CLINICAL STUDY PROTOCOL

Innovation in the Treatment of Persistent Pain in Adults with NF1: Implementation of the iCanCope Mobile Application- Clinical Trial

NCT04561765

Protocol Number

2000029045

Principal Investigator

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Sponsor

Department of Defense

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Confidentiality Statement:

Study Personnel

Principal Investigator Frank Buono
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Synopsis

Study Purpose

OBJECTIVES & HYPOTHESES: To evaluate whether the *iCanCope-NF* program will reduce pain (pain severity and pain interference) in adults with NF1. We hypothesize that by customizing the CBT and the MBAA in the mobile application for adults with NF1, individuals will engage regularly, thus acquiring a new set of skills to facilitate their own pain self-management, while pain will decrease.

SPECIFIC AIM:

To determine the feasibility and preliminary effectiveness of *iCanCope-NF* in adults (n=108) with NF1 suffering from pain in a RCT.

Primary Objective

To evaluate whether the *iCanCope-NF* program will reduce pain (pain severity and pain interference) in adults with NF1.

Secondary Objectives (if applicable)

n/a

General Design Description

A 1x3 pilot randomized control trial (RCT) (*iCanCope-NF, iCanCope-NF* +Contingency Management (CM), Control Group) will be conducted with 108 adults with NF1 who suffer from pain.

Study Date Range and Duration

We predict the pilot RCT to take 18 months to complete (February 1, 2021 to August 2022). The patient networks that we are recruiting from have over 25000 adults across both groups. A conservative estimate of 20% of individuals should be within the appropriate age criterions (~5000). Given that we are seeking to fulfill 36 in each group for a total of 108 for the Pilot RCT and taken in account of a conservative 20% refusal rate. We should not encounter an issue with total number of individuals enrolled within the study within the time frame.

Number of Study Sites

There will be three study sites for this study: Yale School of Medicine, Connecticut Children's Hospital (Hartford, CT), and The Hospital of Sick Children (Toronto, Canada).

Yale School of Medicine: The PI will run the entire clinical trial through Yale School of Medicine. All potential participants will be recruited, consented, orientated to a treatment group (if applicable).

Connecticut Children's Hospital (Hartford, CT): will consult but will not have access to the PHI data

The Hospital of Sick Children (Toronto, Canada): will host the server of the iCanCope and the dashboard of the server but will not see any personal PHI.

Primary Outcome Variables

1.Engagement Activity

Total minutes logged on the mobile application will be evaluated between the two groups using the mobile application.

2.Pain Severity

A comparison within groups change of pain severity measured by the Brief Pain Inventory-Short Form. Respondents rate items on a 0-10 scale to indicate the pain severity and interference, and the total score is the mean of each subfactor. The higher the score indicates more severity and interference of pain.

3.Pain Interference Index

A comparison within groups change of pain interference measured by the Pain Interference Index Scale. Respondents rate items on a 0-6 scale to indicate how much pain has interfered with various activities, and the total score is the mean of the six items. Where 6 indicates high interference.

Secondary and Exploratory Outcome Variables (if applicable)

Secondary Outcome Measures:

1. Treatment Services Review what are perceptions of satisfaction across groups exposed to the iCanCope mobile application using an The Treatment Services Review (TSR)
2. Anxiety comparison within change of generalized anxiety measured by the generalized anxiety disorder scale (GAD-7). After reading each statement, one of four choices are provided and respondents can select one response (1=not at all sure, 2=several days, 3=over half days, 4=nearly every day). Each column is then added, and a total score is obtained, with scores falling into four levels of anxiety, including minimal (1-4), mild (5-9), moderate (10-14), and severe (15-21)
3. Sleep functioning comparison within change of sleep quality measured by the PROMIS Sleep inventory. The higher the total score, the more severe the symptom. Total scores less than 24 suggest no to slight sleep disturbance, 24-28 suggest mild disturbance, 29-38 moderate disturbance, and greater than 38 severe sleep disturbance
4. Short Form/Quality of Life the Short form survey 20- will measure quality of life across 8 subscales on respondent burden (Physical Functioning, Role-Physical,

Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health). Scores were transformed linearly to 0-100 scales, with 0 and 100 assigned to the lowest and highest possible scores, where high value indicated better functioning.

5. Chronic pain acceptance Chronic Pain Acceptance Questionnaire-Revised (CPAQ-Revised) 20-item scale designed to measure acceptance of pain. The acceptance of chronic pain is thought to reduce unsuccessful attempts to avoid or control pain and thus focus on engaging in valued activities and pursuing meaningful goals will be measured across all groups. The items on the CPAQ are rated on a 7-point scale from 0 (never true) to 6 (always true). To score the CPAQ, add the items for Activity engagement and Pain willingness to obtain a score for each factor. To obtain the total score, add the scores for each factor together. Higher scores indicate higher levels of acceptance
6. psychological inflexibility Psychological Inflexibility in Pain Scale (PIPS) 16-item scale used to assess psychological inflexibility (i.e. avoidance, acceptance, fusion, values orientation, dirty discomfort) in people with chronic pain will be measured across all groups. Respondents are asked to rate items on a 7-point scale that ranges from 1 (never true) to 7 (always true). Higher scores indicate greater levels of psychological inflexibility.

Other Pre-specified Outcome Measures:

1. Mindfulness based alternative approaches (MBAA)Do individuals with NF1 utilize the MBAA more readily because they are on the mobile application, via Five Facet Mindfulness Questionnaire. 39-item self-completed questionnaire measuring the five facets of mindfulness: Observing (8 items), Describing (8 items), Acting with awareness (8 items), Non-judgmental (8 items), and Non-reactive (7 items). Participants rated the items on a five-point Likert scale (1 = never or very rarely true to 5 = very often or always true), each facet score ranges from 8 to 40, except for the non-reactive facet which ranges from 7 to 35.

Study Population

A convenience sample of 108 adults with NF1 aged 18-34 will be recruited through mail merge and emails, Internet advocacy web forums (NF Network, NF Northeast:

Number of Participants

A convenience sample of 108 adults with NF1 aged 18-34 will be recruited through mail merge and emails, Internet advocacy web forums (NF Network, NF Northeast: see letters of support).

Power Analysis: An a priori power analysis conducted through G*Power (Universität Kiel, v. 3.1.9.2) estimated a conservative sample size analysis for the RCT. We are expecting a total of 140 participants, given the length of the trial, we estimate 20% attrition rate of the final sample, giving us a total sample of (n=36) per group, for a final sample size of 108.

The power analysis is based on previously utilized research in which estimated effect sizes ranged from 20 to 40 individuals per group (52). We will attempt to enroll equal numbers of male and female individuals to evaluate gender differences through urn randomization process.

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Visit Schedule Table (0ptional)

n/a

Study Flow Chart (optional)

see flow chart below

Abbreviations

Abbreviation	Explanation

Glossary of Terms

Glossary	Explanation

Table of Contents

1.1 Statement of Compliance

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to the Common Rule at 45CFR46 (human subjects) and other applicable government regulations and Institutional research policies and procedures.

2.1 Background

Background: Neurofibromatosis Type 1 (NF1) is an autosomal dominant genetic condition affecting 1 in 2500 individuals (1). NF1 was originally classified as a tumor predisposition

syndrome based on the propensity of affected children and adults to develop benign and malignant tumors (2,3). Over 50% of individuals with NF1 report significant pain and discomfort (4,5) which can be associated with tumors, but is often not localized to a structural lesion, thus presenting treatment challenges for patients and their medical caregivers. Moreover, the increased pain in this population can negatively impact an individual's perceived quality of life (6,7). Due to the complexity of the disorder (e.g., location, severity, number, and type of tumors), there are limited effective therapeutic options for treating pain (3). In this regard, tumor-related pain is primarily managed by either surgery or medication (8,9). To date, there has been limited research exploring the daily impact of living with persistent pain from a qualitative perspective by the individual living with NF1 and evaluating NF1 pain and treatments.

Barriers to Pain Treatment: Individuals suffering from persistent pain have multiple potential barriers to obtaining comprehensive pain specific treatment including: (a) difficulty accessing these services (e.g., no services available in many geographic areas, long wait times); (b) limited availability of trained professionals such as psychologists, particularly in non-urban centers; (c) patient-related issues (i.e., psychological, communication, and attitude); (d) current health care system barriers, (i.e., reimbursement, costs of treatment) and (e) limited access to self-management techniques (10-14). Self-management can be defined as the individual's ability to manage the symptoms, treatment, physical, and psychological consequences and lifestyle changes inherent to living with a chronic illness (15). Self-management interventions that provide individuals with disease-specific knowledge, strategies to manage symptoms such as pain (e.g., cognitive-behavioral therapies; CBT), and social support are needed to promote optimal health outcomes.

Cognitive Behavior Therapy and Pain Treatment: Cognitive Behavior Therapy (CBT) uses assessment and evaluation of current behaviors to identify problem behaviors and develop skills to manage situations as well as to cope with difficult thoughts and feelings (16,17). CBT typically incorporates normalization of the patient's experience through education, training in strategies for managing disease-related symptoms and other stressors, enhancing self-efficacy, as well as guidance on developing and implementing a long-term self-management plan (18-19). Studies have documented the efficacy of CBT across a wide range of diseases and disorders. A recent meta-analysis showed that the most successful interventions in improving pain and associated functional impairments in adults with chronic pain are rooted in CBT (20). It is well documented that the skills learned through CBT continue, sometimes even increase, after treatment has been completed (21,22). To date, there has been little peer reviewed research within the NF1 population utilizing CBT to treat pain symptoms. CBT like many other psychotherapies has multiple disadvantages: (1) mental health clinicians and practitioners require extensive training in both CBT and pain treatment, (2) limited access to appropriate care of trained clinicians, and (3) formalized face-to-face treatment is relatively expensive. Furthermore, mind-body alternative approaches (MBAA) (i.e., yoga, mindfulness), can have impact on pain intensity and have been found to alter pain experience (23). Research has shown that when CBT and MBAA interventions are combined, they can be effective in decreasing negative emotional

responses to pain, decreasing perceptions of disability, and increasing orientation toward self-management during treatment (24,25). A recent meta-analysis confirmed a combination of CBT and MBAA to be as effective as face-to-face CBT with patients suffering from persistent and chronic pain (26). This same review showed patients preferred mobile-based therapy and had more consistent usage than face to face CBT.

Mobile Technologies to Enhance Delivery of Pain Self-Management Care: Mobile technologies can be applied to enhance the accessibility of pain self-management therapies (27,28). In addition to improving access, these technologies can empower individuals to take an active role in managing their condition by providing "in the moment" access to pain coping strategies (29). Additionally, a systematic review showed that incorporating self-management strategies for persistent pain within standard treatment increases treatment efficacy and patient buy-in (30). Over 78% of U.S. adults own or have access to Smartphones; therefore, smartphones offer an ideal platform to prompt practice of CBT-based coping skills in the moment. This technology can be leveraged to build a tailored self-management program that emphasizes empowerment, facilitates the creation and tracking of personalized goals, and offers a peer-based social support platform to prompt practice of CBT-based coping skills as needed. In the current mobile marketplace, there are over 120 pain applications, but few are empirically valid (31). The iCanCope mobile and web-based program provides personalized goal setting to improve pain and function, CBT-based pain self-management training and rehearsal, and peer-based social support, while providing key health information and coping skills to individuals. The iCanCope mobile and web-based self-management program has been empirically evaluated for multiple painful diseases in children and adolescent populations (32,33). Yet, with any mobile application poor adherence is a common problem which can limit the effectiveness of intervention, and the iCanCope mobile application has not been tested within adults. One approach to combat poor adherence and increase patient engagement and retention is contingency management (12,34,35)

Contingency management: Contingency management (CM) arranges systematic application of behavioral consequences of desired behavior and withholds reinforcement of undesired behaviors (36). CM interventions are based on extensive basic and clinical science intervention research supporting that training in a CM setting can develop and improve real world skills; therefore, predicting skill use and quality of use in real life (37,38). By using points, levels, prizes or other rewards, and well-established reinforcement schedules, individuals are actively engaged (39-41) and CM can encourage individuals to practice behavioral change in a novel and entertaining way (42-44) and can be generalized to the person's natural environment and enhance motivation for change.

Neurofibromatosis and Pain: Based on my current findings (in press), over 15% of adults with NF1 are currently using pharmacological interventions and 60% had at least one surgery procedure in the last year for their treatment of persistent pain. Moreover, a majority of these individuals are not aware or have not attempted MBAA for their pain symptoms. Given these findings, as well as (1) the lack of access to qualified care for pain management within NF1, (2) lacking of empirically validated behavioral treatments for persistent pain

within NF1 and (3) an inability to empower individuals to take an active role in managing their condition, I believe by providing an empirically validated treatment in which individuals with NF1 can learn to self-manage their own pain symptoms, while learning new alternative treatments can provide tremendous potential and positive change for those living with persistent pain.

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3.1 Problem Statement

Adults with NF1 are currently using pharmacological interventions and 60% had at least one surgery procedure in the last year for their treatment of persistent pain. Moreover, a majority of these individuals are not aware or have not attempted MBAA for their pain symptoms. Given these findings, as well as (1) the lack of access to qualified care for pain management within NF1, (2) lacking of empirically validated behavioral treatments for persistent pain within NF1 and (3) an inability to empower individuals to take an active role in managing their condition, I believe by providing an empirically validated treatment in which individuals with NF1 can learn to self-manage their own pain symptoms, while learning new alternative treatments can provide tremendous potential and positive change for those living with persistent pain.

3.2 Purpose of Study/Potential Impact

We expect individuals with NF1 utilizing the iCanCope program to have decreased pain severity and interference if they regularly engage in the program. In addition, due to the added contingency management, we expect to see differences between the intervention groups (*iCanCope-NF* and *iCanCope-NF* +CM). By adding contingencies to increased engagement the CM grouping should have more improvements in pain intensity and pain interference in addition to current iCanCope processes. If we demonstrate initial feasibility and preliminary impact, in collaboration with Drs. Zempsky and Stinson, a definitive RCT will be conducted. In future studies, evaluating the sustainability of impact on the outcomes over the course of 12 months is critical to sustaining the impact of the application as well as generalization of treatment. Thus, following the patients in a 1, 3 and 6-month follow-up post-treatment is necessary.

3.3.1 Potential Risks

The main risk associated with the study is the possibility that confidential information obtained during the study will be disclosed given the association of a medical disease and pain symptoms. Patient names and other identifying information do not appear on research records. For patients the iCanCope-NF must enter a unique id and passcode for access. All processes of obtaining information via Qualtrics, or iCanCope-NF will utilize proper data security methods to minimize any risks of for potential loss of confidentially. 3.3.2 Potential Benefits

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4.1 Hypothesis

We hypothesize that by customizing the CBT and the MBAA in the mobile application for adults with NF1, individuals will engage regularly, thus acquiring a new set of skills to facilitate their own pain self-management, while pain will decrease.

4.2 Primary Objective

To evaluate whether the *iCanCope-NF* program will reduce pain (pain severity and pain interference) in adults with NF1.

4.3 Secondary Objectives (if applicable)

n/a

5.1 General Design Description

A 1x3 pilot randomized control trial (RCT) (*iCanCope-NF, iCanCope-NF* +Contingency Management (CM), Control Group) will be conducted with 108 adults with NF1 who suffer from pain.

5.1.1 Study Date Range and Duration

We predict the pilot RCT to take 18 months to complete (February 1, 2021 to August 2022). The patient networks that we are recruiting from have over 25000 adults across both groups. A conservative estimate of 20% of individuals should be within the appropriate age criterions (~5000). Given that we are seeking to fulfill 36 in each group for a total of 108 for the Pilot RCT and taken in account of a conservative 20% refusal rate. We should not encounter an issue with total number of individuals enrolled within the study within the time frame.

5.1.2 Number of Study Sites

There will be three study sites for this study: Yale School of Medicine, Connecticut Children's Hospital (Hartford, CT), and The Hospital of Sick Children (Toronto, Canada).

Yale School of Medicine: The PI will run the entire clinical trial through Yale School of Medicine. All potential participants will be recruited, consented, orientated to a treatment group (if applicable).

Connecticut Children's Hospital (Hartford, CT): will consult but will not have access to the PHI data. There will be no active recruitment or enrollment at the Connecticut Children’s Hospital.

The Hospital of Sick Children (Toronto, Canada): will host the server of the iCanCope and the dashboard of the server but will not see any personal PHI. There will be no active recruitment or enrollment at the Hospital of Sick Children. *Dr. Pham (University of Toronto/University Health Network) will oversee the development of the ICC NF app and ensure that Dr. Buono and the Yale research team receives an intervention that can be trialed with their patient population. She will provide ongoing guidance and support of the technical requirements for the project, including the maintenance and tier 2 technical support*

of the ICC NF app through the trial. She will also lead on the development of the contingency management dashboard used by Dr. Buono's research team to monitor engagement with the ICC NF app. Dr. Pham's academic contributions will involve participating in regular investigator meetings on clinical trial progress and supporting Dr. Buono with data analysis, interpretation, and manuscript preparation. Dr. Pham will not have access to any identifiable data.,

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

Primary Outcome Measure:

1. Engagement Activity

Total minutes logged on the mobile application will be evaluated between the two groups using the mobile application.

[Time Frame: through the completion of the study, on average 4 months.]

2.Pain Severity

A comparison within groups change of pain severity measured by the Brief Pain Inventory-Short Form. Respondents rate items on a 0-10 scale to indicate the pain severity and interference, and the total score is the mean of each subfactor. The higher the score indicates more severity and interference of pain.

[Time Frame: through the completion of the study, on average 4 months.]

3. Pain Interference Index

A comparison within groups change of pain interference measured by the Pain Interference Index Scale. Respondents rate items on a 0-6 scale to indicate how much pain has interfered with various activities, and the total score is the mean of the six items. Where 6 indicates high interference.

[Time Frame: through the completion of the study, on average 4 months.]

5.2.2 Secondary and Exploratory Outcome Variables (if applicable)

Secondary Outcome Measures:

1. Treatment Services Review what are perceptions of satisfaction across groups exposed to the iCanCope mobile application using an The Treatment Services Review (TSR) [Time Frame: through the completion of the study, on average 4 months.]
2. Anxiety comparison within change of generalized anxiety measured by the generalized anxiety disorder scale (GAD-7). After reading each statement, one of four choices are provided and respondents can select one response (1=not at all sure, 2=several days, 3=over half days, 4=nearly every day). Each column is then added, and a total score is obtained, with scores falling into four levels of anxiety, including minimal (1-4), mild (5-9), moderate (10-14), and severe (15-21)[Time Frame: through the completion of the study, on average 4 months.]

3. Sleep functioning comparison within change of sleep quality measured by the PROMIS Sleep inventory. The higher the total score, the more severe the symptom. Total scores less than 24 suggest no to slight sleep disturbance, 24-28 suggest mild disturbance, 29-38 moderate disturbance, and greater than 38 severe sleep disturbance [Time Frame: through the completion of the study, on average 4 months.]
4. Short Form/Quality of Life the Short form survey 20- will measure quality of life across 8 subscales on respondent burden (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health). Scores were transformed linearly to 0-100 scales, with 0 and 100 assigned to the lowest and highest possible scores, where high value indicated better functioning. [Time Frame: through the completion of the study, on average 4 months.]
5. Chronic pain acceptance Chronic Pain Acceptance Questionnaire-Revised (CPAQ-Revised) 20-item scale designed to measure acceptance of pain. The acceptance of chronic pain is thought to reduce unsuccessful attempts to avoid or control pain and thus focus on engaging in valued activities and pursuing meaningful goals will be measured across all groups. The items on the CPAQ are rated on a 7-point scale from 0 (never true) to 6 (always true). To score the CPAQ, add the items for Activity engagement and Pain willingness to obtain a score for each factor. To obtain the total score, add the scores for each factor together. Higher scores indicate higher levels of acceptance [Time Frame: through the completion of the study, on average 4 months.]
6. psychological inflexibility Psychological Inflexibility in Pain Scale (PIPS) 16-item scale used to assess psychological inflexibility (i.e. avoidance, acceptance, fusion, values orientation, dirty discomfort) in people with chronic pain will be measured across all groups. Respondents are asked to rate items on a 7-point scale that ranges from 1 (never true) to 7 (always true). Higher scores indicate greater levels of psychological inflexibility. [Time Frame: through the completion of the study, on average 4 months.]

Other Pre-specified Outcome Measures:

1. Mindfulness based alternative approaches (MBAA)Do individuals with NF1 utilize the MBAA more readily because they are on the mobile application, via Five Facet Mindfulness Questionnaire. 39-item self-completed questionnaire measuring the five facets of mindfulness: Observing (8 items), Describing (8 items), Acting with awareness (8 items), Non-judgmental (8 items), and Non-reactive (7 items). Participants rated the items on a five-point Likert scale (1 = never or very rarely true to 5 = very often or always true), each facet score ranges from 8 to 40, except for the non-reactive facet which ranges from 7 to 35.[Time Frame: through the completion of the study, on average 4 months.]

5.3 Study Population

A convenience sample of 108 adults with NF1 above the age of 18 will be recruited through mail merge and emails, Internet advocacy web forums (NF Northwest and NF Network).

5.3.1 Number of Participants

A convenience sample of 108 adults with NF1 aged 18-34 will be recruited through mail merge and emails, Internet advocacy web forums (NF Network, NF Northeast: see letters of support).

Power Analysis: An a priori power analysis conducted through G*Power (Universität Kiel, v. 3.1.9.2) estimated a conservative sample size analysis for the RCT. We are expecting a total of 140 participants, given the length of the trial, we estimate 20% attrition rate of the final sample, giving us a total sample of (n=36) per group, for a final sample size of 108. The power analysis is based on previously utilized research in which estimated effect sizes ranged from 20 to 40 individuals per group (52). We will attempt to enroll equal numbers of male and female individuals to evaluate gender differences through urn randomization process.

52. Hancock, G. R. and R. O. Mueller, Eds. (2010). *The Reviewer's Guide to Quantitative Methods. Power Analysis*. New York, NY, Routledge.

5.3.2 Eligibility Criteria/Vulnerable Populations

Patients will be included in the study if they meet the following inclusion criteria:

1) adults older than age of 18

2) diagnosis a diagnosis of NF1;

3) permanently reside in the United States and

4) have pain interference aggregate scores of three or more in the last two weeks using the Brief Pain Inventory-Short Form (BPI-SF) scale.

Patients will be excluded if they: 1) have an undiagnosed case of NF1; 2) have documented major co-occurring psychiatric disease; 3) have moderate to severe cognitive deficits; or 4) have depression assessed using the Patient Health Questionnaire (PHQ-9) or anxiety assessed using the Generalized Anxiety Disorder scale (GAD-7) greater than or equal to the appropriate thresholds (10=mild major depression; 5=mild severe anxiety).

6.1 Intervention

6.1.1 Description of Intervention

Figure 1 presents a CONSORT study flow diagram. Potential participants will be required to access an online secure site to learn about the study and to be evaluated for eligibility, provide informed consent, and complete baseline assessments. Eligible participants will be randomly assigned to one of the 3 conditions: *iCanCope-NF, iCanCope-NF* +CM, or the Control Group (treatment as usual or TAU). Individuals in the iCanCope groups will receive 8 weeks of 24-hour access to the program.

The proposed architecture of the iCanCope-NF consists of four theory-based components, integrated across smartphone: self-monitoring (e.g. Real-time symptom tracking via patient self-report. Customizable graphs and reports; smart goal setting (e.g. Set

goals related to improving pain, sleep, mood, physical activity and social activity, Adherence to SMART' framework); personalized self-management instruction and rehearsal (e.g. (In-the-moment access to pain coping strategies, Personalized instruction based on goals); and detailed pain education (Provide information on types of pain, strategies for maintaining physical activity and strategies managing anxiety, stress and emotions).

iCanCope Orientation. At study intake, individuals within the *iCanCope-NF* and *iCanCope-NF* +Contingency Management (CM) groups will receive a 10-minute video orientation to the iCanCope program. The orientation will emphasize daily usage of the CBT treatment platform. Individuals will receive a login and password information, general information and instruction, and contact information for technical problems.

***iCanCope-NF* Group:** In this group, individuals will receive the *iCanCope-NF program*. The intervention will be delivered on a restricted password-protected mobile application. Participants will be encouraged to log onto the pain diary app (via automated alerts) once per day over the 8-week period to complete pain diary entries and develop and track their goals related to their pain, physical, social activities, sleep, as well as work through content based on their goals.

***iCanCope-NF* & CM Group:** In addition to the *iCanCope-NF* activities outlined above, individuals will be rewarded with incentives such as points that are redeemable for prize-based gift card vouchers.[i] (#_edn1) Points will be accrued through access to new sections, daily check-ins, and engagement of the mobile application. Based on research, the total amount of money that can be earned by the patient over the course of the two months is 50 dollars USD. Individuals who are only randomized in the ICC-CM condition earn from $1 to $5 dollar amazon gift card per week for eight weeks (based on their usage). With an additional $10 dollar gift card, if they check in every day. The total of the incentives can reach up to 50 dollars.

Control Group*:* The control group is designed to assess for potential effects on outcomes of time, attention, during the study. In addition to usual care, participants will be required to complete baseline and follow-up assessments similar to that of the intervention groups. They will be given that patient education, through preapproved flyers and information found from national websites regarding pain management, but no self-management strategies or opportunities for social support. They will not have access to the mobile application during the course of experiment; however, the control group will be offered the full *iCanCope-NF* program following the trial (T2) for a period of 2 months after the study is over.

6.1.2 Method of Assignment/Randomization

Participants will be randomized to one of the three conditions using an urn randomization algorithm which modifies ongoing randomization probabilities based on prior group composition groups, and controls for other predictive factors. This process greatly reduces experimenter bias and other internal validity threats to integrity. Gender be the only variable

that will be attempted to controlled for to ensure equal representation across the groups within the urn randomization using stratification.

6.1.3 Selection of Instruments/Outcome Measures

In the pilot RCT, we plan to assess a broad range of subject characteristics, feasibility and clinical outcome measures over the course of the study. (See Table 1). Baseline assessments are designed to ensure that patients meet eligibility criteria and that important predictor treatment variables. Data will be self-reported and will be collected online and stored as per HIPAA privacy legislation. All measures have evidence of reliability and validity in adults in this age range, and include target specific measures of NF1 have recommended in previous trials

6.1.4 Intervention Administration

Individuals assigned to the *iCanCope-NF, iCanCope-NF* +CM will have 8 weeks of 24-hour access to the program. Individuals assigned the Control will not have access to the iCanCope-NF application.

6.1.5 Reaction Management

Patients that have technical problems will be connected to the infrastructure team of the mobile application. Emergency Contact information will be provided within the mobile application (e.g. 911 services, National Suicide Hotline, and referring to their primary care office). Additional support will be provided to NF-community advocacy organizations for non-emergences (NF Northeast, NF Network).

6.2 Assessments

6.2.1 Efficacy

All psychometric measures (see appendix) will be evaluated at intake, discharge, follow-up. All of these measures have evidence of reliability and validity in adults in this age range and include target specific measures of NF1 have recommended in previous trials. The **primary research** question is what is the feasibility of the *iCanCope-NF* program? We define feasibility as (1) rates of accrual and dropout, daily logins, engagement, and outcome measures completed and (2) perceptions regarding intervention acceptability and satisfaction; and what are the levels of engagement. logins, with the intervention? The **secondary questions** are: (1) how does the *iCanCope-NF* program compare with the control condition in differences of pain and pain-related activity limitations, sleep functioning, emotional functioning (depression, anxiety), opioid usage, pain catastrophizing, self-efficacy, respondent burden (i.e. Physical Functioning, R, Vitality, Social Functioning, Role-Emotional, and Mental Health), and psychological flexibility immediately post-treatment (T2), (2) does the *iCanCope-NF* + CM increase the engagement of the *iCanCope-NF* program as compared to *iCanCope-NF* without CM, and do their corresponding levels of pain and pain-

related activity decrease with CM?, and (3) do individuals with NF1 utilize the MBAA to help reduce pain symptoms? We hypothesize that by customizing and including MBAA to the program for adults with NF1, that individuals who engage regularly as seen through Analytics Platform for Evaluating Effective Engagement (APEEE) application, will acquire new sets of skills to facilitate pain management, while pain as reported with the Brief Pain Inventory will decrease.

6.2.2 Safety/Pregnancy-related Procedure

N/A

6.2.3 Adverse Events Definition and Reporting

In the event your behavioral study involves a drug or device intervention consider the following sample language:

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related.

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The following guidelines will be used to describe severity of adverse events.

- Mild — Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate — Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe — Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Related — The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related — There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

OR

- Definitely Related — There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related — There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Potentially Related — There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related — A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related — The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

The PI (Frank Buono) will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI (Frank Buono) will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

6.2.4 Pharmacokinetics (if applicable)

N/A

6.2.5 Biomarkers (if applicable)

N/A

6.3 Study Procedures

6.3.1 Study Schedule

A total of three visits (all virtual) will be completed. The three visits will consist of admission, discharge and follow-up. Admission for control group will consist of 30 minutes, while admission for individuals within the experimental groups, should take 60 minutes. Discharge evaluations for each should be 45 minutes (30 minutes for assessments, 15 minutes debriefing). Follow-up should be 30 minutes for assessments. Individuals who have access to the mobile application are encouraged to provide daily check-in evaluations (estimated time of 2 minutes) and utilize the different modules at their discretion. The participants will have free reign of the mobile application and are not required to spend any time on the mobile application. No other communication with the research team will take place between all participants and the time intervals previously mentioned. For individuals who are placed in the control group, they will be encouraged to utilize the materials found on several chronic pain websites, with no required time commitments. The mobile application will not remind or notify the participant if they have to login or input information.

6.3.2 Informed Consent

A waiver of documentation of consent will be requested considering that the entire research study is performed remotely. The consent will describe in detail the study intervention, study procedures, and risks are given to the participant. The consent will be uploaded through the initial meeting between the research team and the participant. Consent is required prior to starting study procedures/administering study intervention. The following consent materials are submitted with this protocol Phase 3 consent form.

6.3.3 Screening

Subjects will be interviewed by a trained and supervised research assistant to determine interest in participating in the study and eligibility. Participants will be interviewed via Zoom using standardized psychological assessments or will complete similar standardized self-report forms. Eligibility will be evaluated by the research assistant and reviewed with the project director or PI prior to initiation

6.3.4 Recruitment, Enrollment and Retention

Describe how potential subjects will be identified:

Adults with NF1 will be recruited from advocacy groups: NF Network and NF Northeast. NF Network and NF Northeast are the largest direct support and advocacy cohorts for individuals and families with neurofibromatosis in the United States. NF Network has over 28,000 members on their private network, while NF Northeast has over 2,500 individuals on their private network.

Describe how potential subjects are contacted:

Each advocacy group has granted permission for us to contact individuals through their websites via email and private Facebook banners. Examples of the emails are attached (see Recruitment Emails).

Who is recruiting potential subjects?

The Principal Investigator (PI; Dr. Frank Buono) or his research assistant will be responsible for all recruitment of individuals with NF1.

How will this process take place, including obtaining consent in relation to the start of the study procedures?

Individuals with NF1 are consented through the Zoom (www.zoom.com (http://www.zoom.com); A Yale-approved vendor). The consent form will be an attached document, that can be shared with them while the PI (Dr. Buono)/RA reads the consent form. Zoom allows the PI/RA to interact with the individual with NF1 or the clinician to ensure any and all questions are answered prior to the participation of the study.

Use of third parties: N/A

6.3.5 Study Visits

See Appendix 3

6.3.6 End of Study and Follow Up

At the end of the study, all participants in each group (TAU, iCanCope, iCanCope+CM) will be required to complete the identical set of assessments at intake, minus demographic information. Individuals who prematurely left early or who withdrawn from the study will not be asked to complete the end of the study survey. Additionally, individuals with access to the iCanCope mobile application license will end and will not be able utilize the mobile application until the follow-up is complete. For individuals who did not have access to the iCanCope mobile application they will continue not having access to the mobile application.

All participants in each group will complete a 6-week post discharge follow-up. The follow-up will be identical to the discharge evaluation. Individuals will be emailed a secured email by the research assistant to complete the survey one day before the 6-week survey. All participants will have a one-week (7days) to complete the assessment, and a reminder email will be sent on the last day of the survey to the participants. Individuals will not be required to complete but will be encouraged to do so.

6.3.7 Removal of Subjects

In cases of psychological deterioration, we will recommend to patients to contact their physician immediately and consider withdrawing from the study to receive more intensive treatments. When necessary subjects will be withdrawn from this study and research staff will assist patients with appropriate sites for treatment such a physician, crisis center, or emergency room. The mobile application will also have emergency information available that can be tailored by each patient to provide specific contacts that they may need. In instances of suicidal or homicidal risk, appropriate authorities including their primary provider will be informed and necessary actions (seeking crisis/suicidality evaluations and possible hospitalization) taken.

6.4 Statistical Method

6.4.1 Statistical Design

Statistical procedures and models have been selected according to the research questions being investigated and the types of data available. We will use $\alpha < .05$ but will use appropriate corrections for multiple tests. Statistical analyses will be conducted by principal investigator using SPSS, SAS, or R with consultation from the coinvestigators. Using logistic regression for categorical and ANOVA for continuous measures, we will conduct preliminary analyses of the adequacy of the randomization procedure, the comparability of baseline measures across conditions, and the possible need for covariates in the analyses of treatment outcome data.

6.4.2 Sample Size Considerations

An a priori power analysis conducted through G*Power (Universität Kiel, v. 3.1.9.2) estimated a conservative sample size analysis for the RCT. We are expecting a total of 140 participants, given the length of the trial, we estimate 20% attrition rate of the final sample, giving us a total sample of (n=36) per group, for a final sample size of 108. The power analysis is based on previously utilized research in which estimated effect sizes ranged from 20 to 40 individuals per group (52). We will attempt to enroll equal numbers of male and female individuals to evaluate gender differences through urn randomization process.

52. Hancock, G. R. and R. O. Mueller, Eds. (2010). *The Reviewer's Guide to Quantitative Methods. Power Analysis*. New York, NY, Routledge.

6.4.3 Planned Analyses

Statistical procedures and models have been selected according to the research questions being investigated and the types of data available. We will use α< .05 but will use appropriate corrections for multiple tests. Statistical analyses will be conducted by principal investigator using SPSS, SAS, or R with consultation from the coinvestigators. Using logistic regression for categorical and ANOVA for continuous measures, we will conduct preliminary analyses of the adequacy of the randomization procedure, the comparability of baseline measures across conditions, and the possible need for covariates in the analyses of treatment outcome data.

For the primary first outcomes: Can we identify the feasibility of the *iCanCope-NF* program? This will be evaluated using general linear model of count data (logins, dropout rates, completion of outcome measures, engagement activity, (i.e. user and aggregate levels). Additionally, the proportional changes will be evaluated using an ANOVA. Due to potential missing data assumptions, a Cox regression will evaluate for differences in relationship between pre-and post. For second primary outcome**:** what are perceptions regarding intervention acceptability and satisfaction; and what are the levels of engagement with the intervention? Aggregate values will be summed and standardized through a (z-score analysis) to ensure equal representation of groups. Lastly, for the levels of engagement and number of activities tried/TSN exercises will be examined with linear and non-linear Mixed-effects Models (LMM) with autoregressive 1 correlation structure (AR1) to test between conditions, while allowing for intra-participant serial correlation and unequal variance and covariance structure across time.

Secondary analyses will explore three research questions: (1) Does smartphone program (*iCanCope-NF)* compared with control condition lead to differences in pain and pain-related activity limitations, sleep functioning, emotional functioning (depression, anxiety), pain catastrophizing, self-efficacy, knowledge, psychological flexibility immediately post-treatment (T2)? This will be evaluated by incorporating an estimating equation approach to understand the differences in scores and using a sequential multilevel logistic regression models to estimate the independent and combined effects of proposed time-varying (contextual) variables on the probability of pain levels. We will also test interaction effects between stable/trait-level participant characteristics and contextual variables. (2) Does the *iCanCope-*

NF + CM increase the usage of the *iCanCope-NF* program as compared to *iCanCope-NF* without CM, and do their corresponding levels of pain and pain-related activity decrease? This will be evaluated between the two intervention groups and using the difference in nominal data sets, and simple qualitative analyses. (3) Do individuals with NF1 utilize the MBAA more readily because they are on the mobile application? To assess the moderation effect, we will include an interaction term for each separate moderator variable and key predictor of interest (two-way interaction between moderator and group for cross-sectional analysis and three-way interaction between moderator, group and time for longitudinal analysis) in the regression models and test its significance using Wald t-test.

6.4.3.1 Primary Analyses

For the primary first outcomes: Can we identify the feasibility of the *iCanCope-NF* program? This will be evaluated using general linear model of count data (logins, dropout rates, completion of outcome measures, engagement activity, (i.e. user and aggregate levels). Additionally, the proportional changes will be evaluated using an ANOVA. Due to potential missing data assumptions, a Cox regression will evaluate for differences in relationship between pre-and post. For second primary outcome**:** what are perceptions regarding intervention acceptability and satisfaction; and what are the levels of engagement with the intervention? Aggregate values will be summed and standardized through a (z-score analysis) to ensure equal representation of groups. Lastly, for the levels of engagement and number of activities tried/TSN exercises will be examined with linear and non-linear Mixed-effects Models (LMM) with autoregressive 1 correlation structure (AR1) to test between conditions, while allowing for intra-participant serial correlation and unequal variance and covariance structure across time.

6.4.3.2 Secondary Objectives Analyses, if applicable

Secondary analyses will explore three research questions: (1) Does smartphone program (*iCanCope-NF)* compared with control condition lead to differences in pain and pain-related activity limitations, sleep functioning, emotional functioning (depression, anxiety), pain catastrophizing, self-efficacy, knowledge, psychological flexibility immediately post-treatment (T2)? This will be evaluated by incorporating an estimating equation approach to understand the differences in scores and using a sequential multilevel logistic regression models to estimate the independent and combined effects of proposed time-varying (contextual) variables on the probability of pain levels. We will also test interaction effects between stable/trait-level participant characteristics and contextual variables. (2) Does the *iCanCope-NF* + CM increase the usage of the *iCanCope-NF* program as compared to *iCanCope-NF* without CM, and do their corresponding levels of pain and pain-related activity decrease? This will be evaluated between the two intervention groups and using the difference in nominal data sets, and simple qualitative analyses. (3) Do individuals with NF1 utilize the MBAA more readily because they are on the mobile application? To assess the moderation effect, we will include an interaction term for each separate moderator variable and key predictor of interest (two-way interaction between moderator and group for cross-sectional analysis and three-way interaction between moderator, group and time for longitudinal analysis) in the regression models and test its significance using Wald t-test.

6.4.3.3 Analysis of Subject Characteristics

We will evaluate the relationship between iCanCope module use, patterns, gender and change in coping stills and outcomes. Rate and time of specific module use will be evaluated, and LMM will be used to evaluate the relationship between minutes using specific module categories with corresponding change in coping skills efficacy in those categories

6.4.3.4 Interim Analysis (if applicable)

N/A

6.4.3.5 Health economic evaluation, if applicable

N/A

6.4.3.6 Other

N/A

6.4.4 Subsets and Covariates

N/A

6.4.5 Handling of Missing Data

Another set of automatic email reports, sent on a weekly or less frequent basis, provides a set of designated recipients (e.g., the PI) with information about study logistics, such as number of subjects enrolled, number of subjects active in the protocol, gender composition of the sample, percentage of missing data by each assessment instrument, or any other information necessary to monitor the progress of the project and the compliance with the protocol. A fully computerized system allows this type of monitoring without furnishing investigators with data that could influence the outcome of the study. We will evaluate different assumptions about missing data and code it as zero.

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Consent forms will be Institutional Review Board (IRB)-approved and the participant/legally authorized representative (LAR) will be asked to read and review the document. The PI or research assistant will explain the research study to the participant and answer any questions that may arise. This conversation will take place in a private room.

Participants/LAR will have the opportunity to carefully review the electronic consent form and ask questions prior to signing. The participants/LAR should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants/LAR must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The study team will document all verbal HIPAA authorizations, from a study potential participant or LAR for their use of PHI for the current study.

7.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol will

require an approved IRB amendment before implementation. The IRB will have final determination whether informed consent and HIPAA authorization are required.

A study closure report will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per Yale's IRB's policies.

7.3 Subject Privacy, Confidentiality & Data Management

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s)/funding agency. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB), regulatory agencies or study sponsor/funding agency may inspect all documents and records required to be maintained by the investigator for the participants in this study. The study site will permit access to such records.

The study participant's contact information will be securely stored at each study site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, regulatory, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a secure Yale approved server called Box. . This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the [insert location].

7.4 Deviations/Unanticipated Problems

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to identify and report deviations within 2 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the study sponsor, and the reviewing Institutional Review Board (IRB) per their policies.

Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee),

and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.

7.5 Data Collection

Data monitoring procedures involve an organizational structure of clearly defined tasks assigned to all research personnel involved in the conduct of this study. The organizational structure used to ensure quality of data in this project include: 1) extensive training and close supervision of research assistants in data collection; 2) direct entry of most data at time of collection; and 3) utilization of on-line error- checking procedures. The PI supervises data procedures. All error corrections are fully documented in the research records of the study. All research personnel are required to participate in and document training in protection of human subjects and the responsible conduct of scientific research. Data entry and review in this study will be conducted using a web-based data collection and monitoring system. Another set of automatic email reports, sent on a weekly or less frequent basis, provides a set of designated recipients (e.g., the PI) with information about study logistics, such as number of subjects enrolled, number of subjects active in the protocol, gender composition of the sample, percentage of missing data by each assessment instrument, or any other information necessary to monitor the progress of the project and the compliance with the protocol. A fully computerized system allows this type of monitoring without furnishing investigators with data that could influence the outcome of the study. The system meets the highest security and reliability standards. All connections to the systems are secured and encrypted using 128-bit strong encryption protocols and only authorized users are able to access the system.

7.6 Data Quality Assurance

The PI is responsible for monitoring of quality control and assurance through regular communication with the research team via bi-weekly meetings. The PI will train the research assistant on ensuring consistent and reliable methods of recruitment, data management, and training sessions through initial trainings. Additionally, the PI will provide in situ training to the research assistant throughout the research experiment. A standard operating procedure (see appendix) will be implemented and trained on.

7.7 Study Records

Study records consists of the following: 1) Consent forms, 2) inclusion/exclusion screen forms, 3) Process measures (e.g. Patient health questionnaire, generalized anxiety disorder, brief pain inventory, background questionnaire), 4) feasibility measures (e.g. iCanCope Program usage, patient satisfaction survey), 5) clinical measures (e.g. short form survey, chronic pain acceptance questionnaire, psychological inflexibility in pain scale, pain catastrophe scale), 6) regulatory message (appendix) indicating the iCanCope mobile application is a FDA exempted device.

7.8 Access to Source

Survey information taken at admission, discharge, and follow-up will be stored on Qualtrics (a Yale approved vendor), and only the PI will have access to this. The source information

of the mobile application will be controlled by the APEEE developers and will be transferred to the Dr. Buono via access to a secure dashboard that only he has access to.

7.9 Data or Specimen Storage/Security

Data will be stored two in two servers: 1) Box @ Yale is a cloud-based file sharing and storage service workspace which enables people to collaborate, synchronize, and share information. This server will collect, record and store all data regarding any data that is inputted from the PI. 2) All surveys will be stored through Qualtrics. Qualtrics is an approved vendor of Yale University, and will securely store, record and store all participants surveys

7.10 Retention of Records

All records will be maintained on Yale secured server for a minimum of 5 years by the principal investigator. Records will be destroyed after that time by the principal investigator.

7.11 Study Monitoring

The PI is responsible for monitoring the data and conducting performance and safety reviews, at the specified frequency. Either the PI or the IRB have the authority to stop or modify the study. The monitoring by the IRB will occur annually at the time of re-approval. The PI will conduct data and safety review at least quarterly and at any time a serious adverse event occurs. During the review process, the PI will evaluate whether the study should continue unchanged, requires modification or amendment to continue, or should discontinue enrollment.

7.12 Data Safety Monitoring Plan

a. What is the investigator's assessment of the overall risk level for subjects participating in this study? The risks associated with participating in this study can be categorized as minimal (i.e., risks are commensurate with everyday risks associated with chronic pain and data have adequate protection for maintaining confidentiality).

b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A

c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safetymonitoring-plans-templates for Minimal risk

ii. Minimal Risk

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews every month. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator, the Institutional Review Board (IRB) or the funding agency, DOD have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular study meetings, The protocol's research monitor(s), e.g., study sponsors, funding and regulatory agencies, and regulatory and decision-making bodies will be informed of adverse events within 5 days of the event becoming known to the principal investigator.

d. For multi-site studies for which the Yale PI serves as the lead investigator:

i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? Given that no other site (Connecticut Children's Hospital or The Hospital of Sick Children) will be recruiting/enrolling participants, there is no possibility for adverse events or unanticipated events from those sites. With regarding any reviewing or managed data only the Hospital of Sick Children will have managing data. Any unanticipated problem will be reported to the PI (Dr. Frank Buono), within 24 hours and Dr. Buono, will report any serious risk to the appropriate organization (e.g. Army HRPO, Yale IRB).

ii. What provisions are in place for management of interim results? NA

7.13 Study Modification

All modifications will have to be approved by the Yale IRB and the funding agency, DOD processes. Any updates or changes will be identified through track changes and highlighted for the IRB committees.

7.14 Study Discontinuation

N/A

7.15 Study Completion

The proposed research study should be completed by 8-15-22. The PI will report to the IRB through the IRES portal when the study is complete.

7.16 Conflict of Interest Management Plan

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the IRB with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All investigators will follow the applicable conflict of interest policies.

7.17 Funding Source

Salary support for this study is provided by the U.S. Army Medical Research Materiel Command endorsed by the U.S. Army, through the Congressionally Directed Medical Research Programs' Neurofibromatosis Research Program under Award No. W81XWH-19-1-0618.

7.18 Publication Plan

The intent is to publish the findings of the current study. The funding agency Department of Defense will require the following statement:

"This work was supported by the U.S. Army Medical Research Materiel Command endorsed by the U.S. Army, through the Congressionally Directed Medical Research Programs' Neurofibromatosis Research Program under Award No. W81XWH-19-1-0618."

Frank Buono will have primary responsibility for publishing the study results as he is the PI.

Appendices

Appendix #	Title	Section	Topic
1	Flow chart	Synopsis	Study Flow Chart (optional)
2		6 Methods	6.1.2 Method of Assignment/Randomization
3		6 Methods	6.1.3 Selection of Instruments/Outcome Measures
4		6 Methods	6.2.2 Safety/Pregnancy-related Procedure

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