An Open-Label Study of the Apollo Device for Fatigue in Systemic Sclerosis

Test device:	Apollo
Study purpose:	Evaluate the efficacy and use patterns of Apollo
Clinical study phase:	II
Version no:	1
Version Date	February 1, 2021
Sponsor Investigator:	

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Synopsis

Title	An Open-Label Study of the Apollo Device for Fatigue in Systemic Sclerosis
Short title	The Apollo in Systemic Sclerosis
Clinical study phase	II
Study objective(s)	The primary objective of this study is to provide preliminary data on the tolerability and efficacy of the Apollo system for the management of fatigue in systemic sclerosis.
Test device	Apollo System
Mechanism of use	The Apollo system consists of a wearable device whose frequency of use is controlled by the participant. The participant will install the study mobile application on a mobile device of their choosing. The wearable device is controlled by the mobile app through which the participant can choose when and for how long to use it.
Location of use	Wrist or ankle
Duration of use	4 weeks
Background treatment	Patients will continue any existing prescription medication, including prednisone and immunosuppressives, at steady doses for 4 weeks prior to baseline (visit 1) and during the four-week intervention period.
Indication	Scleroderma-associated fatigue
Diagnosis and main criteria for inclusion	▪ Men or women aged 18 years and older, inclusive ▪ Systemic Sclerosis as defined by 2013 the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification. ▪ Steady daily doses of any immunosuppressive medication, vasodilators, antidepressants and anxiolytic use for 4 weeks prior to baseline. ▪ PROMIS-fatigue score of at least 45 ▪ Currently owns and operates a smart phone regularly ▪ Ability to provide informed consent
Study Design	Open label, single-arm, single center US study
Type of control	None
Number of participants	30
Primary outcome variable	Change in the PROMIS-Fatigue scale at four weeks

30

Plan for statistical analysis	The planned sample size of 30 SSc participants is based on practical considerations to obtain estimates of the magnitude of treatment differences for efficacy and safety rather than a desired power for a pre- specified difference. From similar studies on Rheumatoid Arthritis and Systemic Lupus Erythematosus, the improvement of T-score after treatment is about 5. The standard deviation for general population is 10. However, we are restricting our population to participants with fatigue T-scores of less than 54 (with low score indicating high fatigue). With the range of T-score reduced about half, we expect the standard deviation to be about 5. The effect size is expected to be 1 (5/5). Using paired t-test, we have 86% power to detect the effect size of 1 when we recruit 30 patients at a significance level of 0.05. We asked the IRB for the option of increasing the number of patients to 40, which will give us about 81% power to detect a smaller effect size of 0.8 at a significance level of 0.05. Descriptive statistics will be derived for all clinical variables, mean and standard deviation for continuous outcomes and percentages for categorical and dichotomous variables. The primary outcome of interest is fatigue, as measured by the FACIT-Fatigue. We will compare the mean change from baseline and four weeks in a repeated measures model. The p-values resulting from formal statistical tests will be interpreted from a hypothesis-generating, rather than a confirmatory framework.

Table of contents

1. Introduction

1.1 Background

1.1.1 Scleroderma (systemic sclerosis)

Systemic sclerosis (SSc) is an uncommon, multisystem autoimmune disease characterized by small vessel vasculopathy, immune system activation with autoantibody production and fibroblast dysfunction leading to increased deposition of extracellular matrix.

SSc is an orphan disease with an incidence of nearly 20 patients per million per year (1,2) and an estimated point prevalence of approximately 250 per million based on US studies (2). SSc is a female-predominant disease, affecting women three to four times more often than men. SSc may affect individuals of all ages, with the peak incidence occurring between 45 and 64 years of age (2).

The hallmark of SSc is cutaneous and visceral fibrosis, which is reflected in the commonly used term for the disease, scleroderma, which derives from the Greek 'scleros' meaning thick and 'derma' referring to skin. While the cutaneous manifestations are the most obvious, it is the vascular and internal organ manifestations that contribute most importantly to disease morbidity and mortality.

SSc is described as two primary clinical subsets based on the extent of skin thickening: diffuse and limited cutaneous disease. Patients with limited skin disease have no skin thickening or skin thickening limited to the distal extremities (below the elbows and knees, but may have thickness of the face). Diffuse cutaneous patients experience similar distal changes, but also develop skin thickening proximal to the elbows and knees (upper arms, thighs, trunk) during the disease course. This clinical classification is useful as the natural history of the disease is different between the clinical subsets. Diffuse SSc patients develop progressive skin thickening and internal organ involvement early in their disease (first 2-3 years). The natural history of diffuse SSc skin thickening is that it may slowly improve over time even if untreated. Patients with limited SSc tend to develop no or minimal progressive skin changes over time, but may develop new internal organ involvement (particularly vascular complications) years into their disease.

Of the connective tissue diseases, SSc has the highest case specific mortality (3). Published estimates of mortality consistently report lower survival in the diffuse cutaneous SSc subtype compared to the limited SSc subtype (4-7).

SSc has a strong association with morbidity, disability and cost. Just over twenty years ago (1997) Wilson estimated the combined direct and indirect cost of care for SSc patients to be 1.46 billion dollars annually in the US (8). In 2015 a study performed in France assessed the average annual cost of SSc per patient to be 22,459 Euros (25,193 USD) (9). Of this, 10,526 Euros (11,807 USD) was an indirect cost due to an average SSc patient's absence from the labor market.

1.1.2 Fatigue in SSc

Fatigue is defined as an abnormal bodily tiredness that is disproportionate to activity and unrelieved by rest. The term can be used to describe difficulty or inability to initiate activity (subjective sense of weakness); reduced capacity to maintain activity (easy fatigability); or difficulty with concentration, memory, and emotional stability (mental fatigue) (10). Subacute and chronic fatigue are common in many rheumatologic conditions, like fibromyalgia, polymyalgia rheumatica,

systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome (11).

SSc patients frequently have fatigue as a characteristic feature of their disease and fatigue negatively impacts quality of life (12-15). The prevalence of fatigue among SSc patients is 75%, with 61% ranking fatigue among their top three most distressing complaints. Fatigue is also associated with poor sleep quality, greater pain and depressive symptoms (16).

SSc patients, have a prevalence of fatigue that is significantly higher than the general population and similar to patients with rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and current cancer treatment (17). Fatigue has been identified as one of the main factors negatively affecting well-being (18) and it's been associated with fewer visits to doctors (19). Fatigue is one of the main predictors (20, 21) of work disability in SSc patients. Correlations have been shown between fatigue and high scores on two different depression scales that have been validated in SSc patients, the Patient Health Questionnaire (PHQ-9) and the Center for Epidemiologic Studies Depression Scale (CES-D) (22).

Fatigue's recalcitrance to treatment in SSc patients has been shown in multiple longitudinal studies of symptom change over time (23-25). In a two-year longitudinal study of scleroderma patients' change in patient reported outcomes (PROs), fatigue worsened more than the other PROs, which included pain, sleep, disability and global health (26).

Treatment options for chronic fatigue are limited and the prognosis is not favorable (27). When the underlying medical cause of fatigue cannot be treated, treatment options include Cognitive Behavioral Therapy (CBT) and exercise (28, 29). If SSc patients exhibit depressive symptoms, treatment can involve an empiric trial of antidepressants (30). A systematic review of chronic fatigue's prognosis found that less than 10% of participants returned to pre-morbid levels of functioning, 10-20% worsened, and most remained significantly impaired. Risk factors for fatigue's poor prognosis are often present in SSc patients, and include older age, more chronic illness, having a comorbid psychiatric disorder and holding a belief that the illness is due to physical causes (21).

1.2 The Apollo Device

The Apollo System offers a convenient novel non-invasive, non-habit-forming wearable solution to improve performance and recovery under stress in children and adults by delivering gentle wave-like vibrations to the body that improve autonomic nervous system tone in near real time (Siegle & Rabin et al., under review). Apollo is about the size of an Apple Watch and can be worn on the ankle, wrist, or arm with two adjustable fabric straps. Apollo vibrations activate touch receptors in the skin and are perceived as safety signals by the brain resulting in decreased stress, improved recovery, focus, and energy.

In addition to the wearable, Apollo is a software system that curates music for the body, rather than for the ears. The scientific principles guiding the use of Apollo and our mechanistic understanding of its effects on the body are consistent with our understanding of how music and therapeutic touch effect the body to convey feelings of energy, focus, or relaxation by sending safety signals to the emotional cortex (limbic system) in the brain. Similar to music and touch used to facilitate a healing response in the body, there are no known side effects to this type of therapy.

Prior studies of Apollo have demonstrated significant improvements in fatigue and energy in healthy subjects in the real world as well as in subjects with chronic illnesses in clinical trials of Apollo within just a few days of use. Early findings strongly suggest that by improving autonomic tone, Apollo is attenuating biomarkers of persistent unwanted sympathetic activity, such as low heart rate variability (HRV), that over time, correlate with worse prognoses in many chronic illnesses. Low HRV is also a predictive factor in fatigue and poor energy recovery. Not only has Apollo been demonstrated to improve HRV and decrease heart rate, respirations, blood pressure, and other

markers of stress when threat is misappropriated, but it also appears to be inducing Meyer wave patterns in the vasculature (study data under analysis), which are known to correspond with nitric oxide release. As such, there is significant reason to believe that Apollo will improve symptoms of fatigue, inflammation, and vascular dysfunction in subjects with SSc.

The gentle vibrations delivered by the Apollo System are extremely low intensity in that they are typically just barely noticeable or perceptible by the user. From >2000 use cases in subjects ages 4-95yo, there have been no reported adverse events. Additionally, the range of frequencies and intensities of the Apollo System have been safely used in numerous commercial products without adverse events reported. Consistent with learning effects observed in meditation and mindfulness practices on the autonomic nervous system, Apollo case study participants report that continued use of Apollo results in quicker onset and longer duration of benefit. As such, there is significant potential benefit to be gained by the subjects and non-significant risk in the use of this technology in this study, as was also deemed to be the case in all of the prior approved IRBs for studies of Apollo. The devices tested in this study are commercially available Apollo wearables, built to FDA regulatory requirements and HIPAA compliance.

The wearable device used in this and other clinical studies of Apollo has a button on it that can always be engaged by the subject at any time to turn the Apollo vibrations off or back on within less than a second. The wearable can also be controlled by the Apollo mobile app that will be installed on the subjects' mobile smartphones. As such, the locus of control is always in the hands of the subject, providing significantly more autonomy to patients in treatment, which is one healing aspect of the Apollo System.

1.3 Rationale of the study

Fatigue is the symptom ranked highest by SSc patients as affecting quality of life. Thus, any device, therapy or pharmacologic products that could improve fatigue may have great potential benefit with respect to the quality of life associated.

1.4 Benefit-risk assessment

There are currently no disease-specific pharmacotherapies or devices approved for systemic sclerosis in the US. Management of the disease and its symptoms are clearly an area of unmet need. Thus, the potential for benefit is high.

The risks associated with the Apollo system are primarily associated with discomfort in wearing the wrist or ankle band. The design of this pilot and feasibility study is such that the participant determines use, and they have the option to stop at any time. Therefore, the level of risk is minimal.

Risk of breach of confidentiality: All study data collected via the Apollo HIPAA-compliant mobile app will be de-identified and registered to a specific study email account that is not linked to any identifiable information from the user. All paper documents (including consent forms)will be kept in a locked filing cabinet inside of a locked office. In addition, an ongoing review of study procedures will be done to ensure that the privacy of subjects and confidentiality of data is not violated. All data will be deidentified with a password protected master list as the only linkage between names and subject identification numbers. Consent forms, as well as any forms with identifiable information listed will be kept in a locked filing cabinet, separately from each subjects deidentified experimental and interview data. All electronic data collected will be accessible only with a password that is provided to clinical study staff and those individuals responsible for collection, maintaining data integrity and analysis. After the retention period is over, all study records will be de-identified and the linkage codes master lists will be destroyed. Study records will be kept secure under double lock in an office space devoted to long-term

retention of data for the purposes of maintaining scientific integrity.

The Apollo system has been tested and independently validated by individual members of a number of different institutions in the military and many Veterans, several academics at Universities, >10 elite athletics clubs, in pediatric clinics, nursing homes, as well as in two University of Pittsburgh clinical trials with 6 more trials currently underway. The Company has over 2000 beta testers and has conducted over 500 long-term case studies with consistent results. The technology proposed here has also been tested in children (as young as age 4), geriatric users, and other extremely vulnerable populations (such as those with treatment-resistant PTSD) without any reported adverse reactions.

Participants will be informed about any and all potential risks. There are no known long-term risks to the subjects from any of the study procedures, which have been used safely on thousands of men, women, and children. All study personnel examine screening materials before asking the participant to engage in any of the study activities in order to minimize the risks associated with the study procedures. If any additional physiological or mental health conditions are revealed during the screening or enrollment, they will be discussed individually with the clinical team (Dr. Domsic et al.) prior to officially enrolling the subject in the study. If results are best discussed with the participant's physician, the participant will be offered the opportunity to complete a release of information form allowing Dr. Domsic to contact the participant's physician directly.

2. STUDY OBJECTIVES

The primary objective of this study is to provide preliminary data on the efficacy and tolerability of the Apollo device in the management of fatigue in SSc.

The primary efficacy outcome is the change from baseline to four weeks of intervention using the Apollo system in the PROMIS-Fatigue scale. This instrument that has been previously validated in multiple diseases.

2.1 Secondary objectives

The secondary objectives of this study are to provide preliminary data on indices of depression, health-related quality of life, Raynaud symptoms and tolerability/frequency of use with the Apollo device in SSc.

Specific secondary objective measures include:

- Depression, measured by the QUIDS-SR (16 item) score.
- Health-related quality of life (HRQOL) using PROMIS-29
- HAQ-DI
- Visual analog scales from scleroderma-health assessment questionnaire (SHAQ) assessing burden of digital ulcers, Raynaud's disease, gastrointestinal involvement, breathing, and overall disease
- Improvement of Raynaud's phenomenon (RP) (7, 8)
    - Raynaud's condition score
    - Raynaud visual analog scale
    - Patient and physician assessment of RP; pain, numbness, and tingling
    - RP frequency and duration of attacks based on one-day use of the Raynaud application used at baseline and two weeks.
-

3. INVESTIGATORS and PERSONNEL

Role:	Investigator
Name and Contact Information:	Robyn T. Domsic, MD, MPH University of Pittsburgh School of Medicine S707 Biomedical Science Tower 200 Lothrop Street Pittsburgh, PA 15213
Telephone:	+1 (412) 383-8000
Email:	rtd4@pitt.edu

Role:	Research coordinator
Name and Contact Information:	Maureen Laffoon, BA University of Pittsburgh School of Medicine S707 Biomedical Science Tower 200 Lothrop Street Pittsburgh, PA 15213
Telephone:	+1 (412) 383-8000
Email:	laffoonm@pitt.edu

Role:	Graduate student / research assistant
Name and Contact Information:	Krista Hammaker

Data Safety and Monitoring Plan

A data and safety monitoring plan will be implemented by the Principal Investigator to ensure that there are no changes in the risk/benefit ration during the course of the study and that confidentiality of research data is maintained. Each member of the study team will meet with the PI and review confidentiality issues and complete a confidentiality agreement, prior to having contact with research subjects. Investigators and study personnel will meet **every 2 months** to discuss the study (e.g. study goals and modifications of those goals; subject recruitment and retention; progress in data coding and analysis; documentation, identification of adverse events or research subject complaints; violations of confidentiality) and address any issues or concerns at that time. Minutes will be kept for these meetings and will be maintained in the study regulatory bonder. Any instances of adverse events will be reported immediately to the University of Pittsburgh IRB. The IRB renewal for this study will include a summary report of the Data and Safety Monitoring Plan findings from prior renewal period.

4. STUDY DESIGN

4.1 Design overview

This clinical trial is a single-center, open-label, single-arm study of 30 individuals with SSc and fatigue.

The study will allow for subjects to continue standard of care medications for the management of SSc as background therapy.

The study design consists of a single, four-week intervention. The screening and baseline visits can be combined when the screening is not able to be performed over the phone in advance.

- **Screening phase:** up to 4 weeks prior to baseline visit
- **Observation period:** During this one week phase participants will track their daily Raynaud attack frequency and duration using a diary. This will occur in the seven days preceding the baseline intervention phase.
- **Open-label intervention phase:** This consists of a four-week period during which participants will use the Apollo wearable system as needed to manage symptoms including fatigue. During the intervention phase participants may use the wearable at their discretion and control. Participants will track their daily Raynaud attack frequency and duration using a diary during week 4 of Apollo use. Participants will complete questionnaires on day 1 of the open-label and intervention phase, and at their follow-up four weeks later.

4.1.1 Screening phase (up to 4 weeks prior to baseline visit)

After providing written informed consent, participants will undergo a screening evaluation to determine their eligibility (see Section 7.1 for a detailed schedule of events). Participants will complete the PROMIS-Fatigue scale to determine if they have moderate to severe fatigue. If a T score of 45 is obtained, and all inclusion criteria are met, then the patient may proceed to the observation phase. Participants will be given the 7-day diary to be completed starting one week prior to their scheduled baseline visit. They will be reminded be telephone call or text (based on

their preference) to begin their diary collection.

4.1.2 Intervention Phase

At the baseline visit, participants who have met all of the inclusion criteria. At this visit they will complete the following questionnaires:

1) PROMIS-fatigue
2) PROMIS-29
3) The QUIDS-SR
4) HAQ-DQ with SHAQ
5) Raynaud condition score, Raynaud visual analog scale and digital ulcer visual analog scale

They will then be provided the wearable Apollo system device. They will download the mobile application, and be taught how to install it and use it to control the wearable Apollo device by the research coordinator(s). Any questions will be answered at this time. Participants will be able to use the device from the time they leave the visit. Use of the device will be entirely at the subject's control.

In the week prior to their end-of-study visit, participants will complete a daily diary collection of Raynaud attack episodes and symptoms using the paper diary form. This will be provided prior to leaving the baseline visit.

Participants will be sent a reminder call or text the day before and day they are to begin their diary collection on one week prior to their scheduled end-of-study visit.

4.1.3 Early Termination

If participants choose to discontinue using the device, they may remain in the study, and will be requested to return for the four-week follow-up visit and complete all questionnaires.

5. Study population

5.1 Eligibility

5.1.1 Inclusion criteria

Participants must meet the following criteria to be eligible for enrollment in the study:

1. Signed written informed consent
2. Men or women aged 18 years and older
3. Diagnosis of Systemic sclerosis, as defined by 2013 American College of Rheumatology/ European Union League Against Rheumatism classification of SSc.
4. Baseline T score of 45 on the PROMIS-Fatigue scale.
5. Steady daily doses and any immunosuppressive medication, vasodilators, antidepressants and anxiolytic use for 4 weeks prior to baseline.
6. Currently owns and operates an iOS or Android smart phone regularly
7. Ability to comply with the clinical visits schedule and the study-related procedures.
8. Subjects who have struggled with symptoms of SSc (specifically fatigue and Raynauds) who have not received adequate symptom relief from prior treatment attempts (treatment-resistant) will be prioritized.
9.

5.1.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from enrollment in the study:

1. Medical and surgical history
    - Major surgery within 8 weeks prior to screening
    - Participants with an active malignancy.
    - End-stage renal disease with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m^2 (MDRD formula) or on dialysis at the screening visit
    - Hepatic insufficiency as defined by the Child-Pugh criteria
    - Hospitalization for any reason within four weeks of the study baseline visit.
    - History of sympathectomy or stellate ganglion block
    - Significant interstitial lung disease with FVC ≤ 50% of predicted, or DLCO (uncorrected for hemoglobin) ≤ 40% of predicted
    - Pulmonary hypertension with change in medications in the preceding four weeks
    - Actively prescribed standing doses of beta-blockers.
    - Actively prescribed standing doses of sedatives, hypnotics, opioids, or benzodiazepines.
    - Active or unstable psychotic disorder requiring current prescriptions of standing doses of antipsychotic medications
    - Active suicidal/homicidal ideation or a suicide or homicide attempt in the past year.
2. Pregnant or breastfeeding women
3. Other
    - Any other condition or therapy that would make the participant unsuitable for this study and will not allow participation for the full planned study period

5.1.3 Justification of selection criteria

The selection criteria were carefully selected to exclude participants from the study who may have another significant underlying medical condition contributing to fatigue.

5.2 Withdrawal of participants from study

5.2.1 Withdrawal

Participants *may* be withdrawn from the study at their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a participant may decline to participate further.

6. Intervention

6.1 Intervention to be administered

The Apollo System offers a convenient novel non-invasive, non-habit-forming wearable solution to improve performance and recovery under stress in children and adults by delivering gentle wave-like vibrations to the body that improve autonomic nervous system tone in near real time (Siegle & Rabin et al., under review). Apollo is about the size of an Apple Watch and can be worn on the ankle, wrist, or arm with two adjustable fabric straps. Apollo vibrations activate touch receptors in the skin and are perceived as safety signals by the brain resulting in decreased stress,

improved recovery, focus, and energy.

In addition to the wearable, Apollo is a software system that curates music for the body, rather than for the ears. The scientific principles guiding the use of Apollo and our mechanistic understanding of its effects on the body are consistent with our understanding of how music and therapeutic touch effect the body to convey feelings of energy, focus, or relaxation by sending safety signals to the emotional cortex (limbic system) in the brain. Similar to music and touch used to facilitate a healing response in the body, there are no known side effects to this type of therapy.

Prior studies of Apollo have demonstrated significant improvements in fatigue and energy in healthy subjects in the real world as well as in subjects with chronic illnesses in clinical trials of Apollo within just a few days of use. Early findings strongly suggest that by improving autonomic tone, Apollo is attenuating biomarkers of persistent unwanted sympathetic activity, such as low heart rate variability (HRV), that over time, correlate with worse prognoses in many chronic illnesses. Low HRV is also a predictive factor in fatigue and poor energy recovery. Not only has Apollo been demonstrated to improve HRV and decrease heart rate, respirations, blood pressure, and other markers of stress when threat is misappropriated, but it also appears to be inducing Meyer wave patterns in the vasculature (study data under analysis), which are known to correspond with nitric oxide release. As such, there is significant reason to believe that Apollo will improve symptoms of fatigue, inflammation, and vascular dysfunction in subjects with SSc.

Storage requirements:

All wearable devices not in use during the trial will be stored at the investigational sites at room temperature in a place inaccessible to unauthorized personnel, i.e. in a locked cabinet. No special storage conditions are required.

6.2 Treatment assignment

This is an open-label, single-arm trial. No randomization or blinding will occur.

6.4.3 Special populations

The Apollo wearable has been used in a wide array of populations. No adjustments need to be made in use or instructions.

6.5 Device use and compliance

The Apollo system including wearable hardware and software will track each subjects' use of Apollo throughout the study. This usage data will be stored in HIPAA-compliant manner and linked to a de-identified study subject ID number.

If a participant reduces or stops use of the Apollo wearable, this data will be recorded. The participant will still complete the two week (end of study) visit and assessment as planned.

7. Procedures and variables

7.1 Schedule of events

Please refer to the table in Section 7.1.1 for the schedule of events.

Study Visit	**Screening** Visit 0	**Observation** (seven day prior to baseline)	**Baseline** Visit 1	**Week 4** Visit 2
Window (days):			+/	28 +/- 3 days

Type of Contact:	**Office**	**Home**	**Office**	**Office**
Informed consent	X			
Eligibility assessment	X			
Demographics, including smoking & alcohol history	X			
Complete medical history	X			
Prior/Concomitant therapy	X		X	X
Vitals			X	X
Physical examination			X	
PROMIS-Fatigue short form	X		X	X
Physician's Global Assessment			X	X
Patient's Global Assessment			X	X
PROMIS -29			X	X
HAQ-DI/SHAQ			X	X
QUIDS-SR			X	X
Raynaud and digital ulcer VAS			X	X
Raynaud's phenomenon diary			X[c]	X
Assess for Adverse Events			X	

Timing of assessments

If not stated otherwise, all assessments and procedures will be performed by or under the supervision of an investigator.

For timing of assessments and procedures, please refer to Section 7.

7.1.2.1 Visit 0 – Screening

Screening evaluations will be performed only after the participant has provided written informed consent. The following evaluations will be performed and information obtained up to 28 days before the baseline visit.

- Participant information and obtaining of written informed consent
- Eligibility: Assessment of inclusion and exclusion criteria (see Section 5.1)
- Demographic data, including sex, race, ethnic group, year of birth, smoking history and alcohol consumption
- Medical and surgical history
- Prior and concomitant therapy
- Medication history

7.1.2.2 Visit 1 – Baseline

The following assessments will be performed at the Baseline visit

- Reconfirmation of eligibility
- PROMIS-fatigue scale administered
- Patient reported outcomes (QUIDS-SR, patient global assessment, PROMIS-29, HAQ-D1/SHAQ, visual analong scales) and physician global assessment
- Vital signs (blood pressure and heart rate). The blood pressure is measured in a sitting

position after the participant has been at rest for at least 5 minutes. The same arm is always used for these measurements
- Digital ulcer assessment
- Assessment of Raynaud attacks – participant provided the one-day diary and RCS to complete the day following the screening
- Recording and assessment of AEs (see Section 7.5.1.3)
- Downloading of the mobile application and teaching of how to use the Apollo wearable device. The participants will be allowed to use it up to 30 minutes to familiarize themselves with the working of the device while at this visit.

7.1.2.3 Visits 2 (28 days + 3 days from the baseline)

- PROMIS-fatigue scale administered
- Patient reported outcomes (QUIDS-SR, patient global assessment, PROMIS-fatigue, PROMIS-29, HAQ- D1/SHAQ, visual analog scales) and physician global assessment
- Vital signs (blood pressure and heart rate).
- Assessment of Raynaud attacks – diary will be collected.
- Recording and assessment of AEs (see Section 7.5.1.3)
- Digital ulcer assessment

7.1.2.4 Unscheduled visit

Should participants report any difficulty or unexpected issues using the Apollo system at home, they will be able to contact research study staff to arrange for technical support or for an unscheduled (UNSCH) visit to the clinic for additional assistance. Technical support from study staff will be available to subjects within 24 hours of contacting study staff. Subjects will be provided with an email address and phone number for study staff upon enrollment in the study.

7.2 Population characteristics

7.2.1 Demographic

The following demographic data will be recorded:

- Date of birth (age)
- Sex
- Race and Ethnicity
- Alcohol consumption
- Smoking History
- Level of Education

7.2.2. Medical history

A 12-month medical record review will be requested from each subject prior to entering into the study. Medical history findings (i.e., previous diagnoses, diseases or surgeries, medications, etc) meeting all criteria listed below will be collected:

- Considered relevant to the study
- Medical history related to concomitant therapy

7.3 Efficacy

Primary efficacy outcome measure:

- Change from baseline to end of study on the PROMIS-Fatigue scale.

Secondary efficacy measures during double-blind period:

- HRQOL using PROMIS-29
- Physical function as assessed by HAQ-DI, and HDISS-DU
- Visual analog scales from scleroderma-health assessment questionnaire (SHAQ) assessing burden of digital ulcers, Raynaud's disease, gastrointestinal involvement, breathing, and overall disease
- QUIDS-SR
- Improvement of Raynaud's phenomenon
    - Raynaud's condition score
    - Number of Raynaud's attacks/day
    - Patient and physician assessment of RP; pain, numbness, and tingling during an RP attack; and duration of attacks
- Patient's and physician's global assessment on a Likert scale
-

7.5 Safety

7.5.1 Adverse events

The Apollo system has been tested and independently validated by individual members of a number of different institutions in the military and many Veterans, several academics at Universities, >10 elite athletics clubs, in pediatric clinics, nursing homes, as well as in two University of Pittsburgh clinical trials with 6 more trials currently underway. The Company has over 2000 beta testers and has conducted over 500 long-term case studies with consistent results. The technology proposed here has also been tested in children (as young as 4yo), geriatric users, and other extremely vulnerable populations (such as those with treatment-resistant PTSD) without any reported adverse reactions.

Participants will be informed about any and all potential risks. There are no known long-term risks to the subjects from any of the study procedures, which have been used safely on thousands of men, women, and children. All study personnel examine screening materials before asking the participant to engage in any of the study activities in order to minimize the risks associated with the study procedures. If any additional physiological or mental health conditions are revealed during the screening or enrollment, they will be discussed individually with the clinical team (Dr. Domsic et al.) prior to officially enrolling the subject in the study. If results are best discussed with the participant's physician, the participant will be offered the opportunity to complete a release of information form allowing Dr. Domsic to contact the participant's physician directly.

Should any adverse events be detected/reported/observed by subjects or study staff, subjects may easily discontinue use of the Apollo system immediately either by:

1) Turning the wearable off with the buttons on the device or
2) Removing the wearable from their body

7.5.1.1 Definitions

Definition of adverse event

(AE)

In a clinical study, an AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the participant should not be recorded as AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal physical examination findings, symptoms, diseases, laboratory results, and ECG findings.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g., allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as AEs.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the participant was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 hours
   - The admission is pre-planned
     (i.e., elective or scheduled surgery arranged prior to the start of the study)
   - The admission is not associated with an AE
     (e.g., social hospitalization for purposes of respite care).

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another medically important serious event as judged by the investigator

7.5.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

7.5.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.5.1.1 .

7.5.1.2.2 Severity

The severity of an AE is classified according to the following categories:

- Grade 1 Mild
- Grade 2 Moderate
- Grade 3 Severe
- Grade 4 Very Severe
- Grade 5 Death

7.5.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "Related" or "Not Related" An assessment of "Not Related" would include:

1. The existence of a clear alternative explanation, or

2. Non-plausibility, e.g., the participant is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "Related" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence
- Recovery on discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):
- Underlying, concomitant, intercurrent diseases:
    - Concomitant medication or treatment: The other drugs the participant is taking or the treatment the participant receives should be examined to determine whether any of them may be suspected to cause the event in question.

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a “reasonable causal relationship” to protocol-required procedure(s).

Possible answers are “yes” or “no”

7.5.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Device use stopped
- Device use interrupted
- No change
  Not applicable

7.5.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

7.5.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved without sequelae
- Recovered/resolved with sequelae
- Not recovered/not resolved (ongoing)
- Fatal
- Unknown

7.5.1.3 Assessments and documentation of adverse events

The investigator has the obligation to report AEs. All non-serious events will be assessed and recorded during the specified observational phase (from signing the informed consent form up to 30 [+5] days after last study medication intake), whether believed to be related or unrelated to the treatment. AE forms will be included. The record will include clinical symptoms or final diagnosis when available, date of appearance, duration, severity and relationship to treatment. A record will also be kept of the action taken and the follow-up until resolution of the AE.

7.5.1.4 Reporting of serious adverse events

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g., SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the investigator according to all applicable regulations the serious criteria (as defined in Section 7.5.1.1) are applicable.

7.6 OTHER PROCEDURES AND VARIABLES

7.6.1 Raynaud's attacks assessment

Raynaud's attacks will be assessed using the composite of the following 6 individual outcome measures in order to minimize the measurement variability and placebo response(7): Raynaud's condition score, patient assessment of Raynaud's phenomenon, physician assessment of Raynaud's phenomenon, attack symptoms, duration of attacks, and number of attacks per day.

The Raynaud's condition score is a daily patient assessment of Raynaud's phenomenon activity using a 0-10 ordinal scale. It incorporates the cumulative frequency, duration, severity and impact of Raynaud's phenomenon attacks, reflecting the overall degree that Raynaud's has affected use of the participant's hands. The Raynaud's condition score, along with details of the frequency and duration of Raynaud's attacks, will be incorporated into the daily diary that participants will be asked to complete for 1 week (7 days) at the time points shown below.

The patient and physician assessment assesses the severity of Raynaud's phenomenon in the past week using a 0-100 VAS.

Frequency: The diary is to be completed by participant for one-day during the observation period, and one-day at the end of study (to occur the day prior to end of study visit).

7.6.2 Quick Inventory of Depressive Symptoms (QUIDS-SR)

The QUIDS-SR is a 16-item questionnaires that evaluates depression. The QUIDS-SR has been validated and used to screen, diagnose, monitor and measure the severity of depression.

7.6.3 Patient-Reported Outcomes (PROs) / Health-Related Quality of Life (HRQoL) questionnaires

Three patient-reported outcomes (PROs)—the HAQ-DI/SHAQ, and PROMIS-29— will be completed by all participants in the study.

Scleroderma Health Assessment Questionnaire (HAQ-DI/SHAQ)

The HAQ-DI consists of 8 domains from the Health Assessment Questionnaire disability index, a HRQoL instrument that measures self-reported function in 8 domains of activity in 20 weighted responses and a VAS of pain experienced in the past week. It additionally measures 5 domains specific to scleroderma using a continuous VAS: Raynaud's phenomenon, digital tip ulcers, lung symptoms, gastrointestinal symptoms, and a global patient assessment. The VAS subscales of the SHAQ were shown to be significantly correlated with objective parameters and were responsive to change in a cohort and in a Raynaud's phenomenon trial in SSc. The SHAQ requires approximately 5 minutes to complete.

Patient-Reported Outcomes Measurement Information System (PROMIS)-29

The PROMIS-29 is a validated instrument to measure the health status of SSc patients, demonstrating moderate to high correlation with other instruments validated in SSc, including the SF-36 physical component score and HAQ-DI. It incorporates 7 core domains from the PROMIS questionnaire, which specifically relate to physical, mental, and social health aspects of chronic illness: pain, fatigue, depression, anxiety, sleep, and physical function, as well as one 11-point rating scale for pain intensity. It contains 8 items with 29 weighted responses in total,

and requires approximately 5 minutes to complete.

7.6.4 Participant and Physician Global Assessment

A global assessment for patient and physician will be obtained.

The participant assessment represents the patient's assessment of the patient's global scleroderma on a 0-10 Likert scale. "On a scale of 0-10, how was your overall health in the last week? 0=Excellent; 10=Extremely Poor. The physician global assessment represents the physician's assessment of the patient's current disease activity on a 0-10 Likert scale. "On a scale of 0-10, how was your patient's overall health in the last week? 0=Excellent; 10=Extremely Poor". Both assessments are made at baseline and Week 16, OLE Week 0 and OLE Week 16.

8. Statistical methods and determination of sample size

8.1 General considerations

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) will be written for the study that contains detailed descriptions of the analyses to be performed. The SAP will be finalized prior to unblinding of the data.

Continuous variables will be summarized using descriptive statistics including n, mean, median, standard deviation, range (e.g., minimum and maximum). Qualitative variables will be summarized using counts and percentages. Graphical methods will be used in this pilot study to assess the pattern of response over time for key variables and to assess the relationships among variables.

Unless otherwise specified, statistical analyses will be performed using SAS Version 9 or higher. Where appropriate, statistical tests will be conducted at the 0.05 significance level (with no adjustments for multiplicity) using two-tailed tests and p-values will be reported.

Given the rare nature of SSc and the consequent small sample size for this pilot study, the statistical power of any comparisons is limited (i.e., there is sufficient power to detect only large treatment differences). As such the analysis will be largely descriptive in nature. The p-values resulting from formal statistical tests will be interpreted from a hypothesis-generating, rather than a confirmatory framework.

Analysis sets

As this is an open-label study, all participant who have used the Apollo system wearable for at least one dose (one day) will be analyzed. The primary endpoint and all secondary outcomes will be assessed using this analysis set.

8.2 Statistical and analytical plans

8.2.1 Demographic and other baseline characteristics

Demographic variables and baseline characteristics will be summarized by treatment group.

8.2.2 Efficacy

The primary endpoint is the mean change from baseline to end of the two-week intervention in the PROMIS-Fatigue questionnaire. For the primary analysis, changes in score will be compared in the two treatment groups using an repeated measures t-test. If the assumptions of this parametric model are not met, an alternative non-parametric model will be used. This model is based on the extension of the Wilcoxon rank-sum test to allow for covariate adjustment (9). This rank ANCOVA can provide additional power associated with baseline covariate adjustment, even when the outcome variable is not normally distributed 1(10).

Analysis for secondary outcome measures that are continuous will be performed using a similar approach as that for the primary endpoint. We will compare the change in each secondary outcome measure from baseline to week 2 using an ANCOVA model or its non-parametric counterpart if the model assumptions aren't met. Analyses of secondary outcomes measures that are discrete will be performed using Fisher's exact tests. Analyses of secondary outcome measure that are counts will be performed using Poisson regression.

8.3.3 Safety

Descriptive summary statistics for] adverse and serious adverse events will be reported. Adverse events will be grouped by body system and grade and will be tabulated as numbers and percentages; serious adverse events will be enumerated and described as appropriate.

8.4 Planned interim analyses

No formal interim analysis of this short, two-week study will be performed.

8.5 Determination of sample size

SSc is a rare disease. The planned minimum sample size of 30 SSc participants is based on practical considerations to obtain preliminary estimates of the magnitude of treatment differences in efficacy and safety rather than a desired power for a pre-specified difference as would be necessary for a confirmatory study. However, with this proposed sample of 30 participants we can calculate the magnitude of treatment differences (riociguat – placebo) for the primary efficacy endpoint – the change from baseline to end of double-blind treatment in fatigue scales. There would be 80% power to detect an effect size (mean treatment difference divided by standard deviation) of While we expect that 30 subjects will be enough participants to see a significant treatment effect in this study population, we have written this protocol to allow for the inclusion of up to 100 subjects should 30 subjects be found to be an insufficient number for any reason.

8.6 Data recording

It is the expectation of the sponsor that all data entered into the eCRF has source documentation available at the site. The site must implement processes to ensure this happens. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

8.7 Monitoring

Given the enrollment period is dictated by seasonal considerations for DU incidence, we anticipate two monitoring visits per site during the course of the study. Once after the first subject has been randomized at the site and once after the study has closed to enrollment and all subjects have completed study visits. The frequency of monitoring visits may be adjusted throughout the life cycle of the study as study conditions and needs evolve. Additional visits can be scheduled at the request of the Study Team or DSMB.

The Clinical Research Monitor will ensure that:

- Data collected and entered into the database are verifiable against source documents for the randomized participants
- Appropriate consent is obtained for each participant prior to study procedures
- Safety and rights of participants are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Study medication is properly dispensed and accounted for
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

8.8 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request. Study-related files will be archived according to the University of Pittsburgh IRB regulations.

9. Ethical and legal aspects

Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Investigators may implement a protocol change after discussing the details and getting IRB approval. Any deviations from the protocol must be explained and documented by the investigator.

10. Appendices

10.1 PROMIS-Fatigue
10.2 QUIDS-SR
10.3 Promise-29
10.4 HAQ-DI/S_HAQ
10.5 Raynaud Diary and Raynaud condition score

References

1. Steen VD, Oddis CV, Conte CG, Janoski J, Casterline GZ, Medsger TA. Incidence of systemic sclerosis in Allegheny County, Pennsylvania. A twenty-year study of hospital-diagnosed cases, 1963-1982. Arthritis and rheumatism. 1997;40(3):441-5.
2. Mayes MD. Epidemiology of systemic sclerosis and related diseases. Current opinion in rheumatology. 1997;9(6):557-61.
3. Bryan C, Howard Y, Brennan P, Black C, Silman A. Survival following the onset of scleroderma: results from a retrospective inception cohort study of the UK patient population. British journal of rheumatology. 1996;35(11):1122-6. Epub 1996/11/01. PubMed PMID: 8948299.
4. Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G, Bullo A, Cazzato M, Tirri E, Storino F, Giuggioli D, Cuomo G, Rosada M, Bombardieri S, Todesco S, Tirri G; Systemic Sclerosis Study Group of the Italian Society of Rheumatology (SIR-GSSSc). Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. Medicine (Baltimore). 2002;81(2):139-53. PubMed PMID: 11889413.
5. Hesselstrand R, Scheja A, Akesson A. Mortality and causes of death in a Swedish series of systemic sclerosis patients. Ann Rheum Dis. 1998;57(11):682-6. PubMed PMID: 9924211; PubMed Central PMCID: PMC1752504.
6. Lonzetti L JF, Raynauld JP, Roussin A, Rich E, Goulet JR, Raymond Y, Senécal JL. Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. Medicine (Baltimore). 2002;81(2):154-67.
7. Nihtyanova S, Denton, C.P. Autoantibodies as predictive tools in systemic sclerosis. Nat Rev Rheumatol. 2010;6(2):112-6. doi: 10.1038/nrrheum.2009.238.
8. Wilson L. Cost-of-illness of scleroderma: the case for rare diseases. Semin Arthritis Rheum. 1997 Oct;27(2):73-84. doi: 10.1016/s0049-0172(97)80008-x.PMID: 9355206
9. Chevreul K, Brigham KB, Gandré C, Mouthon L; BURQOL-RD Research Network. The economic burden and health-related quality of life associated with systemic sclerosis in France. Scand J Rheumatol. 2015 May;44(3):238-46. doi: 0.3109/03009742.2014.976653. Epub 2014 Dec 18.PMID: 25521915
10. Arkowitz AJ, Rabow MW. Palliative management of fatigue at the close of life: "it feels like my body is just worn out". JAMA. 2007;298(2):217.
11. Manu P, Lane TJ, Matthews DA. Chronic fatigue and chronic fatigue syndrome: clinical epidemiology and aetiological classification. Ciba Found Symp 1993; 173:23. \
12. Haythornthwaite JA, Heinberg LJ, McGuire L. Psychologic factors in scleroderma. Rheum Dis Clin North Am 2003;29:427–39.
13. Richards HL, Herrick AL, Griffin K, Gwilliam PD, Loukes J, Fortune DG. Systemic sclerosis: patients' perceptions of their condition. Arthritis Rheum 2003;49:689–96.
14. Suarez-Almazor ME, Kallen MA, Roundtree AK, Mayes M. Disease and symptom burden in systemic sclerosis: a patient perspective. J Rheumatol 2007;34:1718–26.
15. Basta F, Afeltra AA, Margiotta DPE. Fatigue in Systemic Sclerosis: A Systematic Review. Clinical and Experimental Rheumatology 2017;36(Suppl. 113):S150-S160.
16. Sandusky SB, McGuire L, Smith MT, et al. Fatigue: an overlooked determinant of physical function in scleroderma. Rheumatology (Oxford) 2009; 48:165.

17. Thombs BD, Bassel M, McGuire L, et al. A systematic comparison of fatigue levels in systemic sclerosis with general population, cancer and rheumatic disease samples. Rheumatology (Oxford) 2008; 47:1559.
18. Sandqvist G, Eklung M. Daily occupation performance, satisfaction and time use, and relations with and well-being in women with limited cutaneous systemic sclerosis. Disabil Rehabil 2008;59:279-84.
19. Willems LM, Kwakkenbos L, Bode C, et al. Health care use and patients' perceptions on quality of care in systemic sclerosis. Clin Exp Rheumatol 2013;31(Suppl. 76):S64-70.
20. Hudson M, Thombs BD, Steel, R et al. Clinical correlates of quality of life in systemic sclerosis measured with the World Health Organization Disability Assessment Schedule II. Arthritis Rheum 2008;59:279-84.
21. Hudson M, Steele R, Lu Y, et al. Work disability in systemic sclerosis. Journal of Rheumatology 2009;36:2481-6.
22. Sandqvist G, Scheja A, Hesselstrand R. Pain, fatigue and hand function closely correlated to work ability and employment status in systemic sclerosis. Rheumatology 2010;49:1739-46.
23. Sekhon S, Pope J, Scleroder MA, et al. The minimally important difference in clinical practice for patient-centered outcomes including health assessment questionnaire, fatigue, pain, sleep, global visual analog scale, and SF-36 in scleroderma. Journal of Rheumatology 2010;37:591-8.
24. Willems LM, Kwakkenbos L, Vonk MC, et al. Three-year trajectories of disability and fatigue in systemic sclerosis: a cohort study. Clinical Experimental Rheumatology 2017;35(Suppl. 106): S48-55.
25. Assassi S. Leyva AL, Mayes MD et al. Predictors of fatigue severity in early systemic sclerosis: a prospective longitudinal study of the GENISOS cohort. PLoS One 2011;6:e26061.
26. Joyce J, Hotopf M, Wessely S. The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review. QJM 1997; 90:223.
27. Price JR, Mitchell E, Tidy E, et al. Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD001027.
28. Smith ME, Haney E, McDonagh M, et al. Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015; 162:841.
29. O'Malley PG, Jackson JL, Santoro J, et al. Antidepressant therapy for unexplained symptoms and symptom syndromes. J Fam Pract 1999; 48:980.
30. Joyce J, Hotopf M, Wessely S. The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review. QJM. 1997 Mar;90(3):223-33.