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MEDICAL UNIVERSITY OF SOUTH CAROLINA

Study Protocol

Study Title: The SPARC App: A Smartphone Application for the Management of Sarcoidosis-Associated Fatigue

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2 PROTOCOL SYNOPSIS

Title	The SPARC App: A Smartphone Application for the Management of Sarcoidosis-Associated Fatigue
Clinical Phase	
Objective	To develop, refine, and test a smartphone app intended to decrease fatigue in sarcoidosis patients
Endpoints	Primary • Feasibility and usability Secondary • Changes in SAF, self-efficacy, stress, autonomous motivation, and QoL.
Study Population	Sarcoidosis patients with significant sarcoidosis associated fatigue
Number of Subjects	50
Number of sites	1
Study Duration	12 months
Study Design	Conduct a 12 week, 2-arm (SPARC vs. enhanced Standard Care) feasibility RCT in 50 SPs with SAF. Evaluations will occur at baseline, weeks 4 &12 and a post-trial follow-up at week 24. The SPARC App will include stress and fatigue management tools previously developed using subject input. Standard of care includes education on stress and fatigue in addition to offering referral to outpatient pulmonary rehab. 2a: Primary outcomes of feasibility benchmarks: ≥ 80% recruitment, ≥80 % retention rates & usability; ≥.70 adherence to twice daily BAM sessions; ≥ 75 % of sample will score above average on usability & satisfaction questionnaires (SUS >68, uMARS >64& TSUQ >60). 2b: Secondary outcomes of changes in SAF, self-efficacy, stress, autonomous motivation, and QoL.
Assessments	• Feasibility and usability: ≥ 80% recruitment, ≥80 % retention rates & usability; ≥.70 adherence to twice daily BAM sessions; ≥ 75 % of sample will score above average on usability & satisfaction questionnaires (SUS >68, uMARS >64& TSUQ >60). • Efficacy (exploratory): Changes in SAF, self-efficacy, stress, autonomous motivation, and QoL.
Statistical Analyses	Data will be summarized descriptively for all measures and variables. Analysis of feasibility and usability measures, as well as preliminary efficacy measures will be described in detail in additional sections included in this protocol

3 SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

		Clinical Trial Period			Follow-up
Trial Week		**0 (Screening)**	**4**	**12**	**24**
	Demographics[a]	X			
	Weight	X		X	
	Height	X			
	Medical History	X			
	Concomitant Medications	X	X	X	X
	Eligibility Review	X			
	Percent Recruitment and Drop-out Rate			X	
	System Usability Scale (SUS)			X	
Feasibility and System Usability	uMARS[b]			X	
	TSUQ[c]			X	
	Adherence[d]			X	
	FSE[e]	X		X	
	TSRQ[f]	X		X	
SDT Constructs	VBG[g]	X		X	
	Fatigue Assessment Scale (FAS)[h]	X	X	X	X
	King's Sarcoidosis Health Questionnaire (KSQ)[i]	X	X	X	X
Exploratory Outcomes	Perceived Stress Scale (PSS)[j]	X	X	X	X
	International Physical Activity Questionnaire[k]	X	X	X	X

[a] Age, sex, race, income, education level, employment

[b] User Version of Mobile App Rating Scale (uMARS; α =.90, test-retest [2,3 mos] .66, .70)

[c] Patient/Provider SPARC Treatment Satisfaction & Usability Scale (TSUQ; α=.82-.96, test- retest [1wk] .98)

[d] % adherence to SPARC meditation dose(10min BID for 12 weeks)

[e] Fatigue Self-Efficacy Scale (FSE; α =0.89-0.94)

[f] 94 Autonomous Self-Motivation (TSRQ; α =.81- .84)

[g] 80, Values, Beliefs, Goals Questionnaire (VBG; α =.72-.93; Test-retest (2 week) .52-.89)

[h] Fatigue Assessment Scale (FAS;10 items, α = 0.8-0.89; Test-retest 0.89)[63]

[i] King's Sarcoidosis Health Questionnaire (KSQ)[115]

[j] Stress (PSS-10 items; α = 0.78)[64]

[k] International Physical Activity Questionnaire: (test-retest (8-10days) .8)

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5 LIST OF ABBREVIATIONS

Abbreviation	Definition
SAF	Sarcoidosis Associated Fatigue
BAM	Breathing Awareness Meditation
TT	Tension Tamer
SPARC	Sarcoidosis Patient Assessment and Resource Companion
RCT	Randomized Control Trial
SP	Sarcoidosis Patients
SC	Standard of Care
QOL	Quality of life
PSS	Perceived stress scale

6 INTRODUCTION

Overview of Sarcoidosis and Sarcoidosis associated fatigue

Sarcoidosis is a systemic granulomatous inflammatory disease that disproportionately impacts African Americans. Sarcoidosis associated fatigue (SAF) is the most commonly reported symptom (80%) and considered the most important predictor of quality of life (QoL) due to its negative effects on physical and psychological health.[6-9] Pharmacologic therapy for SAF is unreliable, and while several formal group-based exercise/rehabilitation programs conducted in Europe have been efficacious in reducing SAF, dissemination of such programs is limited by availability and costs in an American sarcoidosis population with high poverty rates and reduced healthcare access.[42] Strong associations (r range: 0.54 to 0.89) have been observed between SAF and stress levels, stress-induced negative affective states (anxiety, depression) and reduced QoL.[22-29] Stress levels and associated negative affective states have been managed in other chronic diseases characterized by high fatigue (e.g., cancer, HIV, COPD) using cognitive behavioral stress management tactics, including various types of relaxation exercise such as breathing meditation.[32-40]

Mobile health technology-based (mHealth) solutions are increasingly being used to help patients improve healthcare knowledge, increase health-promoting behaviors and adherence to medical regimens. Our work and that of others using theory based, patient/provider guided iterative design have found high patient receptivity to mHealth self-management programs.[44-50, 62] To date, no mHealth apps have been developed to assist sarcoidosis patients (SPs) in managing SAF.

7 STUDY OBJECTIVE

The objective of this proposal is to conduct a randomized control trial evaluating the Sarcoidosis Patient Assessment and Resource Companion (SPARC) App, including assessing the feasibility of our study methodology, and estimating variability of outcomes and treatment effect on stress and fatigue and QOL measures. We hypothesize the SPARC App will be deemed a feasible, acceptable tool with high usability among sarcoidosis patients. Additionally, we expect to experience preliminary signals of clinical efficacy and obtain estimates of variabilyt of changes in secondary outcomes such as perceived stress, fatigue, quality of life and self-efficacy due to engagement in the SPARCs breathing awareness meditation module.

Specific aims of this proposal are:

Specific Aim 1. Conduct a 12 week feasibility RCT with a follow-up at 24 weeks with 50 SPs with SAF. They will be randomly assigned to SPARC or an enhanced attention control group stratified by healthcare provider. They will be evaluated at baseline, 4, 12 and 24 weeks.

2a. Demonstrate feasibility of SPARC (benchmarks: ≥ 80% recruitment, ≥80 % retention rates) and usability (≥.70 adherence to twice daily SPARC sessions); usability and treatment satisfaction scores: ≥ 75% will score above average on usability & satisfaction questionnaires (SUS >68, uMARS >64 & TSUQ >60). Back-end analytics will assess uptake of SPARC App (total engagement time) and its features (e.g., frequency of provider service line use, FAQ, video clips- sarcoidosis, fatigue & stress educational modules, sarcoidosis patient testimonials, etc.).

2b. Obtain estimates of variability of changes in secondary outcomes: stress (PSS), SAF,

QoL, fatigue self-efficacy (FSE) & autonomous motivation (TSRQ).

8 STUDY ENDPOINTS

- The primary measures will be feasibility and usability: ≥ 80% recruitment, ≥80 % retention rates & usability; ≥.70 adherence to twice daily SPARC sessions; ≥ 75 % of sample will score above average on usability & satisfaction questionnaires (SUS >68, uMARS >64& TSUQ >60).
- Secondary/exploratory efficacy endpoints: Changes in SAF, self-efficacy, stress, autonomous motivation, and QoL.

9 STUDY DESIGN

9.1 Overview of Study Design

SPs with SAF will then be recruited to participate in a 12-week randomized control trial testing the feasibility and preliminary efficacy of the App to reduce sarcoidosis associated fatigue and impact other QoL measures. All subjects in the SPARC App group will be instructed on the use of the App and instructed to use the SPARC meditation module twice daily. Those in the standard of care group will receive in-clinic education on stress and fatigue in sarcoidosis, and will be offered a referral to pulmonary rehab (current standard of practice in sarcoidosis clinic)

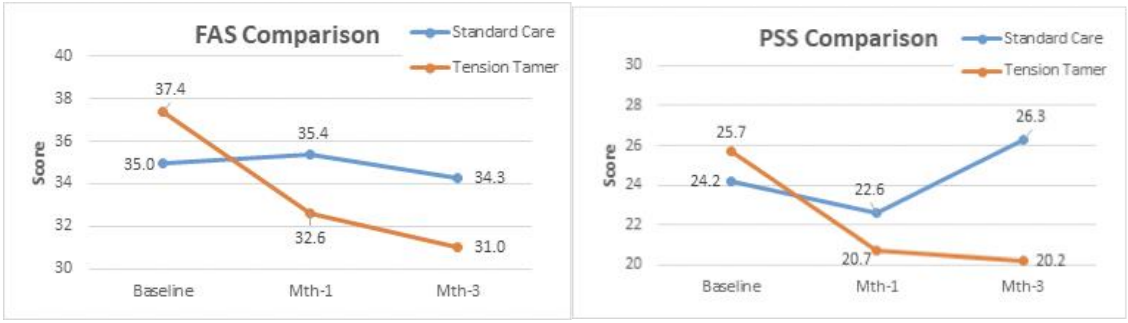
9.1.1 Synopsis of Our Research Pertinent to the Study

Mobile phone & mHealth Attitudes Survey: Out of 194 SPs with SAF (mean age 47 yrs, 65% AAs), 98% owned a cell phone and 84% owned a smart phone with internet activation. They were facile in use of cell phones (e.g., 98% sent /received SMS, 36% browsed internet, 34% sent/received email,42% downloaded apps). SPs reported high acceptability of using apps to manage their stress & fatigue. Following a video demo of the TT app (Fig. 1a,1b) and a Fitbit Walking app, all SPs with "significant" SAF (Fatigue Assessment Scale (FAS) score ≥22) either "agreed" or "strongly agreed" both apps would help them manage stress and fatigue and would be willing to use the apps as directed if they were free. SPs liked the overall design and ease of use of the TT app over the Fitbit walking app (4.1vs3.9 on 5-point scale).[129]

Associations between stress, fatigue and self-efficacy for coping with SAF. The mean FAS score was 31.0, with "significant" fatigue defined as a score ≥22.[64] Using the Perceived Stress Scale (PSS-4), 50% reported significant stress, defined as a score of ≥8.[19, 64] Similar results were reported by Cox et. al., who found 55% of SPs reported PSS-4 scores ≥8.[19] Fatigue levels (FAS score) were moderately correlated (r=0.65) with perceived stress levels. We also assessed fatigue self- efficacy in coping with SAF. We relabeled the 8 item Likert-type Multiple Sclerosis[MS]-Fatigue Self-Efficacy Scale (FSE, internal consistency: Cronbach α 0.89-0.94).[65] SPs confirmed its applicability to SAF, no comprehension issues were identified, and Cronbach α was .97. Mean scores/standard deviations on the FSE indicated low self-efficacy in coping with SAF (e.g., mean scores SPs: 47.3 vs MS data: 46.8; range 0-100 with 100 representing

high FSE).[65,66] FSE scores were highly correlated to both PSS (-0.89) and FAS (-0.97) scores.[16]

SPARC proof of concept trial: Based upon our survey responses indicating overall slightly higher preference for the the SPARC prototype app over the Fitbit app in its design, ease of use & self-efficacy of using if free service assistance provided, a 3 mth. proof of concept trial was conducted with SPs with SAF (n=18). The SPARC group engaged in 10 min sessions twice per day and the other group received standard of care (SC). We observed high acceptability (100% participation: 5.5% attrition), self- efficacy for following the SPARC regimen (mean 4.6 on 5-point Likert scale) and adherence over the 3 months (.mo1:81%, mo2:72%, mo3:65%-1 subject began chemotherapy during mth3). As shown in Fig1a&b, the SPARC group reported greater reductions in stress (PSS) and fatigue (FAS) compared to the SC group at months 1 & 3 (all ps <.05- .07). We received helpful suggestions from the participants for further adapting the SPARC app for SPs (e.g., video module having a SP engaging in BAM, several video testimonials by SPs stating how it helps increase energy levels, reduces stress, fatigue and improves quality of sleep; MD give overview of sarcoidosis & role of stress & fatigue).



9.1.2 Screening

All SPs will be recruited at MUSC's Sarcoidosis Clinic. In the last year 924 unique sarcoidosis patients were seen at the clinic (over 2,000 patient encounters). Dr. James is present in clinic 5 days/week, and sees a relatively high number of new sarcoidosis patients each week (20% of scheduled sarcoidosis patients). All sarcoidosis patients seen at MUSC complete the Fatigue Associated with Sarcoidosis (FAS) scale as part of their standard of care. Sarcoidosis patients with "significant" fatigue, defined by a FAS score ≥22, will be offered the opportunity for screening to participate in the trial (see Inclusion and Exclusion criteria below). Screening for eligibility for participation in the trial will be conducted via a combination of chart review and direct self-report from patients on defined inclusion and exclusion criteria, outlined below. Based on the demographics of MUSC's sarcoidosis patient population, we estimate enrolled subjects will be 65% African American and 63% female.

9.1.3 Randomized Control Trial

Primary outcomes: feasibility of enrolling & retaining SPs (benchmarks: ≥ 80% recruitment, ≥80 % retention) and usability (benchmarks: ≥70% adherence to bid SPARC meditation sessions; usability and

treatment satisfaction (≥ 75% of sample will score above average on SUS(>68), uMARS (>64),TSUQ (>60).

Secondary outcomes: Differences between the SPARC & SC groups in changes in fatigue (SAF), fatigue self-efficacy (FSE), stress (PSS), autonomous motivation (TSRQ) and QoL (KSQ). Any negative effect of SPARC on patients QOL will be recorded as part of the secondary outcomes.

Procedures: Consent will be obtained either on paper or eConsent will be obtained using Redcap. Following informed consent, SPs will be randomly assigned to SPARC or enhanced standard of care (SC) control group using the randomization module of the web-based REDCap study database. Standard of care includes education on stress and sarcoidosis fatigue, as well as recommending referral to pulmonary rehabilitation. Those in SPARC group will have SPARC app downloaded on their phone by the research coordinator. Use of the App will be reviewed and the subject will demonstrate ability to navigate the app, use components without assistance prior to leaving clinic. The research coordinator will assist in ensuring the SP have performed the first SPARC BAM session properly and completed the appropriate questionnaires prior to leaving the clinic.

A review of concomitant medications will be collected at the screening visit and reviewed at all study visits for changes. There are no patient-safety related adverse events possible, but any negative effect of SPARC on patients QOL will be recorded as part of the secondary outcomes. All SPs will return to clinic at weeks 4, 12 and 24 for routine clinical care. During those visits, questionnaires will be given, according to the Schedule of Assessments (Table 1-2). Questionnaires will be given orally or read on their own, based on their preference.

SPARC App Use: SPs who randomize into the SPARC group will engage in BAM sessions for 10 min twice daily. The SPARC app is developed based on reviews of the SAF literature, and adaptation of the original TT app using SP & healthcare provider input with low literacy-based strategies and guided by the principles of Self-Determination Theory (SDT).[76, 79] SDT focuses on developing competence (akin to self-efficacy in Social Cognitive Theory) and autonomous regulation**.**[71] Consistent strong effects of these SDT mediators have been observed for various health behavior changes (e.g., physical activity, smoking cessation, diet).[66,77,78,80-83] We will promote autonomous motivation by sending tailored motivational/social reinforcement messages linking subjects' behavioral changes (e.g., adherence to BID BAM sessions) to their personal values, beliefs and short/long term goals derived from a branch logic questionnaire (Values, Beliefs, Goals Questionnaire).[96] Domains identified include family, faith, friendships, community activities-membership/volunteer work; attendance and/or participation in leisure, sports & recreational activities and work related events. Domains frequently reported by subjects to be important drivers of behavior were "family, faith and friends." For example, God was often linked to having guided them to a "good doctor" or "pills that work and don't make me as tired." Power of prayer was often noted in conjunction with "praising God and showing thanks for the continued gift of life by treating my body as his temple." Family and community cohesiveness and support, especially activities with friends and family members were primary adherence motivators related to short-term life goals (e.g., increased time gardening, fishing, playing with grandchildren, attending church functions, etc.). Responses will guide delivery of >900 different automated motivational/social encouragement messages based upon levels of adherence to their SPARC regimen. A sample SMS feedback for an adherence score of 1.00 is: "*Way to go! Every day of Taming your tension keeps you on track for (patient identified values, e.g., "many more years watching those grandkids grow up").* If partially or completely non-adherent, he/she might receive: *"You must have been really busy yesterday. Get back on track with Tamer to keep reducing stress & fatigue and plan some special time with your grandkids."*

With each use subjects place their finger over the phone's camera, which serves as a plethysmograph to collect the subject's real-time heart rate in response to deep breathing meditation. Compliance with the SPARC Meditation module use will be monitored based on heart rate data collected during a subject's use of the App. Viewing the heart rate graph also serves as a form of positive feedback for subjects. App usage analytics will assess SPARC App uptake (total engagement time) and its features (e.g., frequency of provider service line use, video modules: sarcoidosis & stress educational modules, BAM demo, SP testimonials, etc.).

Subjects will be provided $50 compensation for time and effort at each evaluation. The App will have 2 links to address any issues with the app or their clinical care. Clinical care questions will be routed to the sarcoidosis nurse coordinator. Technical questions will be routed to the TACHL tech service line.

Measures: Table 2 presents all outcome variables, questionnaires and timing of administration. Most scales have been used with 21-59 yr old AAs and Non-Hispanic Whites and have established psychometrics. We provide brief psychometric information (e.g., internal consistency, test-retest reliability).

Table 2. Measurement/Instruments and Time Points for Feasibility Trial

Outcomes	Psychometrics	Time
Primary Outcomes		
Feasibility and System Usability	% recruitment, drop-out rate; System Usability Scale(SUS);[108,109] User Version of Mobile App Rating Scale (uMARS; α =.90, test-retest [2,3 mos] .66, .70);[110,111] Patient/Provider SPARC Treatment Satisfaction & Usability Scale (TSUQ; α=.82-.96, test- retest [1wk] .98);[112,113] % adherence to BAM dose(10min BID for 12 weeks)	Week 12
Secondary & Exploratory Outcomes		
SDT Constructs:	Competence/self efficacy: Fatigue Self-Efficacy Scale (FSE; α =0.89-0.94);[94] Autonomous Self-Motivation (TSRQ; α =.81- .84);[80,114] Values, Beliefs, Goals Questionnaire (VBG; α =.72-.93; Test-retest (2 week) .52-.89)	Week 0 &12
Fatigue, QoL, Stress, Physical activity	Fatigue Assessment Scale (FAS;10 items, α = 0.8-0.89; Test-retest 0.89)[63]; QoL scale in King's Sarcoidosis Health Questionnaire (KSQ)[115]); Stress (PSS-10 items; α = 0.78)[64],International Physical Activity Questionnaire: test-retest (8-10days) .8)[116]	Week 0, 4, 12 & 24
Demographic Variables	Age, sex, race, income, education level, employment	Week 0

Data Management: The Research Electronic Data Capture (REDCap) system will be used for data collection and as the primary database, including assignment of variable names and coding, design of data entry forms, automated data entry error checks, quality control checks, and database access and locking. All assessments and clinical data will be entered into a standardized password-protected database behind MUSC's firewall. Data will be reviewed on a twice-monthly basis. Outlying, inconsistent data values, as well as missing data, will be targets of the data quality review.

10 SELECTION OF STUDY POPULATION

Patients with sarcoidosis with "significant" fatigue, defined by a FAS score ≥22, will be offered the opportunity for screening to participate in the trial.

Screening for eligibility for participation in the trial will be conducted via a combination of chart review and direct self-report from patients on defined inclusion and exclusion criteria, outlined below.

10.1 Inclusion Criteria

- Must have a diagnosis of sarcoidosis based on established criteria (diagnosis in medical

chart)

- Must have "significant" fatigue, defined as a Fatigue Assessment Scale (FAS) score ≥22
- Must be 18 years of age or older
- Must report current or recent daily use of a smartphone
- Able to speak, hear, and understand English
- Owns smartphone with current data plan
- Willingness and ability to use app to engage in BAM
- Must be able to read and provide informed consent as assessed by study staff

10.2 Exclusion Criteria

Subjects will be excluded if they have any of the following:

- Women who self-report being pregnant, currently nursing, or plan to become pregnant during the course of the study
- Self-reported or chart indicated history of psychotic disorder, bipolar disorder, eating disorder, narcolepsy, cancer diagnosis or treatment in past 12 months
- Any history of, or past positive screening for, major depression per medical chart or self-report on diagnosis
- Untreated sleep apnea
- Sarcoidosis exacerbation in past 3 months requiring increase in sarcoidosis medications as determined by medical team
- >2 hr travel distance to medical center
- Self-report of active substance abuse or binge drinking(>21 drinks/week)
- Presence of ongoing or unstable hematologic, endocrine, cardiovascular, renal, gastrointestinal, or neurologic disease (including but not limited to sickle cell disease with recent pain crises, unstable heart failure or peripheral vascular disease, adrenal insufficiency, unstable chronic kidney disease (stage 3 or higher), unstable inflammatory bowel disease, or stroke resulting in permanent neurologic deficits)

11 ASSESSMENTS

11.1 Timing of Assessments

The timing of assessments is shown in Tables 1-2 and 2

11.2 Clinical Assessments

11.2.1 Subject and Disease Characteristics

Demographic information (see table 1-2) will be captured at the screening visit. Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded. Specific to sarcoidosis, organ involvement and diagnostic history (biopsy confirmation) will be recorded.

11.2.2 Concomitant Medications

Information regarding all medications at the time enrollment and through the last study visit will be recorded.

11.2.3 Feasibility/Usability Measures

See table 1.2 and 2

11.2.4 Exploratory Efficacy Measures

See table 1.2 and 2

12 RISKS TO THE SUBJECTS

12.1 Human Subjects Involved and Characteristics

Admission into the study is open to men and women 18 years of age or older, and to all racial and ethnic groups. A total of 50 subjects will be enrolled. The primary source of recruitment will be through screening of sarcoidosis patients seen in the Sarcoidosis Clinic at the Susan Pearlstine Sarcoidosis Center of Excellence at MUSC. We will also advertise the study through MUSC's sarcoidosis website, the Foundation for Sarcoidosis Research's website, and word of mouth among subjects.

12.2 Sources of Materials

1) Research material obtained from individuals will include socio-demographic and clinical data, questionnaires completed using a laptop computer or by hard copy and heart rate data transmitted to the server via the SPARC App. To ensure confidentiality, all subject data will be coded using a number system, and only key investigators with will have access to the master list of codes.

2) The research material will be obtained specifically for the purposes of this research project. All paper documents and questionnaires will be stored in a locked file cabinet in the principal investigators office in the Pulmonary and Critical Care Division, which remains locked when not in use. PHI and patient data obtained for research purposes will be entered into an online standardized database (REDCap) that is password protected behind the MUSC firewall.

12.3 Potential Risks

Risks to subjects in this study include disclosure of protected health information (PHI). In theory participation in this study could lead to increased stress from the requirements of the intervention, but the study is designed to minimize this possibility.

12.4 ADEQUACY OF PROTECTION AGAINST RISKS

12.4.1 Recruitment and Informed Consent

Subjects will primarily be recruited from the Sarcoidosis Clinic at MUSC. Medical records will not be routinely reviewed to identify potential subjects, except when providers suggest evaluating specific individuals who they feel may be candidates. All patients attending the Medical University of South Carolina Pulmonary Clinics who may be eligible will be recruited for participation in the study. In addition, a chart review will be conducted by the research coordinator and/or the PI for research purposes for all patients seen at MUSC who may meet study eligibility. The initial approach to the prospect to ascertain the patient's level of interest will be done by their treating physician (i.e., no cold calling). Interested patients will be offered participation in the study during a routine or previously scheduled clinic visit; or contact by a study team member. The study will also be advertised using flyers in waiting areas, sarcoidosis patient support group meetings (hosted at MUSC quarterly), and the MUSC website. All other patients (outside of MUSC) will be contacted through their providers to be informed of the study if the provider feels it is appropriate.

Eligibility for the study of screened patients will be tracked, and we will keep a record of number of potential participants screened, including reasons for exclusion/refusal. For each potential participant, we will review all eligibility criteria rather than stopping at the first reason for exclusion encountered. Those deemed eligible based on criteria will proceed to consent.

Consent will be obtained by the study PI, a Co-I, or other qualified study staff. The informed consent process will include a detailed description of study procedures and the SPARC app. Subjects will be clearly informed of their right to withdraw from the study at any time without consequences. The informed consent form will be written at an eighth grade reading level and will be explained in easy-to- understand language. Subjects will be instructed and encouraged to read the form carefully prior to signing it. The subject placing their signature on the informed consent form in addition to the signature of the individual obtaining consent will document confirmation of consent.

12.4.2 Protection Against Risk

All study visits will be conducted under the supervision of experienced personnel. Subjects will be instructed on the appropriate use of the “request clinical care provider communication” feature of the SPARC App to ensure subjects do not use this feature to seek help for urgent or emergent reasons. In addition, the SPARC App will have a built-in reminder to ensure appropriate use of this feature, including a prompt to call 911 for urgent or emergent health issues.

To prevent PHI disclosure and ensure confidentiality, all subject data will be coded and only key investigators will have access to the master list of codes. All paper documents containing PHI will be kept in a locked file cabinet in the principal investigators office, which remains locked when not in use. All personnel involved in this study understand the importance of maintaining confidentiality of PHI.

12.5 POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

There is no direct benefit for participating in this study but the information gathered in this study may help develop a useful tool for the management of fatigue and stress, and increase quality of life in patients with sarcoidosis. This study may also provide us with important information about sarcoidosis and fatigue.

12.6 IMPORTANCE OF KNOWLEDGE TO BE GAINED

This study may lead to development of a valuable management tool that can decrease stress and sarcoidosis- associated fatigue, improve quality of life, and provide important insight into the complex interactions contributing to fatigue that could result in future breakthroughs.

12.7 Adverse Events

There are no patient-safety related adverse events possible, but any negative effect of the App on patients QOL will be recorded as part of the secondary outcomes.

12.8 DATA SAFETY MONITORING PLAN

12.8.1 Summary of the Protocol

This application proposes to test and optimize an mHealth app for self-management of sarcoidosis associated fatigue (the SPARC App). Subjects will be required to engage in the SPARC Apps BAM module and to report fatigue levels on a bi-weekly basis. The primary outcomes will be feasibility/usability of the SPARC App. Secondary outcomes will include changes in fatigue self-efficacy, autonomous motivation, stress, fatigue and quality of life(QoL).

12.8.2 Overall Framework for Safety Monitoring

The primary means for monitoring safety in the proposed investigation will include monitoring of subject- reported adverse events. To screen for safety concerns not volunteered by subjects, the research coordinator will contact all subjects on 2 separate occasions separated by at least 4 weeks during the study period to specifically ask if the subjects have identified any potential safety concerns related to the study intervention. In addition, the principal investigator will conduct weekly meetings with study personnel to review subject communications from study clinic visits, research coordinator screening calls, and the SPARC App to identify any potential concerns.
A qualified consultant external to the project and with no conflicts of interest will be selected to serve as an external safety monitor for the study. They will monitor subject participation and safety issues with a focus on study enrollment process, safety and data integrity. They will meet via conference call with the PI and research team at four weekly meetings (weeks 0, 4, 8, 12) to discuss any concerns. Prior to those meetings they will be sent de-identified tables of subject enrollment data and all reported safety concerns for their review.

12.8.3 Data Management and Analysis.

The participants will enter responses to questionnaire and demographic data forms on a laptop using REDCaps or by hard copy. If hard copy, research assistant and key personnel will enter

all data obtained in the course of the study into a standard password-protected database behind the MUSC firewall (REDCaps). The data analysis plan is outlined in the Research Plan. Quality assurance will be ensured through bi-monthly data audits.

12.8.4 Definition of UPIRSOs, AE, and SAE.

An unanticipated problem involving risks to subjects or others (UPIRSOs) is any experience or outcome that is unexpected, related or possibly related to the subject's participation in the study, and suggests that the research study places subjects or others at a greater risk of harm related to study procedures than was previously known or recognized. An Adverse Event (AE) is defined as any untoward medical occurrence experienced by a study subject participating in a clinical trial that may not have a causal relationship with the trial intervention. Any unwanted physical, psychological or behavioral change experienced by a study subject during their participation in the trial is considered an adverse event. For the purposes of this study, a Serious Adverse Event (SAE) is defined as an adverse event that results in death, is life threatening, requires hospitalization or prolongs an existing hospitalization, results in persistent or significant disability, or requires intervention to prevent one of the previously listed outcomes.

12.8.5 Documentation and Reporting.

UPIRSOs, AEs and SAEs are documented and reported as per institutional protocol and IRB requirements. Research staff will identify any UPIRSOs or AEs and evaluate the severity, seriousness, study relatedness/expectedness, outcome and the need for change or discontinuation of the study intervention. All UPIRSOs must be reported to the MUSC IRB and include a description of the event, the date of occurrence, whether it is a local or outside report, how the event affected the rights, safety or welfare of the subject or others, current status of MUSC subjects, and any planned changes or modifications to the project as a result of the event. AEs are documented on AE logs and AE Case Report Forms. UPIRSOs and AEs must be reported to the IRB as soon as possible, but no later than 10 working days after the event or notification to the investigator that the event has occurred. Additional relevant information for UPIRSOs and AEs should be documented in a progress note in the research record to allow for monitoring and evaluation. All UPIRSOs, AEs and SAEs will be followed by research staff until resolution, stabilization or until the subject is no longer in the study.
The MUSC IRB requirements for reporting AEs includes all deaths that occur during the study or within 30 days of study termination regardless if they are expected or unrelated. Other AEs reportable to the MUSC IRB are those that are unexpected AND related or possibly related AND serious or more prevalent than expected. Unanticipated problems that do not meet the definition of an AEs require reporting to the IRB when there are: unexpected changes to the risk/benefit ratio of the research based on new findings, confidentiality breaches, participant or family member complaints, laboratory or medication errors, changes in FDA labeling or withdrawal from marketing of a drug or device, disqualification/suspension of investigators, unintentional changes to the IRB-approved protocol that may involve risks, deviation from the IRB protocol taken without prior IRB review to address apparent immediate hazard to a subject, and any deviation from the IRB-approved protocol that may increase risk or affects the participants rights, safety or welfare. The IRB meets monthly and communication with the IRB can occur via email, memos, official IRB forms and online reporting.
If an AE meets the definition of a SAE, appropriate SAE specific reporting forms are completed. Reportable SAEs must be reported to the MUSC IRB within 24 hours with AE

forms completed in conjunction with the PI. A report will also be sent to the NIH program officer assigned to the project. If complete information is not available within the 24 hour timeframe, follow-up information will be gathered to allow a complete evaluation of the event and outcome and will be forwarded to the NIH program officer as appropriate within 2 weeks. The PI will also provide a signed and dated SAE summary report.

13 Withdrawal from study

If for any reason a subject does not complete the study, the reason will be entered on the CRF. All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. The Investigator must record the reason for the early termination.

14 STATISTICAL AND ANALYTICAL PLANS

Data analysis will be performed by the Dr Martina Mueller.

14.1 Sample Size Determination

Focus of this project lies on demonstration of feasibility (recruitment, retention and adherence rates) and usability (frequency, duration of app use; satisfaction/usability surveys-SUS, TSUQ, uMARS) rather than hypothesis-testing. Thus, sample size was determined for pragmatic reasons such as assessment of recruitment, drop-out and adherence rates.117 For categorical feasibility measures, with 50 SPs (25 per group), we will be able to estimate proportions with precision ±0.08 to ± 0.13 for true population proportion (p) values for each outcome ranging from 0.10 to 0.30 (or correspondingly, from 0.70 to 0.90). For continuous usability measures, 95% confidence intervals (CIs) can be estimated with precisions ranging from ±0.20 to ±0.78 corresponding to estimated standard deviations (SDs) ranging from 0.5 to 2.0, respectively. For continuous impact measures (PSS,FAS, & QoL, FSE & TSRQ change scores), in intent-to-treat analyses, 95% CI estimates of within-group change scores (pre- to post-treatment) will have precisions ranging from ±0.1.5 to ±2.4 corresponding to estimated SD of change scores ranging from 3.7 to 6.1, respectively; between-group change scores differences will have precision estimates from ±2.8 to ±3.7 for SDs of differences in scores from 5.0 to 6.7 SD units.

14.2 Data Analysis

Descriptive statistics will be calculated for all measures and variables. We will use 95% CIs for proportions to estimate dichotomous feasibility outcomes (e.g., proportion who agree to participate out of total approached, proportion adherent to SPARC protocol, and proportion who drop out). Frequency distributions will be developed describing participants' reasons for non-adherence and discontinuation of SPARC app use and problems/issues encountered with the app. For continuous usability measures (e.g., frequency, duration of use; surveys-SUS,TSUQ,uMARS), frequency distributions & median and mean responses (with 95% CIs) will be obtained. Mean change and difference in change between the groups from pre-to-post intervention along with their 95% CIs will be reported for all continuous secondary (impact) outcomes (change in PSS-10, FAS, QoL, FSE & TSRQ scores). Preliminary analyses will

examine a) underlying distributional properties of all outcome variables b) patterns of missing data, and c) patterns of attrition. Linear mixed-models for repeated measures will be used for the continuous impact measures to obtain estimates of intra-cluster correlation (ICC) & variance estimates along with covariance structure of longitudinal scores used as critical information for sample size calculation of a future efficacy RCT. Based upon Shieh's work,[118] we have inadequate sample size & lack of adequate power to run formal moderator analyses. These analyses will be run in the future appropriately powered RCT to examine impact of socio-demographic variables as potential adherence barriers, as well as potential moderating effects of disease severity (i.e. lung function), fatigue-inducing medications and SPARC meditation adherence on secondary outcomes

14.3 Interpretation of Results

This proposal explores the usability/feasibility of the SPARC App to assess and manage stress.The primary outcomes for this study will be usability/feasibility of the SPARC App. Based upon our proof of concept trial(n=18), we anticipate acceptable participation rates(≥80%),low drop-out rates(≤20%),adherence rates (≥.70 to twice daily 10 min BAM sessions),and usability scores (≥75% of sample will score above average on SUS,uMARS,TSUQ).We anticipate signals of improvement in the SPARC group in secondary outcomes compared to SC group including changes in fatigue (FAS), stress (PSS) , self-efficacy (FSE), autonomous motivation (TSRQ) and QOL.

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