Feasibility of Teleyoga for Treatment of Lyme Disease

Study Protocol and Statistical Analysis Plan

NCT #: 04867473

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Background

Lyme Disease (LD) is a debilitating condition, which infects an estimated 300,000 people each year and is associated with high personal and societal costs (1). Lyme Disease is associated with many symptom sequelae, including fatigue, joint and muscle pain, and cognitive difficulties, which impact daily activities (5). In later phases, untreated LD can lead to arthritis and arthralagias, cardiac complications, and even death. Though most early phase LD patients are successfully treated with one course of antibiotics, a minority (10-20%) of those successfully treated continue to experience persistent symptoms of fatigue, depression, musculoskeletal pain, and cognitive complaints, called Post Treatment Lyme Disease Syndrome (PTLDS) (2). The efficacy of a repeat course of antibiotics has not been supported for PTLDS; rather, typical recommended treatments are cognitive behavior therapy (CBT), antidepressants, and low-impact aerobic exercise. The efficacy of these interventions appears to be limited. Consequently, an adjunct treatment to medication interventions for LD that is non-invasive, has a low side-effect profile, and is relatively easy to implement at home could address these primary complaints. Although studies have shown yoga improves symptoms of chronic pain, cognition, sleep, and mood (3), no clinical trial has examined yoga for LD. However, yoga may valuable for treating musculoskeletal pain in LD for several reasons: First, LD patients often report reductions in daily movement and exercise (5), which yoga could address, promoting increased physical strength and stamina. Second, musculoskeletal pain and LD share a pathological overlap of emotional problems and poor cognition, both of which respond positively to yoga. Additionally, the neuropsychological burden often reported by LD sufferers as "brain fog" has not been well established, with some studies demonstrating difficulties in memory, verbal fluency, and/or executive functioning and others finding subclinical changes or failing to replicate these findings (5). To establish the cognitive status of patients reporting LD symptoms, we intend to identify and track changes in measures of memory, verbal fluency, and executive functioning.

We are conducting a feasibility study in a parent project treating Veterans with chronic pain using yoga. That study focuses on chronic musculoskeletal pain as it is the most common type of chronic pain (4) and there is strong evidence it responds well to yoga. However, people who may benefit from yoga often encounter barriers to treatment such as travel costs and time, health conditions and caregiver responsibilities. For these reasons we have focused on a way to provide yoga at home using internet-based technology ("teleyoga"). Teleyoga is an innovative, potentially effective approach for treating chronic pain but research evaluating the acceptability or efficacy of teleyoga is very limited. We suggest that teleyoga offers great potential to treat LD patients remotely. This would be a feasibility study that would be modeled on our current project. Ultimately, a larger clinical trial would be needed to compare at-home teleyoga to in-person yoga and with the inclusion of a control group of treatment as usual for LD and patients. Before such a trial can be performed, a small-scale study is needed to demonstrate feasibility of recruitment, retention, and adherence to teleyoga.

Objectives

Specific Aims and Hypothesis

Specific Aims:

1. Modify an existing teleyoga intervention to use with LD patients and address the technical challenges of at-home teleyoga.
2. Assess neuropsychological and psychological status.

Hypothesis 1: We will demonstrate feasibility by recruiting 15 LD patients over a 9-month period, in cohorts of five patients every three months, maintain a retention rate of >65%, with acceptable adherence (a priori level of ≥65% of classes).

Treatment satisfaction will be at least neutral for all items. We do not expect any serious adverse events.
Hypothesis 2: We hypothesize patients will demonstrate relative difficulties in memory, verbal fluency and executive functioning.

Study Design
We propose to develop home-based yoga for treating LD patients using existing HIPAA-compliant telehealth software (e.g. Doxy.me) led by a certified yoga instructor.

Yoga Intervention:
We will adapt the yoga protocol from the parent award. The protocol is 12 weeks in duration, 1 class/week, class length of 75 minutes, with additional homework 15-20 mins on 5 non-class days/week. The protocol uses seated/standing/supine yoga postures, breathing, and meditation, and contains standard modifications in cases of limited mobility. Participants will also receive a homework manual describing simple and safe exercises to practice for homework. The adapted protocol would be 10 weeks in duration, to allow for recruitment intervals, but would otherwise adhere to the active award protocol.

Recruitment: For each 3-month interval we will recruit N=5 LD and PTLDS patients.
We anticipate recruitment will be via local hospitals, including Stanford, and the Johns Hopkins Lyme Disease Research Center, a research center with an online recruitment resource and ongoing clinical trials.

Baseline: Participants will complete study measures at the study site (see Assessment Materials below). We will record their phone number, physical location, and an emergency contact, which will be confirmed at each teleyoga session.

Week 1: Participants will visit the study center and will be issued an Apple iPad. They will also receive a yoga mat, yoga strap, and yoga blocks. Since the goal is to address the technical feasibility of teleyoga, this session will focus on anticipated technical issues, such as charging the iPad, connecting the iPad to home Wi-Fi, using the volume buttons, using the case as a stand, at-home lighting requirements, etc. We will also provide these instructions in a booklet. These initial steps can be performed remotely if participants cannot visit the study center.

Weeks 2-8: Study staff will call caregivers one day prior to instruction and remind them to charge their iPad and join the upcoming session. The yoga instructor providing instruction will be located at home equipped with standard audiovisual apparatus (i.e., screen size 56” x 32”).

Post-Treatment: Participants will visit the study site individually to complete study measures (see "Assessment Materials” section) and provide feedback.

Statistical Plan and Data Analysis

Primary analyses will be conducted focusing on treatment satisfaction, provider suggestions, retention and adherence. Due to the very small sample size (N=15) the main analytic strategy will be descriptive statistics. We will carefully examine score distributions and

will focus on cases with negative responses for treatment satisfaction. We aim to reach at least 2 on the 5-point MDTSM scale (i.e., satisfaction is neutral or positive) for all items. For retention, we aim to retain at least 65% of all participants in the study during the 10 weeks of treatment. We expect treatment attendance to be ≥65% for the 10 treatment sessions. For feasibility of treatment fidelity we will aim for ≥95% of treatment components. For the outcomes that will be measured repeatedly (i.e., both at baseline and post-treatment), we will estimate how they change over time (pre to post). These results will provide preliminary data on target engagement and therefore will inform and shape the future trial in terms of elucidating the mechanism of action. For all analyses regarding changes in outcomes, we will first employ simple paired t-test (pre vs. post) given the correlation between pre and post measures. In all statistical analyses, we will focus on collecting preliminary data on clinical significance (i.e., effect size) instead of making formal inference (i.e., p-value).

Inclusion/Exclusion Criteria

Inclusion Criteria (As determined by):

- Diagnosis of probable Lyme disease
- Has not begun new pain medications or other treatments in the last month
- English literacy
- Wireless internet connection at home

Exclusion Criteria for (As determined by):

- Participation in another concurrent clinical trial
- Back surgery within the last 12 months
- Unstable, coexisting mental illness or psychiatric condition
- Active, current suicidal intent or plan
- Attended or practiced yoga ≥ 1 x in the past 12 months

Informed Consent Process

Participants will be recruited from the following sources: VAPAHCS Pain Clinic, asking VA providers to refer their patients with chronic pain, web-based advertising, local advertising, social media advertising (Facebook, Twitter and Instagram , and mass-mailings to potential participants who may meet study eligibility criteria. LD patients do not need to be veterans, but veterans with LD may be recruited by asking their VA primary healthcare provider to send a letter of invitation. These sources will result in either 1) the potential participant calling the study team or 2) with the participant's consent, the study staff contacting them directly. Study candidates will be invited to VAPAHCS for a screening visit, during which the Project Manager will obtain informed consent and review the Health Insurance Portability & Accountability Act (HIPAA) document.

1. The Project Manager will explain the information contained in the written informed consent forms (purpose, procedures, risks, benefits, alternatives to participation, etc.) and HIPAA documents to the study candidates verbally, in lay language.
    a. The Project Manager will check for comprehension, allow the study candidates ample opportunity to ask questions throughout the process, and repeat the information, as necessary.
    b. Care will be taken to inform the study candidate that their participation is entirely voluntary, and they may withdraw at any time and for any reason without penalty or loss of benefits to which they would otherwise be entitled.
    c. Study candidates will then be asked to carefully read the informed consent form to consider whether or not to participate in the research and to ask questions.
    d. To ensure that the study candidate understands the research, they will next be asked to summarize the consent form and HIPAA addendum, with a special focus on the discomforts, risks, benefits, and confidentiality sections.
2. If the study candidate demonstrates (by stating in his/her own words) an understanding of the purpose, risks, and benefits of the study and agrees to participate in the study, he/she will be asked to initial each page, in addition to sign and date the last page of the consent form and the HIPAA document.
3. The Project Manager who oriented and obtained informed consent will sign and date the informed consent form.
4. The Project Manager will provide each enrolled participant with a photocopy of the original signed copy and keep the original signed copy in a binder in a locked cabinet.

The emphasis on the voluntary nature of participation is designed to minimize the possibility of coercion or undue influence on participation. The study candidate will be given time to understand the written informed consent form and make an informed decision. All treatments for this study will be provided in group formats, so potential participants will be reminded that full anonymity cannot be maintained. Following the informed consent process, the enrolled participant will complete other measures (See Research Strategy).

Screening Procedures

Potential participants (n=15) will be screened via phone. The Project Manager will obtain informed consent and review the Health Insurance Portability & Accountability Act (HIPAA) document. After obtaining informed consent, a trained researcher will collect demographic information (Demographic Questionnaire).

Study Assessments

Assessment Materials: Demographics Questionnaire; Clinical Questionnaire; Medication Use; Yoga Home Practice Log; BDI-II Beck Depression Inventory-II (BDI-II); Patient Safety; Treatment Satisfaction: PEG; Multi-Dimensional Treatment Satisfaction Measure (MDTSM); SF-36; CANTAB.

Demographics Questionnaire: Documents age, gender, education, and race/ethnicity.

Clinical Questionnaire: Self-report document focusing on the existence of 78 health symptoms taken from a list of ICD-9 codes that are highly likely to represent chronic pain.

Medication Use: Self-report of all current pharmacological and non-pharmacological treatments.

Yoga Home Practice Log: Log for participant to document their yoga home practice on non-treatment days.
BDI-II Beck Depression Inventory-II (BDI-II): Contains 21 self-report questions, scored on a 0-3 scale, related over the past two weeks to sleep, appetite, punishment, suicide, and interest in sex.
Patient Safety: Outcomes will be monitored to record the type and frequency of adverse events, as defined by
standard IRB regulatory reporting requirements.
Treatment Satisfaction: Assessed using the Multi-Dimensional Treatment Satisfaction Measure (MDTSM). The measure consists of 11 subscales assessing treatment process and outcome attributes. Each subscale has 1-8 items (see Table 5). Each question except the Discomfort subscale is rated on a five-point scale ranging from "not at all (0)" to "very much (4)". Thus, a score of 2 represents a rating of neutral satisfaction. The instrument was developed for behavioral interventions and is designed to provide a comprehensive set of treatment attributes to consider when evaluating treatments in the context of pilot studies. It is designed to be completed after exposure to an intervention, to point to aspects of treatments that are viewed favorably or unfavorably. The MDTSM is relevant to many types of behavioral interventions and
can be tailored to our yoga intervention. The MDTSM subscales demonstrates good internal consistency, reliability, and validity.
PEG: A 3-item pain measure derived from the Brief Pain Inventory and validated in ambulatory care settings. It includes 1 severity item (average pain) and 2 interference items (enjoyment of life and general activity).
SF-36: Health related quality of life-short form (69). Eight scales measuring physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health.
Cambridge Neuropsychological Test Automated Battery (CANTAB): Cognitive function was measured with the Cambridge Neuropsychological Test Automated Battery (CANTAB) at baseline and end of treatment. Three tests were administered (PAL, SWM and RVP).

	Data Collection			
	Screening	Baseline	Yoga (wks 1-12)	Post-treatment
Background				
Consent Form	×			
Demographic Questionnaire	×			
Clinical Questionnaire	×			
Yoga Medical Clearance Form	×			
Medical Use		×		×
Yoga Home Practice Log			×	
Mental Health				
BDI-II		×		×
Pain/QOL/Physical				
PEG	×	×		×
Behavioral & Cognitive				
Treatment Satisfaction				×
Patient Safety			×	×

SF-36			×	×
CanTab			×	×

Table 1. Study Measures and Timetable of Data Collection

Department of Veterans Affairs

RESEARCH CONSENT FORM

IRB Use Only
Approval Date: September 10, 2020
Expiration Date: (Does not Expire)

Title of Study: Feasibility of Teleyoga for Treatment of Lyme Disease	
Title of Consent (if different from Study Title):	
Principal Investigator: Peter J. Bayley, Ph.D.	VAMC: VA Palo Alto HCS

What is this research about?

You are invited to participate in a research study to test whether it is feasible to use telehealth to deliver yoga as a supplemental treatment for Lyme Disease symptoms, such as musculoskeletal pain. Our goal is to modify an existing yoga protocol for musculoskeletal pain and to address the technical challenges of at-home teleyoga. You were selected as a possible participant in this study because you have indicated that you have been diagnosed with Lyme Disease and are reporting symptoms associated with Lyme Disease. This research study is looking for 15 patients who exhibit symptoms associated with Lyme Disease and want to use yoga via telehealth to treat those symptoms.

This study is being done by researchers at VA Palo Alto Health Care System and Stanford University, and is sponsored by Stanford University.

What is expected of me? (Procedures)

Baseline (2-3 hours): You will be asked to complete self-report questionnaires about your medication use and experience of Lyme Disease symptoms either in person at the VA Palo Alto or online through Qualtrics or REDCap. During this session we will record your phone number, physical location for at-home teleyoga, and an emergency contact. This information will be used if the video conferencing session disconnects or an unforeseen emergency arises during at-home teleyoga.

Treatment (12 weeks): In the first week, you will be given a yoga mat, yoga strap, and yoga blocks for use during yoga class. You will then be assigned an iPad and given instructions on how to use the video conferencing app to participate in the yoga classes at home. You will determine the part of your home that is most comfortable and appropriate for a yoga class. You will participate in 1 yoga class per week for 12 consecutive weeks, 75 minutes per class, at a time that is convenient for the entire group and the instructor. A member of the study staff will call you the business day before class to remind you of the class appointment and remind you to charge the iPad for class. The yoga instructor will be based at the VA Palo Alto, and you will participate at home using the video conferencing app on the provided iPad.

Post-Treatment (2-3 hours): You will be asked to complete self-report questionnaires as well as provide feedback about the program, including any technical issues you encountered. This will be done either in-person at the VA Palo Alto, or online using REDCap or Qualtrics. You will mail the iPad back to study staff via USPS.

Video Recording: Video recording will be used to monitor fidelity of treatment delivery. Recordings will be made of treatment providers, not the participants. Recordings will be stored on a secure server in accordance with VA guidelines. VA record retention polices

require records, including videos, created during a research project to be maintained for 6 years after study closure, wherein they will be destroyed.

What are the possible risks or discomforts?

The risks associated with this study are minimal. The yoga protocol is developed for participants with chronic pain, and you will be encouraged to move safely and modify postures as necessary. If there is an unforeseen emergency during your at-home teleyoga session, we will take the necessary steps to ensure medical help arrives to the address you provided at the start of the study.

Will I benefit from the study?

We do not and cannot promise any health benefits from this study. It is possible you may experience some relief from Lyme disease symptoms.

What are my alternatives to being in this study?

You may choose not to participate in this study. If this is your decision, there are other choices including the standard treatments provided by a local clinic. Your study investigator will discuss any alternatives with you before you agree to participate in this study. Alternative treatments include medication and behavioral therapy.

Will I get paid?

You will receive $100 as payment for your participation. Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment.

Will I have to pay anything?

You will not have to pay anything to be in this study.

Do I have to be in this study?

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care.

Can I change my mind later and stop being in this study?

You can decide to participate now, but you may withdraw your consent later and stop being in the study without any loss of benefits or medical care you are entitled to.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

Will my information be protected from the public?

We will keep your name and all the information you tell us in this study confidential as possible. We may publish the results of this study for others to read about, but you will not be identified in any articles about the study by name, social security number, address, telephone number, or any other direct personal identifier. Also, other federal agencies as required, such as the VA Office of Research Oversight and the VA Office of the Inspector General may have access to your information.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects. The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of harm to self or others. The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document, including research information in the medical record.

What happens if I think I've been hurt by being in this study? Who can I talk to about a Research Related Injury?

Department of Veterans Affairs

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Principal Investigator: Peter J. Bayley, Ph.D.	VAMC: VA Palo Alto HCS

If you are injured as a direct result of being in this study, medical treatment will be available. If you are eligible for veteran's benefits, the cost of such treatment will be covered by the VA. If not, the cost of such treatments may still be covered by the VA depending on a number of factors. In most circumstances, the treatment must be provided in a VA medical facility. No other form of compensation for injuries is available. However, by signing this form you have not released the VA from liability for negligence. For further information, you may call the Human Protections Administrator at (650) 493-5000, ext. 67593 or the V.A. Regional Counsel at (415) 750-2288.

Who can I talk to if I have questions about the research, problems related to the study or if I think I've been hurt by being a part of the study?

If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the principal investigator, Dr. Peter Bayley (650) 493-5000 ext. 68653. You should also contact him at any time if you feel you have been hurt by being a part of this study.

If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, and would like to speak someone independent of the research team please contact the Stanford Institutional Review Board (IRB) at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

Please print or save a copy of this page for your records.

If you agree to participate in this research, please indicate this to the researchers and complete the following survey.