RESEARCH PROTOCOL

I. TITLE Prevention of Post Intensive Care Syndrome in Family with SĀF-T Intervention: Feasibility Study

II. STAFFING

Name and Title	Responsibility	Address	Phone Number
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III. CONFLICT OF INTEREST

None of the investigators will benefit from participants' participation in this project or completion of the project in general.

IV. RESOURCES

Sigma Theta Tau International Honor Society of Nursing - Delta Beta Chapter-at-Large

V. HYPOTHESIS

In the ICU, spouses often find themselves in a stressful environment, expected to manage surrogate health decisions for their critically ill loved one. Evidence in the literature suggest higher stress levels experienced by spouses in the ICU environment, increases their risk for **P**ost **I**ntensive **C**are **S**yndrome (PICS).[3,4,12,14,17,18,28,34,41] Reducing stress in the spouse during the ICU hospitalization may reduce their likelihood of PICS. We hypothesize that participants who receive the **S**ensation **A**wareness **F**ocus **T**raining (SĀF-T) intervention will experience less PICS than control participants who do not receive the intervention.

VI. SPECIFIC AIMS

The primary specific aim of the proposed project is to test the feasibility and determine effect size of the SĀF-T intervention on PICS, specifically spouses of critically ill, mechanically ventilated patients. We will carefully examine the ability of participants to adequately perform SĀF-T and adhere to the study protocol. A secondary aim of this project is to explore if the effect of SĀF-T and sleep/rest are related. Findings from this feasibility study will be used to design a dissertation study with adequate power to test SĀF-T.

VII. BACKGROUND AND SIGNIFICANCE

Significance

More than 5.7 million patients are admitted to intensive care units (ICU) each year in the United States.[37] The technologically advanced ICU is an unfamiliar frightening environment to patients and their families.[1] Critical

illness is a family crisis. There is strong evidence that family distress in response to critical illness does not disappear after ICU discharge.[2,4,12,16] The Society of Critical Care Medicine[36] has identified a cluster of complications that occur in family members of ICU patients as **P**ost **I**ntensive **C**are **S**yndrome-**F**amily (PICS-F). PICS in family members of adult ICU survivors includes symptoms of ongoing anxiety, depression, and post-traumatic stress disorder (PTSD). Data suggest that 70% of family members have symptoms of anxiety and 33% have symptoms of depression and PTSD, which can persist for ≥4 years.[7,9,13,24] Moreover, symptoms of anxiety, depression, and PTSD are higher and persist longer in family members than in adult ICU survivors.[11] Because PICS-F occurs with greater frequency in spouses and surrogate health decision-makers[4,27,34] this study will focus on participants whom are spouses of mechanically ventilated critically ill adults (typically sedated and unable to make their own health decisions).

To date, the focus of PICS-F research has been on description, detection, and prevalence of PICS-F. The approach in the proposed project focuses on prevention of PICS-F using an innovative rapid stress reduction intervention. The Rosenzweig Center for Rapid Recovery[29] has recently developed an adaptation of their Accelerated Resolution Therapy (ART) for psychological trauma and depression, called **S**ensation **A**wareness **F**ocused **T**raining (SĀF-T), as an approach to rapidly eliminate negative biological sensations of stress. SĀF-T is designed to elicit a calming response; interrupt negative thoughts, negative feelings, and negative behaviors; and ultimately serve as a self-management stress reduction method for individuals. Lateral left-right (saccadic) eye movements are used to elicit an orienting response that activates an investigatory reflex in which first, an alert response occurs and then, a reflexive pause produces decreased arousal in the face of no threat,[5,30,32] which elicits a calming response that rapidly eliminates negative biological sensations of stress. A reflexive pause is our immediate response of exploratory behavior, with more flexible and efficient cognitive processes, to respond in a state of heightened awareness.[43] This response process is consistent with behavior of interpretation and reaction to challenge in McEwen's Allostasis Stress Theory.[21] We expect the SĀF-T intervention will enable spouses to better manage stress and reduce risk of PICS-F.

Sleep deprivation has been self-reported as one of the top stressors of family members of ICU patients.[25,26,40] Sleep adequacy is defined as a combination of three factors: latency (the time it takes to fall asleep), efficiency ([time spent sleeping ÷ total time in bed] × 100), and duration of sleep.[22] According to the American Academy of Sleep Medicine[31] for adequate sleep, persons should fall asleep within 15 minutes, stay asleep for at least 85% of the time they are in bed, and have a total sleep time of no less than 7 hours. Reasons reported by family members for sleep deprivation include anxiety, tension, and fear.[8] Sleep deprivation may play a role in the development of PICS-F.[7,40] Although anxiety, tension, and fear are to be expected when a family member is critically ill, acknowledging these feelings and practicing relaxation techniques can reduce the impact that the feelings have on sleep.[6] Therefore, management of stress in spouses throughout the daytime may also improve nighttime sleep/rest and further reduce risk of PICS-F.

VIII. PRELIMINARY PROGRESS/DATA REPORT

N/A

IX. RESEARCH DESIGN AND METHODS

Research Design

We will use a prospective, randomized, experimental design to accomplish the specific aims. Participants (n=10) will be randomly assigned within 36 hours of the patient's ICU admission and intubation to one of two groups. The intervention group will receive the SĀF-T intervention daily, over a 3-day period (72 hours) or until discharge of the patient from the ICU, if discharged within 3 days. The control group will not receive the SĀF-T intervention. Usual care for spouses of critically ill patients will continue for both groups.

Sample. A feasibility sample size of 10 participants will be randomly assigned (using a blocked design) to two groups (n=5 intervention group, n=5 control group). Eligibility criteria: spouses of patients intubated and

admitted within 36 hours to the adult ICUs are expected to remain in the ICU at least 36 hours, and spouse is aged 18 years or older, and is able to understand English. Exclusion criteria: anticipation by the clinical provider of imminent patient death, spouse does not understand English, under the age of 18 years old, or is actively being treated for a PICS condition (anxiety, depression, PTSD).

Setting. Participant recruitment, enrollment, and interventions will be conducted at Tampa General Hospital (TGH), a level I trauma center with 225 critical care beds. During past and current studies, we have established excellent research relationships at TGH, as both principal investigator (PI) Paula Cairns and her USF faculty adviser/co-investigator Dr. Cindy Munro are credentialed by TGH Office of Clinical Research.

Methods

Group Assignment. Randomized assignment will be used to determine the group (intervention or control) for participants. Each participant will have an equal chance of being assigned to receiving the intervention. Usual care by the healthcare team will be provided to both groups (intervention and control). A randomized block design will be used for equal sample size in each group. Randomized group assignment will be generated at randomizer.org and concealed inside opaque, sealed envelopes. Following signed consent, each participant will have an equal chance of receiving the intervention with the opening of a sealed group assignment envelope.

Description of Intervention and Data Collection Procedures. Data collection will take approximately 30 minutes at four time points: study enrollment, study day 3, study day 30, and study day 90, as shown in Table 1. The actiwatch will take approximately 30 seconds to place on the participant's wrist at the time of study enrollment, which will collect continuous activity and light data over a 3-day period (72 hours) or until discharge of the patient from the ICU, if discharged within 3 days. The SĀF-T intervention will take approximately 15-20 minutes each day, over a 3-day period (72 hours) or until discharge of the patient from the ICU, if discharged within 3 days. Descriptions of procedures for each group are as follows.

1) Intervention Group: The SĀF-T intervention includes coaching from SĀF-T trained research staff on awareness of biological sensations associated with events in the ICU that are perceived stressful. Research staff will sit across from the participant and ask them to use their eyes to follow hand movements that will induce lateral left-right (saccadic) eye movements and elicit an orienting response that activates an investigatory reflex in which first, an alert response occurs and then, a reflexive pause produces decreased arousal in the face of no threat.[5,30,32] The SĀF-T intervention will be administered each day, by trained research staff, over 3-days (72 hours) or until discharge of the patient from the ICU, if discharged within 3 days. The emphasis on the SĀF-T intervention on days 2 & 3 will be practicing to independently use the technique as needed by the participant to self-manage stress. Participants will continue to receive usual care practices by care providers (orientation to ICU patient room and ICU waiting room, use of bathroom and shower in patient's room, review of ICU visiting policy with contact information, optional guest food tray, and other onsite locations to acquire food and beverages, clean towels, warm blankets, and resources for spiritual support).

2) Control Group: The control group will consist of usual care. There will be no SĀF-T intervention, but participants will continue to receive support by care providers, as part of usual care practices (orientation to ICU patient room and ICU waiting room, use of bathroom and shower in patient's room, review of ICU visiting policy with contact information, optional guest food tray and other onsite locations to acquire food and beverages, clean towels, warm blankets, and resources for spiritual support), which may reduce their level of stress. Participants will remain in the study in the ICU over 3-days (72 hours) or until discharge of the patient from the ICU, if discharged within 3 days.

Key Variables and Their Measurement

Following study enrollment and signed consent, key variables will be collected from participants, as outlined in Table 1.

Table 1
Key Variables, Measures, and Data Collection

		Data Collection Time Points			
Concept	Measures	Study Day 1	Study Day 3	Study Day 30	Study Day 90
PICS-F					
-Symptoms of Anxiety -Symptoms of Depression	Hospital Anxiety and Depression Scale (HADs)	*	*	*	*
-Symptoms of PTSD	Impact Event Scale (IES)	*	*	*	*
Stress	Perceived Stress Scale (PSS)	*	*	*	*
Sleep/Rest	Actigraphy (continuous over a 3-day period in ICU)	*			
Behavior Function	NIH Toolbox Emotion Battery	*	*	*	*
Demographic Characteristics	Age, race, ethnicity, sex, history of PICS-F conditions, level of education, & distance of hospital commute	*			

PICS-F. The measures for symptoms of PICS-F conditions (anxiety, depression, and PTSD) are found in the literature associated with spouses of adult ICU survivors.

- **Symptoms of Anxiety and Depression**. Anxiety is defined as worry or fear that does not go away and interferes with daily activities such as job performance, school work, and relationships.[23] Depression is defined as experiencing signs and symptoms most of the day, nearly every day, for at least two weeks.[23] The Hospital Anxiety and Depression (HAD) scale[42] will be used to measure anxiety and depression at four time points: study day 1 (immediately prior to first intervention), study day 3, and by telephone interview at study day 30 and study day 90. The HADs is easy to administer and has been successfully used to measure symptoms of anxiety (7 questions) and depression (7 questions) in the general population and in family members of ICU patients.[4] Scores for each subscale (anxiety and depression) range from 0 to 21 with scores categorized as follows: normal 0–7, mild 8–10, moderate 11–14, and severe 15–21. Although HADs was not designed to be a clinically diagnostic tool, in the event anxiety or depression subscales fall within the severe score range (15-21), the participant will be provided with a copy of their results and encouraged to follow up with their primary care provider for clinical evaluation.
- **Symptoms of PTSD.** Symptoms of PTSD will be quantified at four time points: study day 1, study day 3, and by telephone interview at study day 30 and study day 90, using the Impact of Event Scale (IES), which is the most commonly used instrument to measure symptoms of PTSD in PICS-F research.[7] The IES has been widely used for many years and found reliable across a broad range of traumatic events.[39] The IES is not a tool for diagnosing PTSD, but instead detects symptoms indicating a risk of PTSD. Each of the 15 items is scored on a 6-point scale rated from 0 to 5; so that the total score can range from 0 to 75.[15] Higher scores indicate more severe post-traumatic stress symptoms. In the event the total IES score is > 30, indicating a high risk of PTSD, the participant will be provided with a copy of their results and encouraged to follow up with their primary care provider for clinical evaluation.

Stress. Symptoms of stress will be quantified at four time points: study day 1 (immediately prior to first intervention), study day 3, and by telephone interview at study day 30 and study day 90, using Cohen's

Perceived Stress Scale (PSS), which is a 10-item measure with good psychometric properties that includes questions on how often in the previous month people view their lives as stressful and their ability to cope with stress. Response options range from never (0) to very often (4), with total scores on the scale ranging from 0 to 40.

Sleep/Rest. The gold standard for accurate sleep analysis is full polysomnography (PSG), but full PSG is not feasible. A wrist actiwatch (Actiwatch Spectrum, Philips Respironics, Bend, OR) will be placed on the participant during study enrollment to measure activity and ambient light levels over a 3-day period (72 hours). The actiwatch is a small, lightweight, limb-worn activity-monitoring device. Actigraphy is based on sleep algorithms.

Behavior Function. The NIH Toolbox Emotion Battery[44] testing will be used to measure behavioral function at four time points: study day 1 (immediately prior to first intervention), study day 3, and by telephone interview at study day 30 and study day 90. NIH Toolbox is a multidimensional set of brief measures assessing cognitive, emotional, motor, and sensory function from ages 3-85, meeting the need for a standard set of measures that can be used as a "common currency" across diverse study designs and settings. By using multiple constructs of each domain, the NIH Toolbox monitors neurological and behavioral function over time, and measures the domain constructs across developmental stages. This facilitates the study of functional changes across the lifespan, including evaluating intervention and treatment effectiveness. The Principal Investigator attended the 3-day inaugural training by NIH in Washington, D.C. on all domains in addition to the new 2-day training at Northwestern University for the iPad application.

Participant Demographics. Participant characteristics that may affect the development of PICS-F will be collected during admission to the study including age, race, ethnicity, sex, history of PICS-F conditions, level of education, and distance of hospital commute.

Data Management. Data will be downloaded into research electronic data capture (REDCap), a secure web application database, which will be accessed by a secure USF web connection with authentication and data logging. A unique identifier will be assigned to each participant by the PI in the database to conceal their identity on all research data. The data files will be backed up daily during the data entry process and once a week during other times by the PI. All data files will be housed on the university server, which is backed up every 24 hours and copies, are stored off-site for additional security. Access to the database will be password protected and limited to the investigators.

X. Plan for Control of Investigational Drugs, Devices, and Biologics

N/A

XI. DATA ANALYSIS PLAN

Data Analysis

The defining parameter for feasibility is a minimum of two days participation in the study. Descriptive statistics will be reported as means +/- standard deviation for continuous variables and as frequencies and percentages for categorical variables. We will perform repeated measures models in order to compare symptoms of PICS-F conditions in the intervention and control groups. Specifically, the repeated outcome variables (symptoms of anxiety, depression, & PTSD) will be modeled using generalized linear mixed effects models to account for within-participant variations.[35] Estimates of treatment effects (differences between intervention and control groups) will be summarized with odds ratios and corresponding 95% confidence intervals. Our sample size of 10 participants is reasonable for a feasibility study and perform a power analysis for sample size and effect size for the larger dissertation study to follow. A timeline for the feasibility study is provided in Table 2.

Table 2
Timeline for Proposed Feasibility Study

Activity	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6

Participant Recruitment & Enrollment						
Participant 1 and 3 month follow up						
Data collection						
Data management						
Analysis of final results						
Prepare dissertation study						
Final results manuscript						

XII. Data and Safety Monitoring

Since the project involves minimal risk and will be conducted at a single site, data and safety monitoring will be conducted by the study PI, Paula Cairns and reviewed with USF faculty advisor/co-investigator Dr. Cindy Munro on a bi-weekly basis. The review of data and safety monitoring will include all study processes, protocol compliance with inclusion/exclusion criteria, sex and minority enrollments, and safety of participants, including but not limited to review of adverse events.

XIII. Multi-center Studies

N/A

XIV. Involvement of non-USF institutions/sites (domestic and foreign)

N/A

XV. Involvement of Independent Investigators

N/A

XVI. Human Participants Instructions

Recruitment and Informed Consent. The PI will make daily rounds to the adult ICUs and speak with the charge nurses regarding availability of the spouse of patients intubated and admitted within the last 36 hours, and are expected to stay in the ICU for at least 36 hours. The bedside nurse will approach the potential participant to ask if they would like to be approached by the PI with an invitation to enroll in the study. The potential participant will be provided with an oral explanation of the nature of the study and study information in writing. The information will include all elements required for informed consent, and will include all pertinent contact information as well as information about withdrawal from the study. Written consent will be obtained. If at any time the participant does not wish to continue to participate in the study, no additional interactions with the participant will take place, no follow-up data will be collected, and that participant's data forms will be destroyed. The study PI has extensive experience in obtaining consents from family members of critically ill adults. The PI will work closely with the staff of the Burn Center, Cardiac Care, Cardiothoracic Surgery, Medical, Medical Surgical, Neuro Science, Surgical Trauma, and Vascular Surgery ICUs, the nurse managers, and medical directors to ensure that all eligible spouses of patients have an equal opportunity for inclusion.

Characteristics. Participants will be recruited from spouses of the inpatient population at TGH, which has 1,080 licensed acute care beds served. Characteristics of inpatients at TGH are presented in Table 3. Patients in the study units are representative of the hospital wide patient characteristics in relation to gender and ethnic background.

Table 3. Characteristics of Study Population, Geographic Area and Hospital (2014 data)

Characteristics	Hillsborough County, FL	Hospital (inpatient)
Gender		
Male	48.7%	43.9%
Female	51.3%	56.1%
Ethnic category		
Hispanic or Latino	26.5%	22.8%
Not Hispanic or Latino	73.5%	77.2%
Racial category		
American Indian/Alaska Native	0.6%	0.6%
Asian	4.0%	0.6%
Native Hawaiian/Pac Islander	0.1%	0.1%
Black / African American	17.5%	20.8%
White	75.3%	73.8%
More than 2/ Other / Unknown	2.5%	4.1%

Sources of Materials. Data will be obtained from the participant's verbal feedback, wrist actigraphy, and health assessment instruments. Data will include age, race, ethnicity, sex, marital status, history of PICS conditions, level of education, distance of hospital commute, Perceived Stress Scores, Hospital and Anxiety Scores, Impact Event Scores, and NIH Toolbox Emotion Battery Score. Each participant will be assigned an arbitrary study identification number to conceal their identity, and no individually identifiable private information will be entered into the study database.

Potential Risks. The risks of participation in the study are minimal. Risks include skin irritation from the actiwatch, as well as apprehension with the Perceived Stress Scale, Hospital Anxiety and Depression Scale, Impact Event Scale, and NIH Toolbox Emotion Battery health assessments.

There is no alternative therapy. However, participants may elect not to participate and may withdraw from the study at any time without affecting the care they or the patient receives.

Protections Against Risk. The SĀF-T intervention will be administered in the privacy of the ICU's consultation room to avoid interference with critical care procedures for the patient. At all times, we will place the patient's need for medical treatment, and avoidance with interference with treatment, foremost.

The information obtained will be kept strictly confidential, protecting the identity of participants in all reports or publications that may result from this research. Each participant will be assigned an arbitrary code number to conceal their identity on all research data, and all research data will be maintained in locked file cabinets under the direct supervision of the PI and USF faculty advisor.

To ensure confidentiality, each participant will be assigned an arbitrary study identification number to conceal his or her identity on all research data. All hard copy research material (i.e., consent forms) will be maintained in locked file cabinets, electronic data will be kept on password-protected computers under the direct supervision of the PI and USF faculty advisor. Study information obtained will be kept strictly confidential, protecting the identity of participants in all reports or publications that may result from this research. To ensure privacy, all interactions with participants will be conducted privately in the ICU consultation room.

To reduce skin irritation, the actiwatch will not be placed on skin that is not intact or damaged in any way. The actiwatch will be removed at the end of study day 3 (maximum of 72 hours) or until discharge of the patient from the ICU, if discharged within 3 days.

Prior to beginning the Perceived Stress Scale, Hospital Anxiety and Depression Scale, Impact Event Scale, and NIH Toolbox Emotion Battery assessments, the participant will be told if they feel excessively apprehensive

during the assessment, they may stop. There is no alternative therapy. However, participants may elect not to participate and may withdraw from the study at any time without affecting the care they or the patient receive.

Potential Benefits of the Proposed Research to Human Participants and Others
Participants in the intervention group may benefit from this study if PICS is reduced by the SĀF-T intervention. The results of this study holds promise to translate new knowledge into clinical decision-making about the management of critically ill patient's family members and ultimately improve both family and patient outcomes.

Inclusion of Women, Minorities, and Children
Inclusion of Women. TGH is a diverse clinical setting. Based on the patient characteristics of the study population in our current study, females make up approximately 48% of the population (about 3% less than the proportion of women in Hillsborough County, FL, or the entire TGH hospital population). Our experiences during previous critical care studies show that recruitment of females is similar to that in the admission population. Therefore, it is anticipated that the participants selected for this study will be representative in gender of the population of patients in the TGH ICUs. All women meeting inclusion criteria will be recruited. We will review the enrollment of women at our bi-weekly data and safety meetings to ensure that we are meeting our target enrollment.

Inclusion of Minorities. TGH is also an ethnically and racially diverse clinical setting. Based on admission characteristics of the study population in Table 3, minorities make up approximately 26% of the population. We expect that recruitment of minorities will also mirror these demographics. Our experiences during previous critical care studies show that recruitment of minorities is similar to that in the admission population. It is anticipated that the participants selected for this study will be representative in ethnic background and race of the population of patients in the TGH ICUs. We intend to recruit minorities consistent with our accessible population. The PI will pay special attention to the admission of ethnic minorities to the units. All patients meeting inclusion criteria will be recruited. We will review the enrollment of racial and ethnic minorities at our bi-weekly data and safety review meetings to ensure that we are meeting our target enrollment.

Inclusion of Children. Children less than 18 years of age will not be included in this study, because PICS conditions present differently in children and is dependent upon developmental level.

Publication and Presentation Plans:
The design and methods of this feasibility study will be presented in a poster for Sigma Theta Tau International Honor Society for Nursing, Delta Beta Chapter-at-Large's Research Day. The results of this study are expected to add knew knowledge on the feasibility and practicality of providing interventions for family members of critically ill patients, during the early ICU admission period, as well as the feasibility of longitudinal follow-up measures with family members post hospital discharge and will be submitted as a manuscript for publication.

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