effect modeling for repeated measures will be used to model the change over time. Estimates derived from mixed effect modeling will be more accurate by accounting for within-subject correlation. It also has the advantage of the most efficient use of data. Estimates are derived from all available data, not just data from completers.

***Aim 3B: To explore the preliminary efficacy of 6-week UZIT program on PH-relate symptoms and HRQoL*.** We will compare pre-and post-differences in composite symptoms' presence and severity (PAHSS) and HRQoL (CAMPHOR domains) using McNemar tests for paired proportions and dependent *t*-tests for paired means. As a pilot study to generate information on preliminary efficacy, we will rely on clinical differences. The point estimates and effect sizes from this pilot study will guide the sample size calculation for future larger scale study (efficacy and effectiveness). We will primarily report summary statistics on proportions and 95% confidence intervals at each time point. We will also determine the correlation between changes in PAHSS and CAMPHOR scores with a dose of home practice (minutes/week) to indicate a dose-effect relationship. Furthermore, the frequency and the amount of home practice can serve as an indicator of participants' acceptability of the UZIT program.

IV. Bibliography

Include a reference list of literature cited to support the protocol statement.