

Patient-Partners Stress Management Effects of CFS Symptoms and
Neuroimmune Processes

NCT01650636

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4. Description of Study

Study Protocol

4.1. * Abstract and Specific Aims

Include a brief summary of the significance, purpose or research question, specific aims, and risks/benefits. Specific aims include hypotheses you will investigate.

This is a 5-year study to evaluate the effect of a 10-week patient-partner telephone-based cognitive behavioral stress management (PP-T-CBSM) intervention on chronic fatigue syndrome (CFS) symptoms in 150 CFS patients and their partners. Because many patients with CFS are unable to attend intervention sessions in clinical settings due to unpredictable periods of debilitating fatigue and limited mobility, we created a form of CBSM intervention that is delivered at the participant's home through a telecommunications system (Telephone-based CBSM) T-CBSM. A unique aspect of T-CBSM is that it uses the phone to convene groups of individuals in their homes—thus it retains some of the supportive elements of a group-based intervention. We have observed that over a 5 month period this patient-focused T-CBSM intervention is associated with decreases in CDC-based CFS symptoms and decreases in the pro-inflammatory cytokines and increases in anti-inflammatory cytokines. Greater decreases in pro-inflammatory cytokines were associated with greater increases in the negative pitch of the AM-PM slope of salivary cortisol and greater decreases in CFS symptoms. This supported our neuroimmune model as an explanation for the effects of T-CBSM on CFS symptoms. We also conducted subgroup analyses comparing partnered and unpartnered CFS patients and found that the effects of the intervention were much larger in the partnered group. We have designed a study to follow up on these findings by testing a newly designed partner-patient dual focus videotelephone-delivered CBSM intervention (PP-T-CBSM) that allows the partner to learn stress management techniques with the patient in a group format and to then practice together a set of stress management techniques such as relaxation and cognitive, behavioral and interpersonal skills training. We will compare changes in CFS symptoms, neuroimmune indicators, and psychosocial (patient and partner) functioning in participants assigned to PP-T-CBSM vs an attention time-matched telephone-based health information (T-HI) control condition in a 2 X 3 randomized experimental design with group (PP-T-CBSM, n=75 vs. T-HI, n=75) as the between-group factor, and time (Pre-intervention, 5- and 9-month follow-up) as the within-group factor.

PRIMARY AIM

AIM 1: To determine if PP-T-CBSM intervention improves CFS defining symptoms relative to participants in the T- HI condition.

Hypoth 1.1 CFS patients assigned to PP-T-CBSM will show greater reductions in average CDC-based Symptom Frequency and Duration compared at 5- and 9-month follow-up vs. those in T-HI.

Hypoth 1.2 CFS patients assigned to PP-T-CBSM will show decreases in CFS symptoms of diarrhea, fatigue, muscle pain, unrefreshing sleep, sinus problems and general weakness, at 5- and 9-month follow-up vs. those assigned to T-HI.

SECONDARY AIMS

AIM 2: To determine if T-CBSM intervention improves di-urnal cortisol regulation and immune regulation (pro-inflammatory:anti-inflammatory cytokine ratio ([IL-1B+ IL-6 + TNF-x]:[IL-13 + IL-10]) relative to participants in the T-HI condition and how these changes relate to CFS symptoms.

Hypoth 2.1. CFS patients assigned to PP-T-CBSM will show greater reductions in pro-inflammatory: anti-inflammatory cytokine level ratio at 5- and 9-month follow-up compared to those assigned to T-HI.

Hypoth 2.2. CFS patients assigned to PP-T-CBSM will show greater increases in the AM-PM negative slope of salivary cortisol at 5- and 9-month follow-up compared to those assigned to T-HI.

Hypoth 2.3. The magnitude of reductions in CFS symptom frequency and severity from baseline

to 9 month follow-up will be associated with greater reductions in the pro-inflammatory: anti-inflammatory cytokine ratio and greater increases in the AM-PM salivary cortisol negative slope.

AIM 3: To test whether reductions in total and specific CFS symptoms and neuroimmune process indicators in PP-T-CBSM are associated with greater improvements in patient/partner psychosocial functioning (decreased stress, depression and social disruption and increased social support).

Hypothesis 3.1 Patients/partners assigned to PP-T-CBSM will show greater reductions in stress, depression and social disruption, and greater increases in social support at 5- and 9-month follow-up compared to those assigned to T-HI.

Hypothesis 3.2 The magnitude of reductions in CFS symptoms and pro-inflammatory cytokines and increases in the AM-PM salivary cortisol slope from baseline to 9 month follow-up are associated with greater decreases in stress, depression and social disruption and greater increases in social support.

Risk/benefits: The study involves very minimal risk associated with venipuncture and completing psychosocial questionnaires. The potential benefits include learning techniques that can reduce stress and negative moods and improve the quality of life of chronic fatigue patients and their partners.

4.2. * Research Background

Provide background and previous studies supporting the study rationale. Include a brief summary of existing knowledge relevant to the research. Explain how the research may contribute to the advancement of knowledge.

A. Background:

1. Scope, Epidemiology, Etiology and Impact of CFS. According to the CDC (1) the overall prevalence of Chronic Fatigue Syndrome (CFS) in the U.S. is 235 per 100,000 persons (95% confidence interval, 142327 per 100,000 persons). Up to 80% of those affected are women (2). These individuals suffer from severe fatigue that impairs daily activity, diminishes quality of life for years and has no known cure (3). CFS symptoms bring about severe limitations in the lifestyle behaviors, and vocational activities of previously vital, productive and successful individuals (4). Symptoms include debilitating fatigue, low grade fever, lymph node pain and tenderness, pharyngitis, myalgias, arthralgias, cognitive difficulties and mood changes (5, 6, 7). Current medical treatments focus on symptom management (antidepressants, antifungals, antihistamines, antivirals, CNS depressants or stimulants, immunoglobulins, anti-inflammatories, anticonvulsants, macro-vitamin regimens) (8) but are not curative. Symptoms may emerge at unpredictable times, one of the features of CFS that makes it particularly stressful. CFS represents an economic burden for society (e.g., high rates of unemployment due to disability) and healthcare institutions (9). Hypothetical initiating events for CFS include infections, psychiatric trauma and exposure to toxins though etiology remains unknown (10). Many of the symptoms are inflammatory in nature and have prompted a theory of infection induced illness (11, 12) that presents with acute onset of illness, with systemic symptoms similar to influenza infection that do not subside (13). These observations have led to reports of associated microbial infection or reactivation of latent viral infections (11, 14, 15, 16). There is growing evidence that CFS patients reliably show abnormalities on several indices of immune functioning (e.g., elevated IgG, impaired natural killer cell activity, NKCA, 17), elevated levels of circulating cytokine peptides and/or mRNA (18), and abnormalities in the numbers and activation states of certain lymphocyte subpopulations (17, 19, 20, 21 – 25). Recent work in the U.S. isolating a gammaretrovirus virus (XMRV) in the etiologic pathway of CFS adds strength to the notion of a chronic immune system activation (26) though this XMRV finding has failed to replicate in a UK population study (27).

2. Neuroimmune Model of CFS. CFS symptoms can be understood through a neuroimmune model elaborated by our group (28). CFS patients are hypothesized to have a Hypothalamic Pituitary Adrenal (HPA) axis dysregulation (13, 29, 30,31, 32) (which may be aggravated by stress), and altered Immunoregulation, which serve to maintain the symptom cluster of CFS such as fatigue, muscle pain, unrefreshing sleep and weakness. Patients may experience distress reactions that are secondary to these cytokine-induced flu-like symptoms (33). As CFS patients' ability to carry out activities of daily living decreases, anxiety, depression and

irritability may increase (34). This distress cascade may further deplete energy resulting in additional decrements in attention and vigilance, thus worsening the fatigue symptoms. Distress reactions may further dysregulate the immune system since distress/depressive states are related to several pro-inflammatory cytokines possibly via alterations in HPA axis hormones such as cortisol (35,36). Because distress reactions appear to be a possible common denominator contributing to multiple abnormalities (fatigue, HPA axis alterations, immune dysfunction) characterizing this syndrome, we have reasoned that effective treatment would need to focus upon reduction of the patients' distress reactions in view of the interdependency among CFS symptom severity, psychological response processes, HPA functioning and the immune system. We propose to examine changes in these processes during a stress management intervention designed to modulate CFS patients' distress responses (37, 38).

3. Immune Dysregulation in CFS. Our model proposes that CFS involves an immunologic dysregulation (due to virus infection or unknown causes) characterized by chronic lymphocyte activation with elevated expression of lymphocyte activation markers, episodic increased expression of cytokines such as tumor necrosis factor (TNF)-a and b peptide and soluble receptor in serum/plasma, and mRNA in circulating lymphocytes, and associated decrements in cellular immune function, which may in turn, hamper anti-viral immunity and fail to eradicate viral infections thus promoting further immune activation (39, 28). We showed that CFS patients with the greatest fatigue severity and lowest vigor had lower NKCA and greater signs of lymphocyte activation (increased CD2+CD3+CD26+ T-cells). TNF-a and soluble TNF receptor-type I (sTNF-RI) were greater in the low NKCA group vs the normal NKCA group (40). Thus elevated pro-inflammatory cytokines such as TNF-a may accompany both decrements in antiviral immunity (via NKCA) and greater CFS symptom expression. TNF-a and b are primary modifiers of the inflammatory and immune reactivation in response to injury or infection, and are primarily produced by macrophages. Overproduction, inappropriate expression of TNF, and TNF injections have been associated with fever, slow-wave sleep induction and appetite suppression (41- 44), which may underlie the fatigue, lassitude and excessive sleepiness associated with CFS (45). We found that CFS patients show significantly elevated TNF- a and b levels compared to controls (20, 18). CFS symptoms may be part of a complex referred to as "sickness behavior" wherein fatigue, sleep disturbances, pain and other CFS-like symptoms are believed secondary to chronically elevated levels of pro-inflammatory cytokines (IL-1, IL-6, TNF) (46, 47). This pattern of increased pro-inflammatory cytokine production may be triggered by antigenic stimulation (e.g., viral infection) and maintained by stress/mood-related hypothalamic-pituitary adrenal (HPA) axis alterations (e.g, flattened di-urnal secretion of glucocorticoids, and/or decreased glucocorticoid sensitivity in immune cells that produce pro-inflammatory cytokines) (48). Sickness behavior symptoms and accompanying elevations in pro-inflammatory cytokines (e.g., TNF) are compatible with the symptom picture and cytokine patterns identified in CFS patients by our group (49).

4. Stress and CFS symptom exacerbation. Given the neuroimmunologic association between HPA axis substances such as cortisol and pro-inflammatory cytokines (48), and our observation of altered cortisol di-urnal pattern and multiple CFS symptoms (32), it is plausible that stress-induced exacerbations in CFS physical symptoms (50) are mediated by circulating cytokines. We showed that daily life event stress was associated with greater reports of symptom burden in persons with CFS and that stress effects were moderated by cognitive appraisals (more optimism, less frequent cognitive distortions), coping strategies (more active coping, planning and acceptance and less denial and disengagement), and social support (51). We next demonstrated prospectively that CFS patients who experienced the stress of Hurricane Andrew showed CFS exacerbations (compared to well-matched CFS patients sampled from adjacent counties not directly exposed to the hurricane (50). This included increased clinician-rated symptom relapses and increased severity and frequency of sleep disturbances, muscle weakness and fatigue after modest exercise; worse functional indicators such as work impairment and illness burden; and increased levels of circulating TNF-a. Greater perceived social support and an optimistic attitude (cognitive appraisal) were associated with less likelihood of a clinical relapse and lower reports of symptom burden. So, external stressors may exacerbate CFS symptoms and cognitive-behavioral-interpersonal factors such as cognitive appraisals, coping strategies and social support may moderate these stress effects.

5, Behavioral Intervention in CFS. Meta-analyses find moderate effects for individual-based cognitive behavioral therapy (CBT) interventions focused on physical activity and deconditioning

models in CFS, though drop-out rates range up to 42% (52). Group-based CBT combined with body awareness and exercise training has also been shown to be effective for CFS in recent work (53). In line with our stress model of CFS symptom exacerbation, our work has focused on testing group-based cognitive behavioral stress management (CBSM) intervention which is designed to reduce stress through relaxation, and depression by modifying participants' outlook and cognitive appraisals through CBT, teaching adaptive coping strategies and interpersonal skills such as assertiveness and anger management, and when conducted in a group format may also improve their perceptions of social support (54). Group-based CBSM improves mood and quality of life, modulates cortisol output, improves cellular immune functioning and decreases signs of herpesvirus reactivation among populations suffering from other immunomodulating illnesses or treatments (55- 60). Our conceptual model specifies the ways in which psychological distress, HPA axis functioning and immunologic abnormalities may act as mediators of stress-related exacerbation and/or maintenance of CFS physical symptoms (37). We hypothesize that CBSM affects symptoms through these mediators as well. Stress is experienced not only by the CFS patient but is likely to be also experienced by partners or family members who must make lifestyle adaptations to the patients illness—a well-established phenomenon in family members and caregivers of persons with chronic illness (61). Members of our team have argued for the importance of involving family members in psychosocial interventions for persons dealing with chronic illness (61). In prior work we showed that a patient-caregiver dual target psychosocial intervention improved depression and health symptoms in spinal cord injury patients when compared to either an inert control condition or a patient-focused intervention (62). We reasoned that a CBSM package—designed to reduce psychological stress (relaxation), alter cognitive appraisal aspects of CFS (via CBT), and teach interpersonal skills (assertiveness)—if taught simultaneously to CFS patients and their partners, may be effective in interrupting the biobehavioral mechanism maintaining or exacerbating some of the symptoms of CFS. This intervention may impact physical status and neuroimmune processes by way of stress/depression reduction, reduced social disruption, and improved social support. We propose that CBSM may affect CFS physical symptoms by first modulating a set of CBSM targets. Changes in these intervention targets are hypothesized to improve physical symptoms by improving psychosocial functioning and then reducing distress-related HPA axis dysregulation and modulating immune indicators.

B. INNOVATION AND CONTRIBUTION

Psychosocial Intervention Approach. Our work suggests that adding relaxation and interpersonal skills to CBT when done in groups (i.e., group-based CBSM) may improve multiple physical symptoms characterizing CFS (see preliminary studies). However, because of the nature of CFS, the debilitating and unpredictable course of the disease, it is difficult for participants to commit to clinic-based CBSM sessions. Of 365 individuals screened for a study of group-based CBSM, only 69 agreed to participate. Those who chose not to participate reported that they could not commit due to the fatigue burden as well as the unpredictability of their symptom flare-ups. We reasoned that modifying the delivery format of CBSM such that it can be accessed by even the least mobile CFS individuals might be a key innovation that addresses the special needs of this population. Accordingly we developed a Telephone-delivered CBSM (T-CBSM) protocol and demonstrated its efficacy in CFS (see Preliminary Studies section). Being a family member or partner of a person with a chronic illness affects both members of dyad and perpetuates stress and frustration, which may have exacerbating effects on CFS symptoms, which may occur through neuroimmune mechanisms (63). In prior work (see Prelim Studies section) we found that greater than 50% of our population of CFS patients is partnered and that partnered patients appeared to respond better to the T-CBSM protocol than unpartnered persons. We reasoned that a group-based T-CBSM intervention that actively incorporates the partner into group sessions as well as homework assignments would optimally reduce stress/distress and build social support for the patient, thus optimizing the effects of T-CBSM. However we were concerned that with multiple patient-partner dyads simultaneously involved on a conference call that it would be difficult for the group leader and members to discern who was speaking thus inviting confusion. We determined that the video-display of all dyads and the group leader would facilitate discussions. Thus, for the proposed work we will use a newly developed patient-partner video-telephone delivered CBSM (PP-T-CBSM) intervention. Investigator Dr. Czaja, Director of the University of Miami Center on Aging, has demonstrated the feasibility and

efficacy of videotelephone delivered patient-partner psychosocial support in the context of caregivers for patients with dementia (62). The proposed study is the first such trial in CFS and provides a model offering stress management skills in a videotelephone venue for chronic illness populations.

Experimentally Elucidating Neuroimmune Mechanisms of CFS Symptoms- This is the first study to test a neuroimmune mechanism of CFS symptom changes in the context of a randomized trial using a videotelephone-based group CBSM intervention. The monitoring of changes in the di-urnal cycle of salivary cortisol secretion and a panel of pro- and anti-inflammatory cytokines in association with changes in CFS symptom frequency and severity before and after a stress management intervention will provide stronger evidence of a neuroimmune model of CFS than would be possible with a cross-sectional or longitudinal natural history study. Monitoring concomitant changes in stress/distress and psychosocial functioning in patient and partner will allow us to identify the contribution of cognitive, behavioral and interpersonal processes to neuroimmune and symptom changes so that future group-based interventions can be further refined.

C. PRELIMINARY STUDIES SUPPORTING THIS STUDY

Study 1. Effects Of Group-Based Cognitive Behavioral Stress Management in CFS

The first intervention (1-U01 AI45940) study was designed to test the effects of group-based CBSM on stress, quality of life and symptoms in CFS. We hypothesized that participants randomized to CBSM would report improvements in perceived stress, mood, quality of life, and CFS symptoms from pre-post intervention (T1-T2) compared to those assigned to half a day psychoeducational (PE) seminar. Participants were mainly Caucasian women (76.8%) with a mean age of 45.9, high school diploma or greater (97%), on disability (44.5%), and a mean household income of \$20,000-\$30,000. They completed the Perceived Stress Scale (64), Profile of Mood States (POMS), Quality of Life Inventory (QOLI, 65), SF-36 health survey (66), and the Chronic Fatigue Immune Dysfunction Scale (CFIDS) at T1 and T2. We found a significant group x time interaction for PSS, POMS-total mood disturbance, QOLI, and SF-36 emotional wellbeing, such that those in CBSM showed greater T1 – T2 improvements than in PE. Significant CBSM effects were also found on CFS symptoms, including greater decreases in pain, sore throat severity, stomach pain, and frequency of unrefreshed sleep.

Study 2. Neuroimmunologic Interactions and CFS Symptoms

We next sought to identify neuroimmune associations that might explain CBSM effects on symptoms. We assessed CFS symptoms, HPA axis regulation (di-urnal salivary cortisol output), and circulating pro-inflammatory cytokines among 24 patients diagnosed with CFS. We observed symptoms such as un-refreshing sleep, unusual fatigue, muscle aches and pains, and general weakness in 92.8 – 100% of cases. Salivary cortisol collected across the di-urnal cycle (waking, 30 min post-waking, late afternoon and bed time, assayed by ELISA), for 2 days was used to represent HPA axis activity. Pro-inflammatory cytokines, interferon-alpha (IFN- α) and interleukin-1 (IL-1) in plasma were assayed by ELISA. The Cortisol Awakening Response (CAR) measured as the change between waking and 30 minutes post-waking was on average a 22% increase, which is lower than the normal value of 50 – 75% increase, but is in line with prior reports in CFS patients. Using established algorithms for analyzing salivary cortisol data (67), cortisol output was operationalized as: peak cortisol, average of the four waking cortisol measurements from each day (AVE), and area under the curve for the regression line fitted through raw cortisol values (AUC). Di-urnal cortisol regulation was indexed with: reactivity (RT) = total change in salivary cortisol during the observation period, slope of the regression line fitted through the data (SP), and area under the curve with respect to increase (AUCi). Greater levels of IL-1 were associated with lower cortisol output as indicated by lower AVE, and peak cortisol, and a less negative di-urnal cortisol slope as indicated by SP and RT. This suggested that poorer di-urnal regulation of cortisol was associated with greater circulating levels of pro-inflammatory cytokines. We found that symptoms such as “feeling less pep” were associated with greater levels of IL-1 while greater fatigue in the past week and right now were associated with greater levels of IFN- α , another cytokine reflecting immune system activation. Lower cortisol output, reflected in AVE scores, was also associated with feeling more bushed, more fatigued, less vigor, less alert, and less energetic. A similar pattern of associations was found between these fatigue indicators and peak cortisol and AUC values. Poorer di-urnal cortisol

regulation as indicated by lower negative slope (SP) values was associated with feeling less vigor, less alertness, less energetic, less clear-headed, poorer concentration due to fatigue, and feeling more worn-out, and more sluggish. Similar patterns were found in fatigue associations with other cortisol regulation indices (RT and AUCi). This pattern suggests that (1) CFS symptoms may be associated with greater levels of pro-inflammatory cytokines, and (2) these symptoms and cytokine levels were greater in cases with lower cortisol output and poorer diurnal regulation of cortisol.

Study 3. Effects of a Telephone-Delivered CBSM Intervention in CFS

Upon exit interviews from our first intervention study we learned that many patients found it difficult to attend structured CBSM groups at our site thus suggesting that we might be missing the population of CFS who are in greatest need of intervention. Because many CFS patients are not able to travel to and attend clinic-based groups we designed and tested a 10-session telephone-delivered CBSM (T-CBSM) program in a randomized controlled trial (NIH #1 R01 NS055672-01). Because all of our prior CBSM studies had used a group-based intervention we decided to preserve the group format in the telephone delivery. To do so, we collaborated with the Dr. Sara Czaja, at the NIH-funded Center for Aging at the University of Miami Miller School of Medicine to adapt a teleconference system used for outreach and patient education and support in caregiver research. Since 1997, members of the proposed research team have been using the Computer-Telephone Integration System (CTIS) with caregivers of persons with dementia. Dr. Czaja, Senior Investigator in this application, has used the system with more than 150 persons caring for family members with dementia. This project was part of the Resources for Enhancing Alzheimer's Caregiver Health (REACH) study, a recently renewed five-year multi-site project funded by the NIH (REACH-II). The investigators have demonstrated that the system is well accepted by caregivers and that it has a positive impact on patients and caregivers (62, 68).

We adapted the CTIS by programming the phones with CBSM information (audio play back of all relaxation exercises, pull down screens for review of all CBSM module content, and speed dialing to group members, group leader and CFS Support organizations). The system presents text and voice recordings to the participants through the Analog Display Services Interface (ADSI) protocol and the system also has a conferencing feature to facilitate the group sessions and also allows for their monitoring. The phones were installed in the home, training was provided on site, and the phones were retrieved at the conclusion of the intervention. These phones recorded the total frequency and duration of usage of all features, allowing us to harvest information on dose of information consumed, all intra-group contacts, and access to support organizations. This system is very user-friendly and this telephone linkage allows participants to access information topics for both conditions 24-hours/day, 7-days/week. All participants may listen to the recorded information at their own pace. For example, participants in the T-CBSM may access the system to review information presented by the facilitator in the interactive group session. Those in the T-CBSM condition were provided the specially designed phone and connected to a once weekly, one hour CBSM conference call with up to 6 CFS patients and a clinically trained group leader, who led the group according to a 10- module manualized CBSM intervention protocol. The participant used the system to practice relaxation techniques presented in the session and/or listen to relaxation recordings (e.g., guided imagery, deep muscle relaxation scripts) at his or her leisure. Individuals assigned to the attention-matched control condition received 10 weekly sessions of health information (T-HI) delivered over a phone.

Assessments were conducted pre-intervention and at 5 and 9-month follow-up. We found that adherence to the sessions was excellent (attendance rate > 90% on average). Using the recording system within the phones we measured in several cohorts, the frequency (times/month) and amount (minutes/month) of time participants have spent in reviewing and practicing pre-recorded audio-based intervention materials and techniques. Preliminary results indicate that modules receiving the greatest usage include relaxation, deep breathing, mindfulness meditation, and guided imagery as well as the following stress management modules: Anger Management, Stress Awareness, and Social Support. Results suggest that the T-CBSM program is well accepted by participants and they do engage the system outside of weekly telephone meetings. Of the first 70 cases enrolled in this trial 35 were assigned to T-CBSM and 35 to T-HI. Patients (59 women, 11 men) had a mean age of 51.4 and were mostly non-Hispanic White or Hispanic. There were 44.3% of cases on disability, 14.3% unemployed

and 28% worked full or part-time. The sample was middle class with 87.2% reporting a college education, 60% had an income > 30,000/yr. and 51% were partnered and 33% lived alone. At entry, over 95% reported unusual fatigue, unrefreshing sleep, or general weakness. The average frequency of CDC-based CFS symptoms was 3.3 times/wk. The Sickness Impact Profile (SIP) Recreational and Past-times and Social Interaction scales revealed that the majority of patients reported cutting back on social activities, hobbies, and spending time with other people. As in our pilot neuroimmune studies greater average severity of CDC-based symptoms was associated with greater IFN and TNF- α .

Given the small sample size available for analyses of intervention effects the interim results will be expressed as paired t-tests within the T-CBSM and T-HI groups for the period from baseline to 5-month follow-up. For the primary outcome—CDC-based CFS symptoms—we found that patients assigned to T-CBSM showed significant declines in average symptom frequency compared to T-HI. Patients assigned to T-CBSM also showed greater reductions in diarrhea, muscle pain, unrefreshing sleep, sinus problems and general weakness (p 's = .02 - .08) compared to no changes in the T-HI group. Those in the T-HI condition also reported increases in joint pain and abdominal pain, which were not seen in the T-CBSM groups. Similarly the T-CBSM patients showed decreases in SIP-Total Illness Burden Recreation and Pastimes compared with no similar change in the T-HI condition. In secondary analyses we observed changes in cytokine levels that mirrored these symptom findings. Here we found that those assigned to T-CBSM showed decreases in pro-inflammatory cytokines, IL-1 β and TNF- α and increases in the anti-inflammatory cytokine, IL-13, with no changes in T-HI. Greater decreases in TNF- α were associated with greater decreases in average CDC symptom severity over the pre-post intervention period. Greater TNF- α reductions also related to greater reduction in diarrhea, fatigue, muscle pain, joint pain, headache, and general weakness. Greater increases in the pitch of the negative AM-PM slope of salivary cortisol output (SP) were associated with greater decreases in TNF- α suggesting that a normalization of HPA axis function may relate to decreases in pro-inflammatory cytokines, which related to reduced CFS symptoms occurring during T-CBSM intervention.

We also examined the relative effects of T-CBSM in partnered vs non-partnered patients. We found consistently larger magnitude of effects in the partnered group vs. the non-partnered group in CFS symptom frequency, plasma IL-1 β , and fatigue symptoms and interference. Moreover we noted that partnered patients showed greater reductions in SIP interpersonal disruption scores and much greater increases in total, emotional and instrumental social support received on the Social Provisions Scale (SPS; 69). This suggests a synergy between the CBSM experience and the partner possibly due to: (a) partner support of the patient's CBSM skill acquisition and practice, (b) informal transfer of CBSM skills to partner resulting in reduced partner stress and improved interpersonal skills leading to better ability to provide support to patient, or (c) some combination of these and other changes. This argues for formally including the partner in the CBSM process, including attending groups and joint patient-partner practicing of relaxation and cognitive-behavioral-interpersonal skill building assignments. Since all of our CBSM effects have been obtained in a group-based venue and due to the powerful effects of modeling that are likely operating, we reasoned that the next step was to develop and test the effects of a patient-partner dual focus group-based CBSM intervention. To optimize patient and partner engagement in the group we incorporated a state-of-the art teleconferencing system, making use of a videotelephone that we have been using successfully in patient-partner studies in the context of other chronic illnesses (68).

Summary. The results of this study have major significance since they might offer an intervention approach that is efficacious in reaching a broader population of CFS patients who would not otherwise be able to benefit from these empirically supported techniques. This work is innovative in being the first RCT to test the effects of a patient-partner Telephone-delivered psychosocial intervention (PP-T-CBSM) for CFS patients while examining a neuroimmune mechanism (HPA axis-cytokine regulation) to explain the effects of this intervention on CFS symptoms.

- 4.3. **If you have cited references above, please attach a bibliography, including title, full author list, journal, date and pages. This bibliography should include only those articles referenced above.**

Name	Description	Version
CFS RO1 LitCited		0.01

4a. Description of Study (cont'd)

Rationale and Methodology

- 4.4. *** In non-technical, lay language, describe the study design and all study procedures, in order of sequence and timing. Include length of subject participation, what tasks are involved in the study, what tests or procedures subjects will be asked to complete or undergo, specific measures to be used, etc. If applicable, include frequency of visits, duration of visits, and study procedure calendar.**

Study Design:

This is a randomized controlled trial testing the effects of patient-partner based dual focused videotelephone-delivered CBSM (PP-T-CBSM) vs. a patient-partner attention-time matched health information control (T-HI). This study has a 2 X 3 (group: PP-T-CBSM, T-HI) X time (pre-intervention, about 5mo post, about 9 mo post) design with the primary outcome variable being total CDC-based CFS symptoms (frequency and severity). In addition we will explore selected individual symptoms to evaluate whether the intervention's overall effects are largely accounted for by specific symptom changes. The secondary outcome variable is a composite measure of pro-inflammatory cytokines: anti-inflammatory cytokines measured as the ratio of [IL-1B + IL-6 + TNF-x]: [IL-10 + IL-13]. The other secondary outcome variable is the AM-PM slope of salivary cortisol output over a 48hr sampling window (SP). We hypothesize that patients assigned to PP-T-CBSM will show larger decreases in CFS symptoms vs. those assigned to T-HI. We are also hypothesizing the greatest decrease in the pro-inflammatory: anti-inflammatory cytokine ratio and greatest increase in AM-PM negative SP in patients assigned to PP-T-CBSM vs. T-HI. We will examine whether changes in cytokines and cortisol are associated with psychosocial functioning to explain the effects of PP-T-CBSM on CFS symptoms. All analyses will control for medications, physical activity, and possible confounders per preliminary analyses. A total of 150 CFS patients and their partners between the age of 21 and 75 will be recruited for this study, with an anticipated retention of 124 at final assessment time point T3.

Study Procedures:

The CFS sample will be selected from the patient population of Dr. Klimas' CFS clinics (NOVA Univeristy and her Chronic Fatigue Center for Research and Treatment for Neuroimmune Disorders); community based physicians in Miami-Dade, Broward and Palm Beach Counties; and via community support groups, newspaper and web advertisements, and CFS related internet sites. Potential participants that contact us for information will be provided with a description of the study. If potential participant indicates having an interest in participating in the study they will be asked to complete a brief screening to determine eligibility (only the chronic fatigue patient will complete the screening interview). The screening process will take approximately 10 minutes (please refer to Screening Form in section 4.4A). Chronic fatigue patients will be screened and excluded for DSM-IV panic attack disorder, substance dependency, psychoses, with selected modules of the Structured Clinical Interview for DSM-IV (SCID). Patients who are diagnosed with one of these conditions during the course of the study will be excluded from data analyses and clinical referral will be provided as indicated. A modified Folstein Mini-Mental Status Exam and the Telephone Interview for Cognitive Status

(only participants who live outside our catchment area) will be administered to screen for signs of gross intellectual impairment or attention problems that could threaten the validity of baseline and follow-up assessments. If participant is eligible an appointment will be made to proceed with the consent process and baseline interview instructions. During the face to face visit the interviewer will review and provide a copy of the consent form to both the CFS patient and their identified partner. Participants will be given time to carefully read the consent form and ask any questions about the study. If participants live outside our catchment area they will be sent an electronic copy of the consent forms. CFS patients and their partners will be contacted via telephone to review the consents and answer any questions pertaining to the study. If participants agree to participate they will be asked to sign the consent forms and send them to our office via email (pdf), fax or regular mail. Their consent date will be recorded in our records during the telephone call in which we review the consent and will later be reconfirmed by the signed hard copy. Once participants consent to participate in the study the participants will be provided with instructions on how to complete the baseline interview via SurveyMonkey, a data collection program (please refer to section 4.4A). The core battery for the CFS patient will consist of the following focus areas: 1) Demographic information; 2) Lifestyle behaviors; 3) Physical factors related to CFS; 4) History of CFS; 5) Service utilization; 6) Perceived life stressors; 7) CFS symptoms; 8) Psychological functioning; 8) Social support; 9) Quality of patient-partner relationship; and 10) Changes in perceived CBSM skills. The core battery for the identified CFS partner will consist of demographic information, psychological functioning, social support, quality of patient-partner relationship, and changes in perceived CBSM skills. The time duration of the interviews is estimated to be 1-2 hours for the CFS participants and 30 minutes for the partner. Participants will be asked to complete a project evaluation questionnaire at the second (5 month) and third (9 month) interview and is estimated to take 15-20 minutes to complete. Participants (chronic fatigue patients only) will also be asked to collect four saliva samples on two consecutive days and provide us with a blood sample (about 2 ounces) at each measure point (baseline, about 5 month and about 9 month follow-ups). Chronic fatigued patients will be provided with a saliva kit and detailed instructions on how to collect the saliva and blood draw collection protocol (e.g. lab schedules and appointments and locations). For those participants who live outside our catchment area they will be sent a package via FedEx with instructions on how to collect the saliva samples and visit one of our contract labs near their area. Once they collect their samples they will send them to our lab processing center at the Papper Clinical Immunology Laboratory at the University of Miami (1600 NW 10 Avenue, Miami, FL 33136).

Intervention Protocol:

After participants complete the interviews, and chronic fatigue patients complete the collection of saliva and blood, they will open an envelope that will advise them of the group they were randomly assigned to (PP-T-CBSM or T-HI). Participants who live outside our catchment area will be contacted to inform them of their randomization group. Randomization will occur in waves of eight, four dyads will be randomized to PP-T-CBSM and 4 to P-HI). Subjects randomized to PP-T-CBSM will receive 10 weeks of group intervention as described herein. A total of 4 dyads (CFS patient and their identified partner) will meet once weekly by videophone for approximately a one hour session at a mutually convenient set time. The content of the PP-T-CBSM protocol will comprise two broad domains: Cognitive, behavioral and interpersonal skills training and relaxation/imagery. The Cognitive, Behavioral and Interpersonal skills component presents information concerning stressors and stress responses from a biopsychosocial perspective. The initial 5 weeks emphasize: (1) the importance of appraisals in the stress response and in symptom occurrence; (2) understanding automatic thoughts and cognitive distortions; (3) identifying and monitoring automatic thoughts; (4) disputing and restructuring cognitive distortions into more rational thoughts, and (5) learning adaptive problem-focused and emotion-focused coping skills. By monitoring automatic thoughts associated with negative emotions, participants increase their awareness of cognitive appraisals that precede changes in emotion. Stressors of primary importance in this study are those concerning the physical symptoms of CFS and the losses associated with the illness. Participants learn how automatic thoughts, including cognitive distortions may contribute to symptom magnification and ensuing feelings of loss of perceived control. The remaining 5 weeks focus on

strategies to improve interpersonal communication, self-esteem, and quality of life, and to encourage appropriate emotional expression and assertion skills. During the sessions individual problems are addressed and homework is reviewed. Based on our experience, the combination of social support and self-reinforcement seems to increase participants' use of these strategies and foster self-efficacy, self-esteem, and a sense of perceived personal control. The Relaxation/Imagery component includes targeting anxiety reduction through training in deep muscle relaxation. Participants use imagery of muscle groups rather than progressive muscle relaxation (tensing and relaxing muscle groups) because in our previous clinical work, we have found that tensing of muscle groups often increases joint and muscle pain-related symptoms that many CFS patients experience. In addition to reducing anxiety, relaxation training has been helpful for many of our participants in overcoming sleep problems associated with CFS. Autogenics, guided imagery, deep breathing and meditative techniques are taught in later weeks. We found that some members tend to learn and acquire skills better when presented in a didactic form while others may assimilate information better if it is introduced through images and metaphors. All sessions begin with a brief review of the previous meeting. The lively interactive format of our sessions enhances understanding and retention of the intervention materials through active participation. This multimodal/interactive approach should maximize the effectiveness of PP-T-CBSM in teaching stress reduction strategies simultaneously to patients and partners. Participants also receive a Participant Workbook, which contains a summary of the rationale for each module, outlines of each technique taught, and homework exercises and self-monitoring sheets to be completed by patient and partner. Finally, key points of all PP-T-CBSM strategies are available in text, audio and/or video form through pull-down screens in our Telecare system, which participants can access at any time. The video telephone is menu driven and has tri-modal output (text, speech, video).

Subjects randomized to Telephone Health Information (T-HI) condition will receive 10 weeks of individual telephone sessions of approximately one hour. This control condition is designed to provide equal amounts of attention and contact time without any active treatment (CBSM) being given. T-HI is designed to control for common factors such as attention, supportiveness, empathy and enthusiasm. Social support processes (e.g., group cohesiveness) are an "active ingredient" in the T-CBSM intervention and social support changes will be tested as part of our hypothesized model. By providing T-HI in an individual format, we are controlling for facilitator's time and attention, supportiveness, and empathy, but we retain the ability to test whether a supportive group intervention facilitates better quality of life and health outcomes. If we were to provide T-HI in a group format, we would be equalizing the groups on a factor that we are actually aiming to test. Moreover, once a group is assembled, it is very difficult to deter social processes as they may occur within the group or as part of ancillary group contact. The sessions cover the benefits of titrated physical and leisure activity, sleep, and proper nutrition (e.g., balanced diet, nutrition guidelines for adults), and the importance of receiving regular medical care and follow-up. Participants will be encouraged to ask questions and to discuss material at a personalized level to increase its relevance (e.g., asked to complete dietary log to increase awareness of eating habits; monitor physical activities; etc.). The material presented will be comprised of information that is commonly available and is designed to complement the ongoing medical care that participants receive from their medical treatment provider(s). Each session consists of a didactic presentation of the topics and activities to promote discussion. Patients report that they find the material to be useful. Participants will receive a Participant Workbook, which contains a summary of the information presented in each individual session and health resources. In addition, participants will be encouraged to inform their provider(s) about their study participation and to consult with provider(s) before initiating any health behavior changes (e.g., increasing physical activity). In addition to printed materials, participants will have access to system with recorded T-HI information. Usage of the system will be monitored as an indicator of dose.

Treatment fidelity will be monitored by audio taping a random sample of the intervention sessions. Participants will be asked for their permission to be audio taped at the end of the consent form. If participants do not feel comfortable being audio taped this will not affect their participation in the study. Those participants refusing to be audio taped will not be audio-taped at any point of the intervention. In addition audio tapes will be destroyed upon participant's request.

Follow-up Interview Protocol:

Upon completion of the 10 week program for both PP-T-CBSM and T-HI, participants will be contacted by a study staff member to coordinate the 5 (approximate) month follow-up interview. Participants will be sent their interview via email to complete electronically using SurveyMonkey. They will also be mailed a saliva kit with instruction on how to complete it. Participants will have a 2-3 week window to complete the interview and saliva collection before scheduling a blood draw at one of our lab locations. Participants who live outside our catchment area will follow the same lab collection protocol outlined above. This procedure will be repeated in four months when the last collection point at about the 9 month follow-up.

Blood Draw Protocol:

Chronic fatigue patients will be asked to provide about 2 ounces of blood at each time point. The blood collection will be conducted at one of the designated lab locations. An appointment will be made by one of our staff members who will also be meeting the participant at the lab location. No identifying patient information will be shared with the lab sites; appointments will be made using the study name and subject ID and pre-printed labels with subject's ID will be used on collected blood samples. A member of the study staff will be with the participant at all times to insure that the blood collection is conducted safely. The saliva samples and blood sample will be taken to Dr. Fletcher's Immunology Lab (E. M. Papper Laboratory of Clinical Immunology). Participants who live outside our catchment area will be asked to visit one of our contracted lab (for example Labcorp) in their area. Participants will be sent a package with detail information about the blood draw protocol (including lab request forms, tubes and instructions to the lab) and how to send back the samples to Dr. Fletcher's Immunology Lab.

Technical Support and Installation of the VideoPhone System:

Participants will receive a VideoPhone System as part of their study program and will be asked to return the system after completing the study. The VideoPhone system will be installed either by one of our technical staff member (if participant lives within our catchment area) or we will send those participants who live outside our catchment area detail instructions on how to install the system (a detailed email with a demonstration installation video link). In addition our technical support team will contact each participant to check that that system is working properly. Each participant will also receive instructions on how to use the different features of the system either in person at the installation appointment or via email by sending participants a video with details instructions. The therapist assigned to work with the dyad will contact them to make sure they understand how to use the VideoHealth system and answer any questions regarding the features and use of the system.

- 4.4.A. **Standard Measures:** Click the "Add" button to open the search window, then click the "Find" button to browse and select measures.

Name of Measure	Brief Description	Type of Measure
There are no items to display		

NOTE: A copy of the first page of each standard measure is provided in the [Library of Standard Measures](#) for verification. Ensure that the version being used in this study is the same as the version that has been selected.

Upload any questionnaires and/or assessment tools to be used that are not listed above:

Name	Description	Version
CFS Core Battery-CFS		0.01
CFS Core Battery-Partner		0.01
CFS Patient Project Evaluation 4-16-12		0.01
CFS Screening Form 9-20-10		0.02
Partner Project Evaluation 4-16-12		0.01
Short Version of PT follow up interviews Apr2013		0.01
TICS Telephone Interview for Cognitive Status Form		0.01
VideoHealth CFS Patient Assessment Surveymonkey 6-3-11		0.01
VideoHealth Partner Assessment Surveymonkey 6-3-11		0.01
VideoHealth Screening Rev-Clean 4-1-13		0.01
VideoHealth Study Assessment (CFS) Track Changes 6-3-11		0.01

4.5. Identify and distinguish between those procedures that are standard treatment versus those that are experimental/research-specific.



Not applicable

The use of CBST techniques (e.g. relaxation) in the experimental condition is not part of the standard care for CFS. Beyond these techniques patients in each study condition will be receiving standard of care. Research-specific techniques include things such as relaxation training, cognitive behavioral therapy and group support. Standard treatment for CFS includes but is not limited to medications designed to reduce symptoms. The experimental procedure in this study will not involve medications.

4.6. Describe any therapeutic alternatives that may exist for the study population.



Not applicable

Medication to diminish symptoms and exercise intervention designed to prevent de-conditioning.

4b. Description of Study (cont'd)

Risk/Benefit Assessment

4.7. * Describe the nature, degree, and if available, expected frequency of all potential economic/financial, legal, physical, psychological, social or other risks to which research participants may be exposed as a result of their participation in this research. If applicable, please describe the risk of investigational agents or devices (side effects).

Participants will incur no appreciable physical risks through participation in this study, though they may undergo psychological discomfort at some time points. During the psychosocial intervention, participants will be given specific CFS-related information, as well as be asked to participate in assessment of sensitive topics that may lead some to experience transient and mild anxiety. In addition, some participants are likely to manifest symptom increases from time to time throughout the longitudinal component of the study, and some may experience affective distress. In these cases, every attempt will be made to provide relief and to ameliorate the source of the discomfort. Should participants experience extreme acute or persisting affective reactions at any point during the study period, they will be referred to a psychiatrist or clinical psychologist associated with the site for care. In the event that a participant reports symptoms or concerns of extreme distress (e.g., severe symptoms of depression and/or anxiety suggesting clinical concerns, suicidality, etc.), our interventionists will directly target such symptoms and assess the severity of such distress within the group context while maintaining the group process and eliciting support from other participants. Subsequent to the intervention session, the participant will be contacted individually by one of the interventionists for a more comprehensive assessment of distress. If it is determined at that point that the participant needs individual care, our interventionists and research staff will

be prepared to refer the patient to a source of clinical intervention other than our PP-T-CBSM intervention (a list of referrals will be available). Similarly, should participants experience extreme, acute or persisting affective reactions at any other point during the study period (e.g., assessment, individual contact), they will be referred to the appropriate channels within the UM Department of Psychiatry or Psychology, as well as to a list of community resources/catchment sites in the South Florida area prepared to deliver resources to deal with extreme distress. Similar procedures will be followed for participants in our T-HI condition. The information obtained in this project will help in the development of strategies for promoting quality of life among individuals living with CFS. All participants will receive fair compensation for the time they invest in completing the research protocol.

Participants will also be required to provide blood samples at each time point. Blood samples (about 2 ounces at each of the measurement points) will be taken from a vein in their arm using a needle and blood tube (venipuncture). This will be done by a trained nurse or phlebotomist. Participants may experience discomfort during blood sampling. The risks of blood sampling by venipuncture include the occurrence of a bruise at the site of the needle puncture and, in rare cases, infection or the formation of a small blood clot, swelling of the vein and surrounding tissue, bleeding at the needle puncture site, and fainting. In the event that a subject experiences an injury due to these procedures, medical treatment will be made available through the investigators and staff. The participants will be encouraged to contact the study investigators and staff should they have any questions or concerns at that point in time.

4.8. * Are there potential direct benefits of this research to the subjects?

☒ **Yes** ☐ **No**

4.8.A. If yes, provide a description of the potential direct benefits and indicate if all, or only some, of the subject groups may derive this potential benefit.

It is anticipated that participants will experience more benefits than risks as a result of their participation in the study. In particular we anticipate that the those participants in the intervention condition (PP-T-CBSM) will experience a decrease in illness burden, perceived stress, and distress relative to participating in the attention control group (T-HI condition).

4.9. * Are there potential benefits of this research to society?

☒ **Yes** ☐ **No**

4.9.A. * Please explain:

Helping CFS patients to function better may help them return to employment, and increase their ability to fulfill other responsibilities within their family. The results of this study may provide scientific contributions to society by providing additional insight about the effects of home-based telephone-delivered stress management intervention among other chronic illness and hard-to-reach populations who might benefit from these techniques.

4.10. * Explain why the risk/benefit ratio supports conducting this research.

The investigators believe that this study possesses no greater than minimal risk and that the benefits to the individual and society are greater than its risk.

4c. Description of Study (cont'd)

Data

4.11. *** Describe follow-up, data storage methods, data security, authorized access to records and record retention, including site name and address.**

Participant will have a total of 3 assessment time points, at the beginning of the study, and at approximately 5- and 9-month follow-ups. The participants will also be asked to provide samples of their saliva and blood at each time point. The screening forms, assessments, and consent forms will be safely stored at the Center on Aging (1695 NW 9th Avenue Suite 3208Q) under double lock and key. Electronic information of the data will also be safely secured using access privileges and passwords. Saliva and blood samples will be stored in Dr. Fletcher's lab in the E.M Papper Clinical Immunology Lab, Rosenstiel 8th Floor. Only study related personnel will have access to the participant's files.

4.12. *** Support the study validity by describing the statistical design, including quantitative and qualitative methods used to analyze data.**

The study is a 2 (experimental, control group) X 3 (pre-intervention, post-intervention, follow-up) randomized controlled design that will test the effects of a PP-T-CBSM intervention on hypothesized psychological, physiological and clinical/physical health indicators in a sample of patients diagnosed with CFS. Psychological data is derived from valid and reliable interview and questionnaire methods based upon published psychometric studies. Physiological data is derived from bioassays of collected biological specimens (blood, saliva) using standardized methods for quantitating concentrations of hormones and cytokines. The primary outcome is CFS physical symptoms and secondary outcomes include indicators of psychological and physiological functioning hypothesized to mediate the effects of the intervention on physical symptoms. Study hypotheses are tested using multivariate repeated measures statistical procedures designed to test for differences in the changes in study outcomes over time as a function of random assignment to study groups. Statistical controls (covariates) are employed where appropriate. All analyses have been guided by underlying theory and the study sample size was determined by power analyses based upon prior published work and pilot studies.

Privacy/Confidentiality Agreements

4.13. **Describe any privacy agreements or certificates of confidentiality, if applicable.**

Participants will be provided with a copy of the consent form as part of their initial interview or telephone contact. The consent form outlines the study's protocol and guidelines regarding confidentiality. In addition the assessor will review each section of the consent form, including the section about confidentiality.

4d. Description of Study (cont'd)

Deception

4.14. *** Is the use of deception part of the study design?**

☐ Yes ☒ No

If yes, please answer the following 3 questions:

4.14.A. **Describe in detail the nature of the deception and explain why this is necessary for the research.**

4.14.B. **State how, when, and by whom the research subjects will be debriefed.**

4.14.C. **Upload a copy of the debriefing script.**

5. Study Participants

Per 45 CFR 46, human subjects (participants) means a living individual about whom an investigator (whether professional or student) conducting research obtains:

1. data through intervention or interaction with the individual; or
2. identifiable private information (i.e. pathological specimens, medical records, etc.)

5.1. * Participant Age:

Check all that apply	Notes
<input type="checkbox"/> 0-6	<i>Parent Permission/Consent required for each participant</i>
<input type="checkbox"/> 7-17	<i>Parent Permission/Consent & Child Assent required for each participant</i>
<input checked="" type="checkbox"/> 18-65	<i>Consent required for each participant unless a waiver of consent is approved by the IRB</i>
<input checked="" type="checkbox"/> 65+	<i>Consent required for each participant unless a waiver of consent is approved by the IRB</i>

**5.2. For the following questions, please use integers for your responses. For any question that is not applicable, please enter the number 0.
(Do not enter commas, decimal points or special characters)**

5.2.A. * Maximum number of subjects in the Protocol to be *screened* at all sites (regardless of PI):
600

5.2.B. * Total number of subjects in the Protocol to be *studied* at all sites (regardless of PI):
300

University of Miami

5.2.C. * Maximum number of subjects to be *screened* by this PI at *UM*:
600

*** Maximum number of subjects to be *enrolled* by this PI at *UM*:**
300

*** From the above, how many are expected to *complete* this study (participate in the study beyond initial enrollment)?**
255

Jackson Health Systems

5.2.D. * Maximum number of subjects to be *screened* by this PI at *Jackson Health Systems (JHS)*:
0

*** Maximum number of subjects to be *enrolled* by this PI at *Jackson Health Systems (JHS)*:**
0

*** From the above, how many are expected to *complete* this study (participate in the study beyond initial enrollment)?**
0

Miami VA Medical Center

5.2.E. * Maximum number of subjects to be *screened* by this PI at *Miami VA Medical Center*:

0

* Maximum number of subjects to be *enrolled* by this PI at *Miami VA Medical Center*:

0

* From the above, how many are expected to *complete* this study (participate in the study beyond initial enrollment)?

0

5a. Study Populations

5.3. * Study populations to be included in this study where PI will be conducting research and those sites where the UM IRB will have oversight responsibility:

Check all that apply

Notes

Other

5.3.A. If *other*, please specify:

Chronic Fatigue Syndrome patients and their identified partners

5.3.B. Describe below any additional safeguards that have been included to protect vulnerable subjects:

Please refer to section 4.7

5b. Inclusions/Exclusions

5.4. * Is the population being enrolled in this study at high risk for incarceration?

☐ Yes ☒ No

5.4.A. If *yes*, will the subjects be withdrawn from the study once they are incarcerated?

☐ Yes ☐ No

5.4.A.(i) If the above answer (question 5.4.A.) is *no*, describe how re-contacting/re-consenting, treatment, and/or follow-up will occur:

NOTE: If a subject becomes incarcerated while enrolled in a study, all research interactions and interventions with that subject, and the obtaining of identifiable private information about the subject, must cease until the requirements of subpart C have been satisfied with respect to the relevant protocol.

If notified that a previously enrolled research subject has become a prisoner, the principal investigator must promptly seek IRB re-review of the protocol in accordance with the requirements of subpart C if the principal investigator wishes to have the prisoner-subject continue to participate in the research. **In special circumstances in which the principal investigator asserts that it is in the best interests of the subject to remain in the**

research study while incarcerated, the IRB Chairperson may determine that the subject may continue to participate in the research until the requirements of subpart C are satisfied.

5.5. * What are the criteria for exclusion of participants from the research?

Participants will be excluded from the study if:

1. They do not have a current CDC case definition of having Chronic Fatigue Syndrome
2. If they are under 21 years of age or over 75 years old.
3. If they have a history of severe psychiatric disorders; DSM-IV diagnosis for panic attacks, substance dependency, psychoses or any expressed a current suicidal thoughts.
4. If they do not identify a partner that will also agree to be part of the study.
5. If they are unable to read, speak and write English (the program intervention is in English only)
6. If they are receiving any treatment for a terminal condition or are diagnosed with Lyme's disease, Lupus, Rheumatoid arthritis, acute or chronic hepatitis, HIV disease, or any other autoimmune disease.
7. If they do not have internet capability (a broadband line).

5.6. * Will any population be systematically excluded in this study?

☐ Yes ☒ **No**

5.6.A. If yes, provide rationale/justification for this exclusion:

5.7. * What are the criteria for inclusion of participants in the research?

Participants are eligible to participate in the study if:

1. Have a CDC diagnosis of Chronic Fatigue Syndrome.
2. If they are 21 years or older and under 76 years old.
3. They are fluent in English (the program intervention is only in English)
4. Are able to identify a partner living together or separate and are willing to participate in the study for 9 months.
5. Are willing to cooperate with the study's objectives and guidelines as reflected in the consent form.
6. Have internet capability (broadband line) and are willing for us to install the study's equipment.

5.8. * Will only one group of individuals be systematically selected and recruited for this study (e.g., welfare patients, racial and/or ethnic minorities, persons confined to institutions or persons determined to be incapacitated)?

☒ **Yes** ☐ No

5.8.A. If yes, please state how this participant group will benefit from the results of the research and provide the reasons and justifications to target this group:

Chronic fatigue syndrome patients and their identified partners.

6. Subject Recruitment

6.1. * From what sources or by what methods will subjects be recruited?

Check all that apply

Flyers/newsletters

Internet (web postings)

Contact letters (physicians, teachers, etc.)

Primary physician/physician specialist

Outpatients/clinics

Direct contact

Newspaper

Posters

Radio

Telephone

6.1.A. If *postings within hospital*, please indicate name of facility:

6.1.B. If *emergency room*, please indicate name of facility:

6.1.C. If *other*, please specify:

6a. Subject Recruitment (cont'd)

6.2. * Provide a step-by-step description of the recruitment procedures used to identify and/or contact prospective participants:

The CFS sample will be selected from the patient population of Dr. Klimas' CFS clinics (NOVA University and Chronic Fatigue Center for Research and Treatment for Neuroimmune Disorders); community based physicians in Miami-Dade, Broward and Palm Beach Counties; via community support groups, newspaper and web advertisement, and CFS related internet sites. Individuals interested in the study will be able to call our recruitment telephone number or approach one of our staff member for information. A recruitment specialist will contact the called and explain the study. If the interested person would like to participate in the study the recruitment specialist or a member of our staff will ask verbal permission to proceed with a brief screening questionnaire (please refer to preliminary Screening uploaded on section 4.4A).

Flyers will be posted on the above mentioned locations, and will also be made available to participants upon request. A public announcement script will also be used to inform positional participants via newspaper announcements and advertising venues, such as community flyers, magazines, websites of CFS organizations, etc.

6.2.A. Please upload copies of scripts, recruiting materials, and advertisements:

Name	Description	Version
Chronic Fatigue Postcard NEW VERSION		0.01
DO YOU HAVE CFS Poster		0.01
Letter to professionals		0.01
Recruitment Post-Card		0.01
VideoHealth Flyer without taps		0.01
VideoHealth Flyers with taps		0.01
VideoHealth Public Announcement 2-3-11		0.01

NOTE: Any materials that will be given to or seen by potential subjects must be reviewed and approved by the IRB. This includes assessments, instruments, diaries, questionnaires, and all screening and recruitment materials, including advertisements, web postings, letters, and telephone scripts. Only IRB approved versions of these materials may be used during the course of the study.

6.3. * What measures will be taken during the recruitment process to safeguard against the potential coercion or the appearance of coercion of participants, particularly vulnerable populations?

All recruitment personnel will be trained in study procedures including the treatment of human subjects and will be required to complete the CITI certification program, which covers issues pertaining to coercion. Activities of the recruitment personnel will be monitored on a weekly basis by the Project manager with oversight by the PI. There is the potential for undue influence. Thus, all study personnel will undergo training on how to approach potential participants. There will also be a telephone script developed to insure that the information on the study is consistent and clear.

6.4. * Are there specific criteria to prematurely end a particular subject's participation in the study (e.g., predetermined safety endpoints, unexpected clinically significant findings, distress or serious adverse events, etc.)?

Select one
<input checked="" type="radio"/> Yes
<input type="radio"/> No
<input type="radio"/> Not Applicable

6.4.A. If yes, please describe:

If the participant presents a danger to him/herself or others and requires immediate mental health services the participant will be terminated from the study. Mental health referral will be provided in these instances.

If the participant conducts him/herself in such a manner that is disruptive to other participants and/or the intervention process he/she may be terminated from the study since the procedures require interactions among group participants on a regular basis and these interactions constitute an element of the intervention. Termination due to the development of a serious medical condition will be handled on a case-by-case basis in consultation with the study physician.

6.5. * Will subjects be remunerated for their participation in the study in any way other than credit toward a course requirement?

☒ Yes ☐ No

6b. Remuneration

6.5.A. * List type, frequency, interval, and total value of remuneration:

Type of Remuneration	Frequency	Total Value
View Gift Certificates	3	150 (50X3)
View Parking	3	15 (5X3)
View Gift Certificates	3	150 (50X3)

6.5.B. * If a subject withdraws from the study early, will remuneration be prorated?
no

6.5.B.(i) If yes, describe plan for prorating payments and ensure that this plan is defined in consent forms:

6.5.B.(ii) If no, justify why prorated payment is not being offered:
Participants are remunerated for completing the entire assessment process (core battery, provision of the saliva and blood samples) at each time point. Parking costs are not provided for assessment visits that are not attended.

6c. Financial Liability

6.6. * Financial Liability for Study Participants:

Complete the table below, indicating the responsible party for payment of research activities and procedures.

☒ Not applicable

Procedure or Activity	Frequency
There are no items to display	

6.7. * Select all categories indicating costs which participants or their insurance companies will be responsible for:

Check all that apply	
<input checked="" type="checkbox"/>	Participants will have no costs associated with this study
<input type="checkbox"/>	Study-related procedures which would be done under standard care
<input type="checkbox"/>	Study-related procedures not associated with standard care

☐ Administration of drugs/devices

☐ Study drugs

☐ Study devices

☐ Other

6.7.A. If *other*, please specify:

6.8. * In the event of study-related subject injury, who will be responsible for compensation?
Not Applicable

6.8.A. If *Other 3rd Party*, please specify:

7. Informed Consent

7.1. * Is an alteration of the consent process being requested?

☐ Yes ☒ No

NOTE: "Alteration of consent" is when the consent procedure does not include, or alters, some of the required elements of informed consent. This only applies to studies conducted by state or local government on public benefit or service programs. See <http://www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm>

7.2. * Is a waiver of informed consent being requested?

☐ Yes ☒ No

NOTE: This indicates there is no consent process; waiver criteria need to be justified.

7.3. * Is a waiver of signed consent being requested?

☒ Yes ☐ No

NOTE: This indicates that the consent process will occur, but there is no signed consent (i.e., verbal script or consent letter).

7b. Informed Consent (cont'd)

7.8. * Under which of the following criteria does this research qualify for Waiver of Signed Consent?

Check one	Description
<input checked="" type="radio"/> 45 CFR 46.117 (c) (1)	The only records linking the subject and the research would be the consent document, and the principal risk would be the potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern.

<div style="display: flex; align-items: center;"> <div style="margin-right: 10px;"> <div style="border: 1px solid black; border-radius: 50%; width: 15px; height: 15px; display: flex; align-items: center; justify-content: center;"> <div style="width: 10px; height: 10px; border: 1px solid black; border-radius: 50%;"></div> </div> </div> <div> 45 CFR 46.117 (c) (2) </div> </div>	This research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.
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7.8.A. *** Please state the justification for the criterion selected above:**

Potential participants will be asked for their permission to answer questions from a screening form to determine their eligibility in the study.

7c. Informed Consent (cont'd)

7.9. *** Describe the specific steps for obtaining informed consent (e.g., by whom, his/her credentials, language, where, when, etc.):**



Not applicable

Individuals who call our recruitment line or approach one of our staff member will be provided with information on the study. If the CFS person is interested in participating in the study, he/she will be asked for their verbal permission to proceed with a screening questionnaire that will determine their eligibility (please refer to preliminary screening uploaded in section 4.4A). If the CFS person is eligible she/he will be asked to indicate a convenient time and place to meet in order to proceed with the consent process and baseline interview of the CFS patient and their identified partner. Both CFS patient and their identified partner will be provided with thorough explanation of the study and consent process. If they agree to participate in the study the CFS and identified partner will be asked to sign the consent form and a copy will be provided for them to keep. The consent forms are written in simple language (non technical terms) and in English.

Participants who live outside our catchment area will be sent an electronic copy of the consent form. CFS patients and their partners will be contacted via telephone to review the consents and answer any questions pertaining to the study. If participants agree to participate they will be asked to sign the consent forms and send them to our office via email (pdf), fax or regular mail. Their consent date will be recorded in our records during the telephone call in which we review the consent and will later be reconfirmed by the signed hard copy.

7.10. **Consent may be required from a parent, legal guardian, legal representative, court-appointed representative, or health care surrogate where research involves children/minors, wards of the state, cognitively or developmentally impaired individuals, comatose or traumatized or emergency subjects, as well as any other subjects lacking capacity to consent. Such surrogate/representative/guardian can only consent if the IRB has approved the research under HHS or FDA regulations. For court-appointed guardians, court assent is required.**

If your study involves any of these groups, please specify below whether consent will be obtained from such surrogate/representative/guardian and describe the process for obtaining such consent:

N/A

7.11. *** What protections will be offered to persons with cognitive impairment or to persons determined to be incapacitated? Describe how capacity for consent will be determined, whether cognitive capacity is expected to change significantly during the study, whether a legally authorized representative or health surrogate has been designated for purposes of obtaining informed consent, and whether court approval**

has been obtained (for court-appointed guardians). Describe plans to re-consent subjects after a change in the subject's cognitive capacity.

☒ Not applicable

7.12. * How will informed assent for children and parental consent/permission be obtained?

☒ Not applicable

7.13. * Describe plans to re-assent or obtain consent for child subjects during the study if the subject reaches the age of majority (18 years) or if there is a significant change in cognitive capacity (i.e. gets older or regains consciousness).

☒ Not applicable

7.14. * How will non-English speaking participants be consented? (Federal regulations require the equitable selection of minorities as research subjects to assure that they receive an equal share of the benefits of research and to ensure that they do not bear a disproportionate burden.)

Check one	Notes
<input checked="" type="radio"/> Not Applicable	
<input type="radio"/> A translated written informed consent document in a language understandable to the participant	This should be an accurate translation of the IRB-approved English version of the full informed consent document. Translations of IRB-approved informed consent documents must be made by a certified translator. Click here for list of certified translators.
<input type="radio"/> Orally, using a qualified translator to translate the English informed consent document to the participant, and a translated short form in a language understandable to the participant.	See IRB Policy IV.B. "Documentation of Informed Consent"

7.15. * Informed Consent Document Templates

☐ Not applicable

Please attach all consent and assent templates associated with this study. (This includes genetic consent, HIV consent, tissue banking consent, etc.)

Name	Description	Version
20100771_ICF_IRBApp_CFSPartner.doc		0.02
20100771_ICF_IRBApp_CFSPatient.doc		0.01

8. Protected Health Information

Protected health information (PHI) is individually identifiable health information that is or has been collected or maintained by the University of Miami or JHS or created for purposes of providing medical care/treatment and can be linked back to the individual participant.

8.1.(a) * Will Protected Health Information (PHI) be accessed (used or created for treatment) *prior to contact with subjects* in this research?

☐ Yes ☒ No

8.1.(b) * Will PHI be accessed (used or created for treatment) during the course of the proposed research?

☐ Yes ☒ No

11. Use of Human Biological Samples

11.1. * List all samples to be used in this research:

Type of sample
View Blood
View Saliva

11.2. * Will it be possible, if so requested, to provide the participant with the sample/data for this study?

yes

11.2.A. If *no*, please explain:

11.3. * Will you allow participants to request the samples/data in this study be destroyed?

yes

11.3.A. If *no*, please explain:

15. Conflict of Interest

As the Principal Investigator, you must be aware of any conflict of interest of the protocol team or institution. Please note that the thresholds of ownership described below apply to the aggregate ownership of each individual investigator (or other key personnel, to the best of their knowledge) and their immediate family. The immediate family includes each investigator's spouse, domestic partner and dependent children (e.g., if an investigator together with his/her spouse, domestic

partner and dependent children own a total of \$10,000 or 5% worth of equities in the sponsor, it should be reported below).

"Conflicts of interest" apply to each investigator or other individuals listed as key personnel. Do not consider the combined ownership of all investigators/key personnel. Do not consider compensation for the % effort on a study.

- 15.1. *** Does any person obtaining consent have any existing relationship (family, social, or professional, including physician-patient or student-teacher) with the subject(s)?**

☐ Yes ☒ **No**

- 15.1.A. **If yes, describe the relationship(s) and how subjects will be protected against undue influence or coercion:**

- 15.2. *** Will there be any programs, bonuses, rewards or other incentives that may be offered to this site and/or its faculty or staff by the sponsor or others for rapid enrollment?**

☐ Yes ☒ **No**

- 15.2.A. **If yes, please describe:**

Note: Before accepting any awards, the IRB must be informed of the nature and value of these incentives.

- 15.3. *** Do any of the investigators or members of their immediate families receive from the sponsoring entity salaries, consulting fees, or other compensation for services that exceed \$10,000 in any twelve month period? (Note: if the sponsoring entity is the full time employer of the investigator, co-investigator or key personnel (i.e. UM or JHS) then answer "No." Do not consider compensation for the % effort on a study.)**

☐ Yes ☒ **No**

- 15.4. *** Do any of the investigators or members of their immediate families serve as an officer, director, or as a member of any advisory board with the sponsoring entity?**

☐ Yes ☒ **No**

- 15.5. *** Do any of the investigators or members of their immediate families have an equity interest that exceeds \$10,000 in value or represents more than 5% ownership in the sponsoring entity?**

☐ Yes ☒ **No**

- 15.6. * Do any of the investigators or members of their immediate families have any intellectual property rights (patents, copyrights, royalties) in any article(s), product(s), drug(s), device(s) or other material(s) that will be involved in this research?

☐ Yes ☒ No

- 15.7. * Do any of the investigators or members of their immediate families have any other financial interest or relationship that would reasonably be affected by this research?

☐ Yes ☒ No

- 15.8. * Do any of the investigators or others know of any institutional conflict of interest pertaining to this study?

☐ Yes ☒ No

15.8.A. If yes, please describe:

- 15.9. * Has any of the technology used in the study been developed in whole or in part at the University of Miami?

☒ Yes ☐ No

16. Monitoring Plans

- 16.1. * Select the item below that most accurately reflects the plan for data and safety monitoring for this study:

Select one

- ☐ The study will be monitored only by the study investigators and/or sponsor.
- ☐ The study will be monitored by at least one individual who is not associated with the study, but not by a formally constituted Data and Safety Monitoring Board (DSMB).
- ☒ A formally constituted Data and Safety Monitoring Board (DSMB) will monitor the study.
- ☐ Not applicable

- 16.2. Has an internal (UM or JHS) data safety monitor or board/committee been established to provide additional oversight or monitoring of this study for safety and adherence to the study protocol?

☒ Yes ☐ No

- 16.2.A. If yes, describe the composition of the committee and how they will communicate findings to the IRB:

An internal DSMB will be formed by a panel of experts in behavioral medicine, CFS and/or medicine. They are independent agents that serve as research consultants. The Board's functions will predominately be to insure ethical data management/integrity, and review of safety issues (AE's and SAE's). Further details

will be provided to the IRB upon the final formation and proposed operations of this Board.

- 16.3. **Has an external (non-UM or JHS) data safety monitor or board/committee been established to provide additional oversight or monitoring of this study for safety and adherence to the study protocol?**

☐ Yes ☒ **No**

- 16.3.A. **If yes, describe the composition of the committee and how they will communicate findings to the IRB:**