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Title: Mind-Body Program Delivered via Live Videoconferencing to International English-Speaking Adults with Neurofibromatosis: Study Protocol for a Single-Blind Randomized Controlled Trial

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ABSTRACT

**Background:** Neurofibromatoses (NF) are rare genetic conditions with substantial psychosocial burden and impaired quality of life (QoL). We developed the first NF tailored mind body program, the Relaxation Response Resiliency Program for NF (3RP-NF) and adapted it for delivery via live video to decrease barriers to participation and increase reach. In a pilot RCT we found that the 3RP-NF has excellent feasibility and acceptability when delivered via live videoconferencing. The 3RP-NF also showed proof of concept in improving QoL over and above an NF tailored health education control, The Health Enhancement Program for NF (HEP-NF). A fully powered trial is needed to ascertain the efficacy and durability of the 3RP-NF delivered via secure live video among geographically diverse patients.

**Objectives:** The aim of this study is to evaluate the efficacy of the 3RP-NF versus HEP-NF, both delivered in groups (maximum 8/group) via secure live videoconferencing, to geographically diverse patients with NF from across USA and internationally (N=224). Primary outcomes are physical and psychosocial QoL. Secondary outcomes are social and environmental QoL, psychosocial and resiliency variables. Outcomes are assessed at baseline, post-training, and at 6 and 12 month follow-ups. Here we describe the protocol, manualized treatments, evaluation plan and overall study design.

**Methods:** This is a single blind RCT. Patients are told that they will be randomized to one of the 2 stress management programs (SMP1 is 3RP-NF and SMP2 is HEP-NF). Patients are recruited through NF specific national and international foundations and NF clinics from across USA though study ads and a video with clips from past study participants. Interested participants are screened for eligibility on line (self-reported stress and difficulties coping, no change in antidepressant medication in the past 3 months, no psychotherapy in the past 3 months, no major upcoming surgeries in the next 12 months, English speaking, able to complete questionnaires on line and participate in live video interventions), and consented prior to participation. Both programs are manualized and entail 8 sessions delivered via secure live video by trained clinical psychologists.

**Results:** The trial is ongoing. So far we recruited 55 participants. Recruitment will close May 2020. We project to have complete analyses by June 2021.
Conclusions: This trial will answer key questions about the efficacy and durability of the 3RP-NF via live videoconferencing and globally to English speaking adults with NF. If found efficacious, this program can be readily implemented through national and international NF foundations as well as NF specific clinics. The virtual model of deliver has extensive applications to patients in rural areas, though with disability or illness that preclude travel to clinic, as well as other to patients with rare diseases.

Trial Registration: ClinicalTrials.Gov NCT03406208.

Key Words: Neurofibromatosis, Quality of Life, Stress Management, Symptom Management, Mind-Body, Videoconferencing, 3RP-NF, HEP-NF
MANUSCRIPT BODY

Introduction

NF is the most common genetic neurological condition in the world, and affects men and women of all races and ethnic groups[1,2]. NF comprises 3 genetically distinct conditions, NF1, NF2 and Schwannomatosis, unified by the predisposition to nerve sheath tumors that tend to be histologically benign. Each NF type has characteristic symptoms: NF1 is typically associated with disfiguring cutaneous tumors[3,4], NF2 is associated with hearing loss, facial weakness, and poor gait[5], and Schwannomatosis is associated with chronic disabling pain[6]. There is no cure for NF; treatment is limited to symptom management by surgical and palliative means[7].

Despite their distinct pathophysiology patients’ psychosocial profile is similar regardless of NF type[8]. As a group, patients with NF have lower quality of life (QoL), and more pain when compared to general population norms[8,9], and comparable rates of depression, anxiety, and stress to patients with cancer and coronary heart disease[9,10]. Despite this heavy psychological burden, there are no evidence-based psychosocial treatments that directly address the specific needs of this population.

We developed the first psychosocial treatment designed to meet the specific needs of patients with NF. Using a sequential approach that included focus groups, in-person open-pilot testing with exit interviews[8], and a preliminary randomized controlled trial (RCT)[11], we adapted an evidence-based mind-body intervention[12], for the specific needs of patients with NF and for live video delivery. The transition from in-person to live videoconferencing delivery was done based on feedback from patients about burdens of traveling for weekly visits and to increase feasibility and extend our reach to patients from across the US and internationally. In our pilot RCT[11], we showed that the 3RP-NF is highly feasible and acceptable when delivered via live videoconferencing. We also showed that participation in the 3RP-NF resulted in greater sustained improvement in QoL, psychosocial functioning[11] and resiliency variables[13] when compared to an active control the HEP-NF[14], Health Enhancement Program for Neurofibromatosis (HEP-NF), also delivered via videoconferencing.

We are now conducting the first fully-powered efficacy RCT in adults with NF (N=224). The primary aim of this study is to determine the efficacy and durability of 3RP-NF vs. HEP-NF on the co-primary outcomes
of physical health QoL and psychological health QoL. Secondary outcomes include social relations QoL, environmental QoL, and psychosocial and resiliency measures. We hypothesize that the 3RP-NF will be more efficacious in improving co-primary and secondary outcomes from baseline to the end of active training compared to HEP-NF, and that the benefits of 3RP-NF participation will be maintained at 6- and 12-month follow-up. The secondary aim is to examine the degree to which treatment-dependent improvements in the co-primary outcomes are mediated by improvements in depression, anxiety, pain intensity, pain interference, social support, gratitude, optimism, mindfulness, empathy, coping ability and stress (conceptual mediators), and modified by NF type, age, race/ethnicity, learning disability and education level. We also plan to develop NF specific minimally clinically important difference for QoL variables. This paper describes the study protocol.

Methods

Study Design

This is an ongoing, single-blind, RCT of the efficacy and durability of 3RP-NF vs. HEP-NF in improving QoL and psychosocial functioning in adults with NF1, NF2 and Schwannomatosis. Both programs are delivered via secure live videoconferencing, which allows enrollment of English Speaking participants from across the US and internationally. In order to maintain the single-blind design, we refer to 3RP-NF and HEP-NF as Stress Management Programs 1 and 2 (SMP1 and SMP2, respectively) in all study materials. We began enrolling participants in September of 2017. A flowchart of the study design is presented in Figure 1.

Figure 1: Study Design
This study is based in a large academic medical center in the Northeast region of the USA. The use of virtual recruitment and live videoconferencing for intervention delivery allows participants from US and internationally to engage in the study from the comfort of their own homes or any location with internet access. Participants are recruited through the NF Registry at the Children’s Tumor Foundation (CTF), which has over 7,000 members within the USA and internationally, various NF groups and clinics from across the USA, and international NF centers (e.g., England, Australia).

**Inclusion/Exclusion Criteria**

Study inclusion and exclusion criteria are detailed in Table 1. Criteria were selected following guidelines for psychosocial treatment development\[15\] and for bridging efficacy with effectiveness\[16\]. Criteria were meant to be as inclusive as possible to maximize reach and uptake, while reducing potential study confounds. Consistent with prior research that has utilized the Perceived Stress Scale 4-item\[17\] (PSS-4) measure as a screening tool for elevated stress, potential participants are required to score at least 6 on the PSS-4\[18,19\]. Screening is conducted by a study therapist via secure live videoconferencing.

**Table 1: Study Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has a diagnosis of NF1, NF2 or Schwannomatosis.</td>
<td>Has major medical comorbidity, not NF-related, expected to worsen in the next 12 months.</td>
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<tr>
<td>18 years of age or older.</td>
<td>Recent (within past 3 months) change in antidepressant medication.</td>
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<tr>
<td>Capable of completing and fully understanding the</td>
<td>Recent participation in cognitive behavioral therapy or relaxation therapy (within past 3 months).</td>
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<tr>
<td>informed consent process, study procedures and</td>
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<tr>
<td>assessments in English.</td>
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<tr>
<td>At least a 6th grade self-reported reading level.</td>
<td>Has significant mental health diagnosis requiring immediate treatment (e.g., untreated bipolar disorder, psychiatric disorder, active substance dependence) by self-report and observation during pre-screening.</td>
</tr>
<tr>
<td>Self-reported difficulties coping with NF symptoms.</td>
<td>Unable or unwilling to complete assessments electronically via REDCap.</td>
</tr>
<tr>
<td>Score of 6 or higher on the PSS-4.</td>
<td>Unable or unwilling to participate in group videoconferencing sessions.</td>
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</tbody>
</table>

**Recruitment**
The IRB-approved study advertisement is distributed electronically (e.g., email listserv) and on paper through the CTF registry, NF groups, and NF Clinics. In addition, an IRB approved recruitment video with snippets of patients’ experiences with study participation was created and disseminated at NF patient forums and at the CTF site. Potential participants email our study coordinator who responds within 24-hours using a scripted email describing the study and offering potential participants the opportunity to schedule a live videoconference screening with a study therapist (advanced clinical psychology graduate student or PhD in clinical psychology). The study coordinator attaches the informed consent to the email to allow individuals time to review the study procedures, but instructs the potential participant not to sign the consent form before the screening appointment. Potential participants are given two days after the initial email contact to respond before the study coordinator sends a follow-up email. The study coordinator ceases attempt to contact potential participants after three unanswered emails.

**Vidyo Software Installation**

All study appointments are conducted using the secure, HIPAA-approved live videoconferencing software, Vidyo, which is a user-friendly platform used clinically within our academic medical center. Prior to the screening appointment, potential participants are emailed instructions to download, install, and access Vidyo on their personal web-cam equipped, internet-connected devices (e.g., laptop and desktop computers, tablets). Participants are informed that devices with screens that are as large as possible are preferred, to provide them with the best video-viewing experience. However, to increase generalizability and reach, participants who do not own compatible computers or tablets are permitted to use smartphones if necessary. The study coordinator also offers telephone appointments to assist potential participants with software installation and configuration (e.g., ensuring the software is granted access to microphones and web-cams) as needed.

**Technical Considerations**

Participants have different levels of experience using technology, and many have NF-related learning disabilities. These issues present several challenges in installing and configuring the videoconferencing software. First, when using a tablet or smartphone, the software must be downloaded as an “app” acquired through an application distribution platform (e.g., app store, Google play store), which requires the user to have
and access their own accounts. Users who are unfamiliar with “app stores” may require assistance creating or accessing an account and initiating an app download and installation. Second, the Vidyo software is designed to auto-detect speakers, microphones, and web-cams installed on the device. However, in instances in which the device has multiple forms of hardware installed or auto-detect is unsuccessful, the study coordinator may be needed to assist patients in software configuration. Third, different types of operating systems (e.g., Mac OS X, Microsoft Windows) have slight variations regarding the installation and configuration process, as well as the user interface. The study coordinator has undergone extensive training to be able to assist participants with various technical challenges, to ensure that all participants are given the opportunity to enroll regardless of prior experience using technology. The coordinator has also received specific training on how to interact with potential participants who might feel intimidated by the technological aspect of the project, to make them feel comfortable and at ease. Further, the team has prepared simple, easy to use step-by-step instructions that are distributed to participants.

**Screening and Enrollment**

After potential participants have successfully installed Vidyo, the study coordinator schedules a virtual screening appointment during which the study therapist determines eligibility and performs the informed consent process. Eligibility is determined based on the inclusion and exclusion criteria delineated in section 2.3 and Table 1. All eligible participants are provided with an overview of the study procedures. The study therapist ensures that potential participants have a thorough understanding of the study procedures and are comfortable with the program format. Potential participants are encouraged to ask any questions about the informed consent document and the study procedures that they might have, and the study therapist answers all study related questions before consent is obtained. Eligible individuals who agree to participate are scheduled for the next available group, and are provided with instructions for returning the signed consent form to the study coordinator electronically (i.e., via email or fax). Our IRB considers participants to be enrolled in the study at the time that they return the informed consent document.

**Scheduling Considerations**
The use of secure live videoconferencing allows participants the ability to access the groups wherever they have a reliable internet connection and privacy. Thus, both participants and study therapists have flexibility in scheduling by having the option to access the treatment from home or office if privacy and internet needs are met. The ability to enroll geographically diverse participants is a strength of the current protocol. However, geographic diversity, which spans time-zones across the globe, and an individual randomization schedule (see below) create challenges to scheduling that are addressed in the following ways. First, each pair of treatment groups (i.e., 3RP-NF and HEP-NF) is run back-to-back in a 3-hour window (i.e., 90 minutes per group) by a single study therapist. Participant availability is required for the full 3-hour window to ensure that the participant will be able to attend either group to which s/he is randomized. Second, we assess a wide range of participant availability, including nights and weekends, to find a common time that will accommodate the study therapist’s schedule and as many participants as possible.

**Assignment to Treatment Arm**

Participants are randomly assigned in a 1:1 fashion to either the 3RP-NF or HEP-NF groups by a permuted-block randomization (random blocks of 2 and 4), stratified by diagnosis (NF1, NF2 or Schwannomatosis), using a computer-generated randomization schedule developed by a biostatistician. Randomization occurs individually for each participant after the baseline assessments have been completed. After randomization, the study coordinator emails each participant to inform them of their assigned group and confirm when their group will meet within the original 3-hour window (i.e., in the first 90-minutes or the second 90-minutes). To maintain blinding, participants are simply told whether they have been randomly assigned to SMP1 or SMP2.

**Randomization Considerations**

Multiple randomization methods are available to assign participants to treatment arms within an RCT, including individual and cluster randomization. We considered a cluster randomized design to facilitate scheduling feasibility – requiring participants to be available for only a 90-minute window and then randomizing that time-slot to a treatment condition. However, given that our unit of inference is at the individual level and that cluster randomization can reduce statistical power[20], we selected an individual
randomization schedule and enacted scheduling considerations. We also considered a block-randomization that would allow us to assign even numbers of participants to each pair of treatment groups. The current permuted-block design has considerable statistical and experimental design advantages by preventing the study team from deducing the next possible assignment. Due to limitations in the Vidyo software, we are unable to accommodate more than eight participants in a single group. As we assign participants to a 3-hour block and then randomize them to treatment condition, we could ensure equal groups (i.e., 8 per group) by using blocks of 16 for each time-slot. However, that would allow the study team to deduce the final allocation before randomization. Thus, we elected to randomize patients in a permuted-block design, accepting the potential for uneven groups. Once one group has reached 8 participants, randomization for that full 3-hour time-block is closed so as not to risk randomizing a 9th participant to a full group. While this can result in uneven groups (e.g., 8 in one group and 6 in another), it maintains the integrity of the randomization schedule and has been feasible in our design to date.

Treatment Conditions

Both treatment conditions include eight weekly 90-minute group sessions delivered via secure live videoconferencing. Sessions are delivered on the same day and time each week for eight consecutive weeks. Both treatments follow respective patient manuals, which are emailed as PDF documents to participants two days prior to their first session. The patient manuals are designed for a 6th grade reading and comprehension level. To further accommodate learning disabilities or other cognitive difficulties, participants are asked to have the manual with them during each treatment session, either electronically or in print, to follow along and take notes during the session. Participants who are not comfortable using the manual electronically and are unable to print the manual are mailed a paper copy.

Each week, participants receive a reminder email on the day of their group with instructions for logging into the Vidyo software. Participants are asked to email or call the study coordinator if they have any technical difficulties, and to email their study therapist if they are not able to attend the session. Participants who do not log into the session within 15 minutes of the start time receive a phone call from the study coordinator to inquire whether they are having technical difficulties and ask if they will attend the session. The study coordinator is available for the duration of each group, and, in the event of technical difficulties, assists participants with
trouble-shooting in real time with the goal of getting participants logged into the session as quickly as possible.

3RP-NF

The 3RP-NF is a comprehensive, multimodal treatment designed to improve ability to cope with NF symptoms and stress. The program retains the main components and structure of the parent program, which combines elicitation of the relaxation response (RR) with cognitive behavioral theory and the evolving field of positive psychology[21–29]. The 3RP has three core components: 1) RR-elicitation strategies to help patients decrease the stress response associated with NF symptoms and general life stress (e.g., mindfulness skills, meditations, guided imagery, body scan); 2) stress/medical symptoms appraisal and coping to help patients understand the interrelations among thoughts, behaviors, feelings, and sensations and learn adapting coping skills (e.g., cognitive restructuring, problem solving, activity scheduling); and 3) growth enhancement/positive psychology skills to help patients experience pleasure, gratitude and engage in pro-social and empathic behaviors (e.g., appreciations, use of humor, empathic communication). All skills have been modified to specifically address NF concerns identified through focus groups and exit interviews during the 3RP-NF development process. Skills are taught using NF examples. The program also provides educational information on nutrition, exercise and sleep hygiene.

Videoconferencing sessions consist of the study therapist and up to 8 participants, who are all visible to each other but can block their video if desired. Each session begins with setting an agenda and a review of the material from all previous sessions. Each session introduces at least one RR skill and an additional cognitive behavioral or positive psychology skill, with presentation of NF-specific examples. The study therapist leads in-session exercises to demonstrate each skill, and assigns home-practice of the skills to facilitate mastery. In-session practice and review of all the skills taught in prior sessions is unique to the 3RP-NF and done to compensate for the high rates of cognitive and learning disabilities in the NF population. Before each session participants receive an MP3 file recording with the particular RR skill that will be taught and practice within the particular group session, to aid with home practice. Between sessions, participants are asked to practice the skills daily, complete a home practice log and email it to the study therapist at least two hours before the start of each group session, in order to allow enough time for the study therapist to review each participant’s practice.
Home practice includes three core elements: 1) setting 1 weekly goal; 2) practice of an RR skill starting with five minutes daily for the first week and gradually increase length, frequency, or both, of practice throughout the 8-week program; and 3) writing down one to three appreciation statements daily. Each session includes a review of home practice, including problem-solving of barriers as needed, with specific feedback from patients. A complete description of treatment content by session is presented in Table 2.

Table 2: Outline of 3RP-NF

<table>
<thead>
<tr>
<th>Session</th>
<th>Topics</th>
<th>Skills</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom Management, Stress Management, and Resiliency Training</strong></td>
<td>1. The stress response</td>
<td>• Single-pointed focus meditation</td>
</tr>
<tr>
<td></td>
<td>2. The relaxation response</td>
<td>• Energy battery</td>
</tr>
<tr>
<td></td>
<td>3. Resiliency</td>
<td>• SMART goals</td>
</tr>
<tr>
<td></td>
<td>4. The mind-body connection</td>
<td>• Gratitude and appreciations</td>
</tr>
<tr>
<td><strong>The Relaxation Response</strong></td>
<td>1. Developing routines for consistent skills practice</td>
<td>• Body scan</td>
</tr>
<tr>
<td></td>
<td>2. Recuperative sleep</td>
<td>• Diaphragmatic breathing</td>
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<tr>
<td></td>
<td>3. The relaxation response and emotions</td>
<td>• Sleep hygiene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Identifying emotions and physical sensations</td>
</tr>
<tr>
<td><strong>Stress and Symptom Awareness for NF Patients</strong></td>
<td>1. Mindful awareness</td>
<td>• Mindful awareness meditations (e.g., mindful eating)</td>
</tr>
<tr>
<td></td>
<td>2. Stress awareness</td>
<td>• Identifying stress warning signals</td>
</tr>
<tr>
<td></td>
<td>3. Social support</td>
<td>• The social support diagram</td>
</tr>
<tr>
<td><strong>Mending the NF Mind And Body</strong></td>
<td>1. Movement to elicit the RR</td>
<td>• Stretches and chair yoga for relaxation</td>
</tr>
<tr>
<td></td>
<td>2. Negative automatic thoughts (NATS)</td>
<td>• Adaptive thinking: identifying NATS and thought distortions</td>
</tr>
<tr>
<td></td>
<td>3. Thought distortions</td>
<td>• Pleasant experiences to build resiliency</td>
</tr>
<tr>
<td><strong>Creating an Adaptive Perspective</strong></td>
<td>1. Adaptive thinking</td>
<td>• Generating adaptive thoughts through reframing, use of positive emotions/beliefs, and acceptance</td>
</tr>
<tr>
<td></td>
<td>2. Healthy eating</td>
<td>• Stop, breathe, reflect, choose</td>
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<tr>
<td></td>
<td></td>
<td>• Guided imagery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Food pyramid</td>
</tr>
<tr>
<td><strong>Promoting Positivity</strong></td>
<td>1. Positive psychology</td>
<td>• Loving kindness meditation</td>
</tr>
<tr>
<td></td>
<td>2. Optimistic explanatory style</td>
<td>• Telling our stories with optimism</td>
</tr>
<tr>
<td></td>
<td>3. Physical activity</td>
<td>• Identifying relaxation signals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Guidelines for health activity levels</td>
</tr>
</tbody>
</table>
**Healing States of Mind**

1. Empathy towards self and others
2. Choosing appropriate coping strategies
3. Acceptance

- Contemplation
- Problem-solving and acceptance strategies
- Coping decision tree
- Mindful awareness of another
- Letter to self

**Humor, Empathy and Staying Resilient**

1. Staying resilient
2. Humor

- Idealized self-imagery
- Laughter in daily life
- SMART goals for continued skills practice

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**HEP-NF**

The parent HEP (HEP)[14] is a group-based health education that addresses multiple domains of healthy living that are known to impact stress management, including sleep, diet and physical activity. The HEP-NF has been adapted to address specific needs of patients with NF, including educational information on NF-specific stressors and medical symptoms, NF-specific barriers to healthy lifestyle behaviors (e.g., appearance concerns, pain), self-management of medical care, and navigating the medical system. Adaptations were made using educational materials from the CTF website, research literature on NF, and information from focus groups. The program does not teach any of the 3RP-NF skills.

As with the 3RP-NF sessions, each HEP-NF session is composed of the study therapist and up to 8 participants who are present in a shared videoconferencing meeting. Each session of the HEP-NF begins with setting an agenda and review of previous material. The study therapist presents educational information on the session topic and invites participants to provide examples from their own lives. Participants are encouraged to pick a lifestyle skill learned in-session for use between sessions. A complete outline of content by session is presented in Table 3.

**Table 3: Outline of HEP-NF**

<table>
<thead>
<tr>
<th>Session</th>
<th>Topics</th>
<th>Skills</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Connection Between</strong></td>
<td>1. Stress and mental health</td>
<td>• Knowledge of lifestyle behaviors</td>
</tr>
<tr>
<td></td>
<td>2. Stress and physical illness</td>
<td>• Goal setting</td>
</tr>
<tr>
<td></td>
<td>3. Connection between lifestyle behaviors, physical, and emotional health</td>
<td></td>
</tr>
<tr>
<td><strong>Physical and Mental Health</strong></td>
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</tr>
</tbody>
</table>
**NF and Stress**
1. Types of NF
2. Stress associated with each NF type
   - Identifying personal NF stressors
   - Identifying shared stressors across NF types
   - Goal setting

**Sleep and Wellness**
1. Sleep and physical and emotional well-being
2. The sleep system (e.g., circadian rhythm)
3. Behavioral patterns and sleep
   - Sleep hygiene
   - Stimulus control
   - Checklist for better sleep

**Exercise and Wellness**
1. Physical activity recommendations
2. Maintaining health weight
   - Identifying current activity patterns
   - Identifying and problem-solving barriers to activity
   - Goal setting

**Nutrition: Basic Information**
1. Food groups and portion sizes
2. Calories and nutrient density
   - Reading and understanding nutrition labels
   - My healthy plate guidelines
   - Visualizing portion size

**Nutrition: Healthy Weight and Weight Loss**
1. Healthier meals and snacks
2. Eating out healthy
3. Weight and health
4. Healthy weight loss
   - Preparing a shopping list
   - Tips for eating out
   - Calculating body mass index

**Managing Healthcare**
1. Communicating with healthcare providers
2. Preparing for a medical visit
3. Medication adherence
   - Maintaining up to date records (e.g., lists of doctors, medications, recent tests)
   - Health diaries
   - Role plays of preparing and asking questions of medical providers
   - Tips for managing medications

**Review**
1. Review of healthy sleep
2. Review of physical activity
3. Review of nutrition
4. Review of NF and stress
5. Review of health care management

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**Treatment Fidelity**

We use guidelines depicted by the NIH Behavior Change Consortium (BCC) to monitor 5 areas of treatment fidelity. 1) **Design:** All study staff attend weekly team meetings to monitor and record participant progression through the study, including treatment “dose” (e.g., session attendance, out of session contact with therapists) and any deviations from the prescribed dose. In addition, the study coordinator and project director meet individually each week to review progress and upcoming tasks. The principal investigator participates in
weekly meetings and does quality control checks on a monthly basis. 2) Training: All study therapists are advanced graduate students or PhD-level clinical psychologists with experience in mind-body therapy. Each study therapist attends the 8-week parent program 3RP, led by a seasoned clinician at our academic medical center, as a participant observer. Study therapists also undergo study-specific training including learning general information about NF, watching videos of patients with NF1, NF2 or Schwannomatosis describing their symptoms, and specific training on the adaptation and delivery of skills to NF patients. Therapists receive training in the importance of adherence to the treatment manual and completion of study-related forms. Study therapists attend weekly in-person group supervision to assure adherence to the protocol, discussion of specific patient concerns (e.g., home practice challenges), and review of upcoming group sessions. 3) Treatment Delivery: All study therapists deliver session content according to the respective patient manuals and complete adherence checklists after each session. The adherence checklists are reviewed by the PI weekly during clinical supervision. Further, all study sessions are audio recorded, and 15% are randomly selected to be reviewed for adherence. 4) Receipt of Treatment: Study therapists monitor and support patients’ ability to comprehend and utilize treatment by reviewing previous content and setting an agenda at the start of each session. Study therapists elicit feedback from patients about their comprehension, goals, motivation, and use of skills throughout each session as new material is taught. Participants are instructed to follow along and take notes in their treatment manual, and to review the manual out of session, to facilitate comprehension. 5) Enactment of Treatment Skills: Participants are instructed to set weekly goals for applying skills and information presented in each session. Study therapists review home practice and problem-solve barriers weekly.

Considerations for Participant Safety during a Virtually Delivered Program

The safety of participants is evaluated at multiple study points. At the time of enrollment, participants are asked to provide the names and phone numbers of two family members or friends who could be contacted in case of emergency or if study staff have concerns about the participant’s safety (e.g., inability to contact participant following endorsement of suicidal ideation). At baseline, participants complete a measure of depressive symptomatology which asks about frequency of “Thoughts that you would be better off dead or of hurting yourself in some way.” If participants provide any endorsement (i.e., any response greater than “not at
to this item, the electronic data capture system automatically emails the study coordinator, project director, and PI. The study coordinator and project director communicate with the PI to provide patient contact information and emergency contact information if needed. The PI, a licensed clinical psychologist, immediately contacts the participant by phone to conduct a suicide risk assessment, including development of a safety plan and determination of need for higher level of care. If the PI is unable to contact the study participant within 24 hours, the PI then calls the patient’s individual emergency contacts to locate the participant and assess safety. The safety of participants is always prioritized over study participation. Participants who are determined to need a higher level of care or refuse to comply with safety procedures (e.g., refuse to conduct a risk assessment over the telephone) are removed from the study and provided with information about resources for care as appropriate. Participants who are determined to be at low suicide risk and appropriate for continuation in the study are monitored by the study therapists and discussed in weekly clinical supervision. At follow-up, the same procedures for risk assessment and referral to higher levels of care, as needed, are followed.

Assessments

Participants complete assessments online through the secure web application, Research Electronic Data Capture (REDCap)[30]. Baseline assessments are completed following informed consent, prior to randomization, and no more than two weeks prior to the first group session. Post-training assessments are emailed to participants within 24 hours of the final group session. Participants who have not completed the post-training assessments within three days receive a reminder email from the study coordinator and a phone call from the study therapist. Study therapists contact remaining participants daily (via phone or email as appropriate) to facilitate completion of assessments within one week of the final group session. Six- and 12-month follow-up surveys are emailed to participants one-week before the respective assessment due date. Participants who do not complete questionnaires within that week then receive three additional email reminders and up to three phone calls from the study therapist or PI. Study staff cease attempts to obtain six-month follow-up after two months (i.e., month 8). Participants who do not complete six-month follow-up are contacted as usual to complete the 12-month assessment. Participants who do not complete 12-month follow-up after two months (i.e., month 14) are considered lost to follow-up and their participation in the study is terminated.
**Sociodemographic Information**

Gender, age, race/ethnicity, marital status, NF type, presence of learning disability, and education level are collected from a demographics questionnaire. This assessment is only delivered at baseline.

**Primary Outcomes: Physical and Psychological Quality of Life**

The World Health Organization Quality of Life Brief version (WHOQOL-BREF)[31] is a 26-item self-report survey that is used to measure four domains of health-related quality of life: physical health (7 items), psychological health (3 items), social health (3 items), and environmental health (8 items). The physical and psychological health QoL domains are co-primary outcomes of this study. The physical health domain assesses ability to participate in activities of daily living, dependence on medicinal treatments and medical aids for daily functioning, energy and fatigue, mobility, pain and discomfort, sleep and rest, and work capacity. The psychological health domain assesses satisfaction with bodily image, frequency of negative and positive emotions, self-esteem, spirituality/religion, and ability to concentrate. Scores are reported as transformed domain scores (0-100) with high scores depicting greater QoL. No NF specific minimal clinically important difference (MCID) has been established for the WHOQOL-BREF, but a 6.25-unit improvement has been extrapolated from the MCID for patients with cancer available for the parent scale WHOQOL-100[31]. Thus, a 6.25-unit increase is used as an indicator of clinically meaningful improvement in physical and psychological QoL in the current study. The WHOQOL-BREF is assessed across all study time points.

**Secondary Outcomes: Social QoL and Environmental QoL**

The social QoL and environmental health QoL domains of the WHOQOL-BREF are secondary outcomes of this study. The social health domain assesses satisfaction with personal relationships, availability of social support, and satisfaction with sexual relationships. The environmental health domain assesses perceived financial resources, physical safety and security, accessibility and quality of healthcare and social services, home environment, opportunities for learning and growth, opportunities for recreation and leisure activities, physical environment (pollution, noise, climate, traffic), and transportation. Domains are scored in accord with instructions noted above.

**Conceptual Mediators**
Depression

The Patient Health Questionnaire 9-Item version (PHQ-9)[32] is a self-report survey used to measure frequency of depression symptoms (e.g., little interest or pleasure in doing things, trouble falling or staying asleep, poor appetite or overeating, and trouble concentrating) over the past two weeks. Responses are formatted as a 4-point Likert-scale ranging from 0 (“Not at All”) to 3 (“Nearly Every Day”). Items are summed to generate a total score, with higher scores indicating greater severity of depression symptoms. This assessment is delivered across all time points.

Anxiety

The Generalized Anxiety Disorder 7-Item version (GAD-7)[33] is a self-report survey used to measure frequency of anxiety symptoms (e.g., feeling nervous or on edge, not being able to stop or control worrying, being restless, and becoming easily annoyed or irritable) over the last two weeks. Responses are formatted as a 4-point Likert-scale ranging from 0 (“Not at All”) to 3 (“Nearly Every Day”). Items are summed to generate a total score, and higher scores indicate greater severity of anxiety symptoms. This assessment is delivered across all study time points.

Pain Intensity

The characteristic pain intensity subscale of the Graded Chronic Pain Scale (GCPS)[34] uses three separate 11-point numerical rating scales (0 = no pain, 10 = pain as bad as could be) to assess current momentary pain, worst pain, and average pain over the previous week. Items are summed to generate a total score, with higher scores indicating greater pain intensity. This assessment is delivered across all time points.

Pain Interference

The PROMIS Pain Interference version Short Form 8a (PROMIS Pain Interference-8a)[35] is an 8-item self-report survey used to measure the extent to which pain interferes with activities of daily living, including household, work, social activities, over the past seven days. Responses are formatted as a 5-point Likert-scale ranging from 1 (“Not at All”) to 5 (“Very Much”). Items are summed to generate a total score, and cross-referenced with the score conversion table to translate the raw score to a T-score for each participant. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation of 10.
Therefore, an individual with a T-score of 40 is one SD below the mean. This assessment is delivered across all time points.

**Stress**

The Perceived Stress Scale 10-Item version (PSS-10)[36,37] is a self-report survey that assesses frequency of thoughts or feelings related to stress (e.g., becoming upset with something unexpected, feeling unable to control important things in life, and feeling incapable of coping with things to do) in the past month. Responses are formatted as a 5-point Likert-scale ranging from 0 (“Never”) to 4 (“Very Often”). Negatively worded items (4, 5, 7, and 8) are reverse scored, and then all items are summed to generate a total score, with higher scores indicating greater perceived stress. This assessment is delivered across all time points.

**Social Support**

The Medical Outcome Study Social Support Survey (MOS-Social Support)[38] is a 19-item self-report survey used to measure perceived social support. The survey asks how often different kinds of support are available to the respondent as needed, divided into three domains: emotional/informational support, affectionate support, and positive social interaction. Responses are formatted as a 5-point Likert-scale ranging from 1 (“None of the Time”) to 5 (“All of the Time”). Items are averaged, with higher scores indicating greater availability of social support. This assessment is delivered across all time points.

**Gratitude**

The Gratitude Questionnaire 6-Item version (GQ-6)[39] is a self-report survey used to measure a general tendency to experience gratitude (e.g., being appreciative of people, events, and situations). Responses are formatted as a 7-point Likert-scale ranging from 1 (“Strongly Disagree”) to 7 (“Strongly Agree”). Negatively worded items are reverse scored, and then all items are summed to generate a total score, with higher scores indicating greater gratitude. This assessment is delivered across all time points.

**Optimism**

The Life Orientation Test Revised (LOT-R)[40] is an 11-item self-report survey used to measure a tendency towards optimism (i.e., expecting the best in uncertainty and expectations on whether good or bad things will happen). Responses are formatted as a 5-point Likert-scale ranging from 0 (“Strongly Disagree”) to
4 (“Strongly Agree”). Negatively worded items are reverse scored and then all items are summed to generate a total score, with higher scores indicating greater optimism. This assessment is delivered across all time points.

**Coping Ability**

The Measure of Current Status Part A (MOCS-A)[41] is a 13-item self-report survey used to assess perceived abilities recognize stress and utilize appropriate coping strategies (e.g., able to use coping techniques, able to recognize stress). Responses are formatted as a 5-point Likert-scale ranging from 0 (“I Cannot Do This At All”) to 4 (“I Can Do This Extremely Well”). The measure yields four subscales: relaxation, awareness of tension, assertiveness, and coping confidence. Items pertaining to each subscale are summed, with higher scores indicating on each subscale indicating greater ability to cope in each respective manner. This assessment is delivered across all time points.

**Mindfulness**

The Cognitive and Affective Mindfulness Revised (CAMS-R)[42] scale is a 12-item self-report survey used to measure mindfulness (i.e., the ability to pay attention to the present moment in a non-judgmental manner). The survey asks the respondent to indicate how often they related to their thoughts and feelings mindfully (e.g., focused on the present moment, ability to concentrate). Responses are formatted as a 4-point Likert-scale ranging from 1 (“Rarely/Not at All”) to 4 (“Almost Always”). Negatively worded items are reverse scored, and then all items are summed to generate a total score, with higher scores representing greater mindfulness. This assessment is delivered across all time points.

**Empathy**

The 7-item empathic concern subscale of the Interpersonal Reactivity Index (IRI)[43] is a self-report survey use to measure empathy (i.e., feeling concerned for others, being protective of others, and being sensitive to others). Responses are formatted as a 5-point Likert-scale ranging from 1 (“Does Not Describe Me Well”) to 5 (“Describes Me Very Well”). Items are summed to generate a total score, with higher scores indicating greater empathy. This assessment is delivered across all time points.

**Perceived Improvement**
The Patient Perception of Improvement (PPI)[44] is a single self-report item that asks, “Do you think that you are now better, about the same or worse as compared to before the intervention?” The item was modified for our study to assess perceived improvement in QoL by asking, “Do you think your quality of life is now better, about the same or worse as compared to before the intervention?” Response options are “Substantially worse”, “Minimally worse”, “About the same”, “Minimally better”, and “Substantially better”. Separate items are used for each QoL domain (physical, psychological, social, and environmental). This assessment is delivered at post-training, 6- and 12-month follow-up.

**Data Analysis**

**Power Analysis**

The effective standard deviations (SD) for the change from baseline to post-training in physical health QoL and psychological health QoL based on a repeated-measures ANOVA of our preliminary data[11] were 14.7 and 10.4 units, respectively. The effective SDs from post-training to 6-month follow-up were 11.4 and 10.0 units, respectively. Based on these estimates, assuming an MCID of 6.25 units, allowing up to 5% loss to follow-up by post-training assessment, and testing each of the co-primary outcomes at p < 0.025 two-sided, a total N of 224 will afford 80% power for Physical QoL and 96% power for Psychological QoL. Allowing up to 20% loss to follow-up by the 6-month assessment, the study will have 99% power to declare non-inferiority of 3RP-NF vs. HEP-NF if the true treatment-dependent difference in maintenance of any change from baseline to post-training is zero.

**Primary and Secondary Outcomes**

Treatment effects on primary and secondary outcomes will be analyzed using a shared-baseline, linear mixed model with fully unstructured covariance among up to four repeated measures (baseline, post-training, 6- and 12-month follow-up). The shared-baseline assumption reflects the true state of the population prior to randomization and has the benefit of adjusting for chance differences at baseline[45]. For each outcome, we will compare the effect of 3RP-NF vs. HEP-NF on changes from baseline to the post-training, 6- and 12-month follow-up times using linear contrasts. Persistence of a benefit from 3RP-NF at 6- and 12-month follow-up times will be analyzed as a non-inferiority test of durability. Non-inferiority of 3RP-NF in maintaining benefits
relative to HEP-NF will be declared if the lower one-sided 95% confidence bound for a given co-primary outcome is less than 6.25 units (the estimated MCID) in favor of HEP-NF. Several sensitivity analyses will be explored using alternative models. Change scores calculated from baseline at post-training, 6-months, and 12-months will be separately analyzed by Wilcoxon rank sum test to avoid any parametric assumptions about the data. More parsimonious covariance structures will be considered using random participant-specific intercepts, slopes, and quadratic terms (i.e., growth curve analysis). Baseline parameters such as NRS pain and their interactions with visit will be included to account for chance differences due to randomization and to explain sources of variation in response that are independent of treatment group. All randomized participants will be included in our primary efficacy analyses as randomized, following the intention-to-treat principle.

**Mediation and Moderation Analyses**

If the 3RP-NF intervention improves some or all of the co-primary and secondary outcomes relative to the HEP-NF, we will explore the extent to which this relationship is mediated by psychosocial variables (e.g., depression, anxiety, pain interference and pain intensity). The degree to which a given psychosocial variable mediates the effect of 3RP-NF treatment on a given outcome will be estimated from the pure natural indirect effect from a causal model that includes potential interaction between the intervention and the mediator but assumes no unmeasured confounders[46]. Change scores from baseline to each follow-up assessment will be analyzed. Evidence of mediation will be inferred if the confidence interval does not cover zero. The mediation effect size will be determined by the proportion of the total effect that is attributable to the mediation (i.e., the mediated effect divided by total effect). This method is consistent with Baron and Kenny (1986)[45] and updated by Kraemer et al (2002)[47]; however, it extends the analysis by allowing us to test significance of the mediated effect, and quantify the magnitude of the mediation.

The possible effect of moderators of a beneficial effect of 3RP-NF will be investigated by adding a given moderator (e.g., contrasting treatment response by NF1, NF2, and Schwannomatosis diagnosis), moderator x treatment and moderator x treatment x visit interaction terms to the repeated-measures ANOVA using methodology described for analyses of primary outcomes. Specific linear contrasts of the moderator x treatment x visit interaction terms will be used to test for differential 3RP-NF dependent benefit in
improvements from baseline to post-training, 6-month, or 12-month follow-up that are a function of diagnosis, age, or race/ethnicity. While we have not designed the study to have good power to detect differences by NF type, we have optimized our power to detect differences by NF type by stratifying randomization by diagnosis given the available sample size and distribution of NF types.

We will develop WHOQOL-BREF MCID thresholds specific for NF using an anchor-based approach based on participants' self-report of important change on the PPI. We will use mixed model cumulative logistic regression to model ordinal responses on the PPI. Each model will include fixed effects of physical or psychological QoL and follow-up visit and random participant-specific intercepts to account for correlation among repeated measure. If the visit term is not significant, then it will be dropped. The estimated MCIDs will be those that best discriminate participants who report being “About the same” vs. “Minimally better” on the PPI, i.e., the physical or psychological QoL score for which the predicted probability of being “About the same” and “Minimally better” on the PPI are equal.

**Data Management**

To maximize accuracy and security, all survey data are collected and stored on a secure, and HIPAA-compliant web-based REDCap[30] data system hosted by our academic medical center. Data are stored on password-protected computers that are kept in secure locations. Paper data files (with coded subject identification) are stored in a locked filing cabinet accessible only to the research team. A unique anonymous identifier is assigned to each subject; subsequently, all data collected are associated exclusively with this identifier. This includes all questionnaires administered over the course of the study, as well as home-practice logs.

**Discussion**

NF is a prevalent and incurable condition associated with decreased QoL and high psychosocial comorbidities. The current standard of care for NF is predominantly biomedical. Using a sequential approach and direct feedback from patients, we adapted an evidence-based mind body program, the 3RP, for the specific needs of patients with NF (3RP-NF). In a pilot RCT, we showed that the 3RP-NF has excellent feasibility and acceptability[11]. We also showed that participation in the 3RP-NF was associated with sustained improvement
in quality of life, psychosocial functioning\cite{11} and multiple dimensions of resiliency\cite{13} (e.g., perceived coping ability, perceived social support, and mindfulness) relative to an educational program tailored for the needs of patients with NF (HEP-NF). To remove barriers to care for this rare disease and to increase generalizability, both programs were delivered to patients with NF1, NF2 and Schwannomatosis from across the US and internationally using live videoconferencing.

This paper describes the study design and specific strategies used to conduct an innovative, fully powered RCT of the 3RP-NF versus HEP-NF administered via live videoconferencing to adult patients with NF from across the US and internationally. We provide details on the benefits and challenges of delivering psychosocial care using secure live videoconferencing, procedures for keeping participants blinded throughout study participation, means of accommodating patients from different time zones, techniques for keeping patients engaged in treatment, and methods of monitoring and addressing the safety of participants. This information is invaluable for future trials using live videoconferencing and represents a novel model for delivery of care to patients with rare diseases or those in remote areas.

Results of this trial will provide important information not only on the efficacy and durability of 3RP-NF versus HEP-NF across the course of a year, but they will also allow us to understand whether the specific targets of the 3RP-NF interventions – mindfulness, coping, social support, optimism and others – are plausible mechanisms for improvements in the primary outcomes. We will also be able to address whether any benefits of 3RP-NF are dependent on demographic variables, type of NF or self-reported learning disability. Further, using direct feedback from patients, we will be able to calculate NF-specific minimally clinically important difference scores for the physical and psychological quality of life measure, which will allow patient-specific evaluation of improvement in the four domains of QoL.

Both the 3RP-NF and HEP-NF have been adapted iteratively based on feedback from patients with NF, and have showed excellent feasibility, acceptability and preliminary efficacy in our prior work. If the current trial replicates our prior pilot study\cite{11,13} and confirms our hypotheses that the 3RP-NF is superior to HEP-NF in improving physical and psychological quality of life, as well as other secondary outcome, we aim to implement and disseminate the 3RP-NF as part of standard of care through the major NF centers within the US.
and internationally, as well as through Children’s Tumor Foundation (CTF). Using the CTF-sponsored annual clinic’s meeting and general support from CTF, we would aim to train a variety of providers (e.g., psychologists, social workers, nurses, genetic counsellor). The original 3RP has been delivered successfully in clinical practice at our institution by non-psychologists.

Despite the novelty of this trial, there are several limitations. First, although we are using extensive national and international recruitment modalities, recruiting ethnically and racially diverse participants is challenging. Our pilot RCT enrolled primarily white patients\textsuperscript{11} and we have strategies in place to diversify our patient population. Specifically, we have a strong presence in the NF community and have developed a recruitment video that includes racially diverse NF patients who positively describe their experiences within the study. Second, although we are recruiting international patients, we are delivering the program and assessments in English only. As such, patients who are not fluent in English are not able to enroll. Future work will involve translation of the 3RP-NF as part of internationally dissemination efforts. Further, the majority of patients with NF1 enrolled in both our pilot study and current trial do not have severe cutaneous tumors, suggesting that these patients may not be comfortable with participation in a group intervention due to appearance concerns. Further, although we took extensive measures to keep participants blinded to HEP-NF and 3RP-NF, we risk unbinding participants who look up our research\textsuperscript{[11,13]}.

In sum, this is the first psychosocial randomized controlled trial delivered via live videoconferencing in patients with NF, and provides valuable information for the design, structure, challenges and benefits associated with this study design and delivery modality. Results will inform implementation efforts as well as future clinical trials in other NF populations (e.g., adolescents with NF1 and NF2, parents of children with NF1 and NF2, adults with NF2 who are deaf), as well as other trials targeting geographically distributed individuals with rare diseases. Results will also potentially extend the applicability of the 3RP mind body program to other medical populations and increase our understanding of the mechanisms of its efficacy across medical populations.
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Roles and responsibilities:

AMV designed the study, wrote the manuscript, and is the PI of the DOD grant.

EZ cowrote manuscript and is the program manager on the DOD grant.

CF cowrote manuscript and is the research assistant on the DOD grant.

EM wrote the analyses plan.

JM provided edits to the manuscript.

EP provided edits to the manuscript.

JJ provided edits and referred participants.

SP provided edits and referred participants.
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