STUDY TITLE:
A Pilot Trial of Audio-Visual Relaxation Techniques for Pediatric Amplified Musculoskeletal Pain Syndrome

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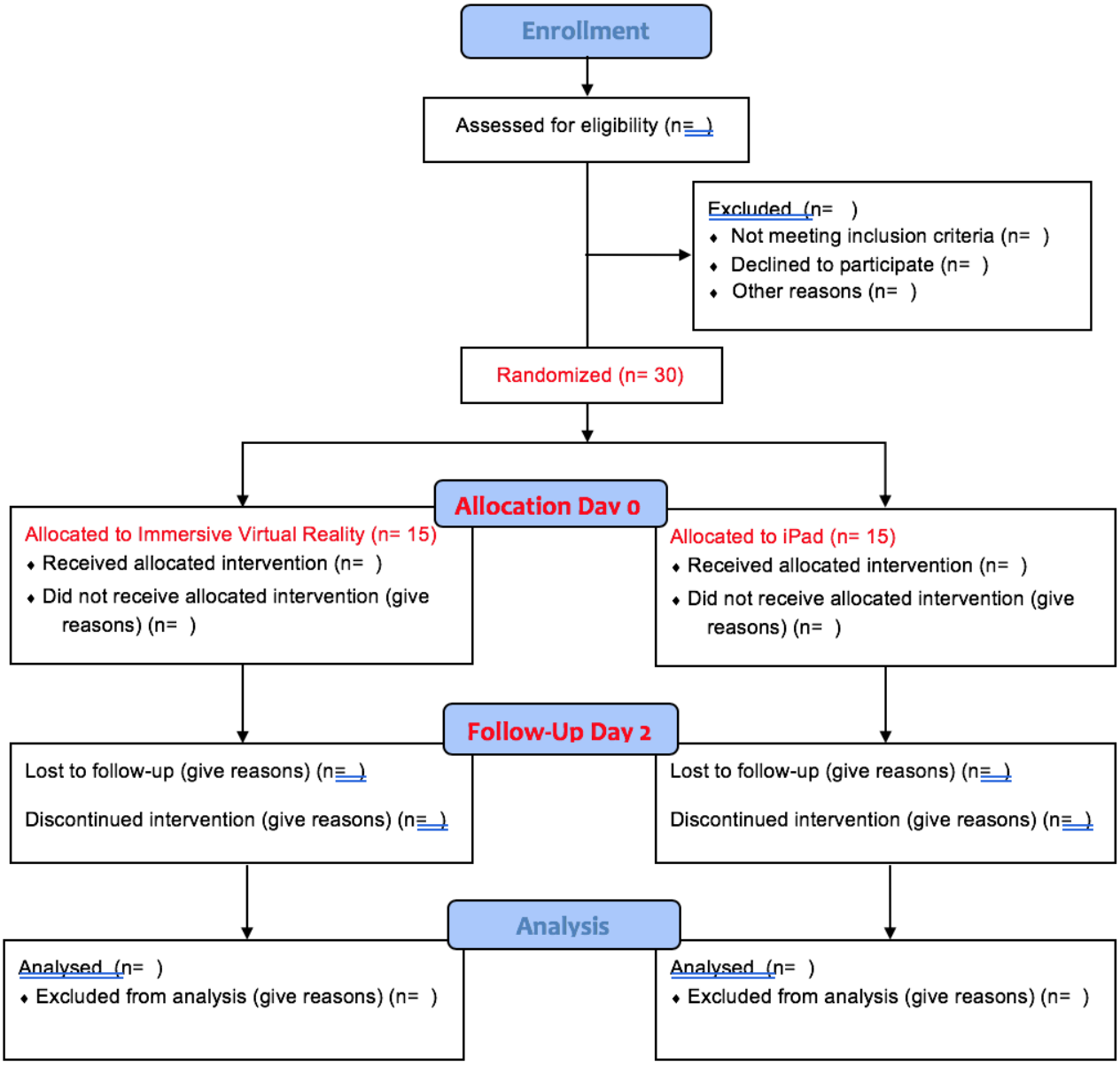
CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



2. Introduction

2.1 Background and Rationale

2.1.1 Impact of AMPS on the health of individuals and healthcare system:

One in every four adolescent experiences chronic pain (1), which is defined as recurrent or persistent pain for more than three months (2). Chronic musculoskeletal pain is prevalent in children and adolescents and increasingly being recognized as a public health concern (1,3,4).

Amplified Musculoskeletal Pain Syndrome (AMPS) is a pain syndrome with excessive musculoskeletal pain without a primary organic etiology. This includes Complex Regional Pain Syndrome (CRPS), localized and diffuse amplified musculoskeletal pain syndromes, the latter also called as Juvenile Fibromyalgia Syndrome (JFS). Prevalence of JFS in children is as high as 7.5% (5) with higher rates of depression (5, 6), lower quality of life (6) and greater school absenteeism, while parents suffer financial, social, and psychological consequences (1, 7).

The cost of care for adolescents with chronic pain without rheumatic diseases is almost three times as high as those with rheumatic diseases (7). The total costs to society for adolescents with chronic pain are estimated to be $19.5 billion annually in the United States (8). Adolescents with chronic pain have a higher likelihood to transition into adults with chronic pain (9, 10), which is one of the costliest conditions in the modern western society (7) with the annual costs greater than heart disease and nearly 30 percent higher than the combined cost of cancer and diabetes (11).

Adolescents with AMPS have considerably higher level of disability than those with juvenile idiopathic arthritis (36, 37, 38). The monetary costs of AMPS are significant even before the diagnosis is made as there is a long diagnostic delay close to a year (36). Across tertiary care pain centers in the US, the mean annual cost of caring for a child with persistent pain is estimated to be $11,787 comparable to Attention Deficit Hyperactivity Disorder (8). Many pediatric rheumatologists believe they are seeing increasing numbers of children with AMPS in the past two decades, although this may represent a recall bias (39). Further investigation into novel treatment regimens for pediatric AMPS is needed to replace or act as adjunctive options to relieve pain, improve function and reduce its overall socioeconomic burden.

2.1.2 Critical gaps between AMPS treatment plan and implementation:

A multimodal approach including cognitive behavioral therapy (CBT), aerobic and neuromuscular exercise with improving sleep hygiene and family functioning is the standard of care for AMPS patients (12). Most of these recommendations are founded on clinical experience only, with the most robust efficacy data for CBT pain coping skills. Recent evidence suggests that CBT pain coping skills training has a significant, although modest and potentially only short-term effect, in reducing pain and disability for youth with chronic musculoskeletal pain (13).

Furthermore, there are critical gaps between the treatment plan and implementation as these multicomponent treatment regimens are difficult to coordinate, often expensive, not fully reimbursed by insurance companies, and poorly accepted by many families. One study reported only 54% of families pursued any aspect of the recommended treatment plan and CBT interventions were pursued by less than 25% of the patients (14). Surprisingly 25% of adolescent AMPS patients receive an opioid and another quarter are treated with polypharmacy (15). AMPS patients become increasingly medicalized every year, resulting in unnecessary medical costs and an increased risk of iatrogenic injury (16). Poor availability of psychological and non-pharmacological services and treatments have been suggested as potential reasons for this unwarranted opioid exposure to the youth (15).

2.1.3 Evolution of Virtual Reality as acceptable tool to treat acute pain in children:

Virtual Reality (VR) is a state-of-the-art technology that consists of elements including a computer-generated virtual world, immersion, sensory feedback and interactivity (17). VR technology is a rapidly evolving field with an immense potential of use in medicine especially in pain-medicine. Hoffman in 1996 was the first to report that VR could alleviate pain perception during painful burn care in adolescent patients (40). The past two decades have seen

the evolution of VR to become an acceptable, safe and effective tool to provide analgesia for acute painful procedures in children and adults alike. At present, there are 8 randomized controlled trials reporting the efficacy and safety of Immersive VR using a Head Mounted Device (HMD) in children and adolescents undergoing burn care, wound care, venipuncture and dental care (41-48). In addition to patient-reported subjective pain outcomes, there is evidence from neuroimaging studies reporting VR distraction alone significantly reduced pain-related brain activity in the pain matrix (insula, thalamus, and secondary somatosensory cortex) comparable to opioids for acute pain (49).

2.1.4 Emerging evidence for use of VR for chronic pain in adults:
The application of VR for chronic pain is fairly recent. The first application of VR for a chronic painful condition was reported by Leibovici in 2009 for chronic pruritus (50) and the first mention of Virtual Reality as a potential intervention for fibromyalgia appeared in the scientific literature in 2010 by Ramchandran (25). Since then VR technology has been successfully applied for chronic neuropathic pain (19), phantom limb pain (20), CRPS (21, 22), chronic neck pain (23, 24) and fibromyalgia patients (25, 26, 27, 28, 29, 30, 31, 32, 33, 34). Small sample sizes, non-immersive VR applications, and lack of a control group limits most of these studies. There is one RCT (reference) reporting immersive VR as an intervention for chronic musculoskeletal pain. The literature is wholly absent on the use of VR for diffuse amplified musculoskeletal pain in children or adolescents.

Early acceptability and efficacy studies for Fibromyalgia patients emerged from Spain starting 2013 (28, 29). The first RCT evaluating efficacy of a projector-based VR intervention in adult fibromyalgia patients was published in 2015 which reported improved disability and quality of life in the intervention arm (30). The same year a proof of concept study reported that exposing patients with fibromyalgia to visuals of exercises elicited neurophysiological changes in functional brain areas associated with pain catastrophizing (27). More recent studies in adult chronic pain patients report the use of immersive VR that uses a Head Mounted Display showing promise for acceptability, safety and efficacy to reduce pain in the immediate period (31, 32, 33). However, they are limited by potential sources of bias and lack of a control group.

2.1.5 Dearth of literature for the use of Virtual Reality for pediatric chronic pain:
Our systematic review of literature of VR for chronic pain in pediatric patients found only two small studies (51, 52), first in chronic headaches (n=10) and the other in Reflex Sympathetic Dystrophy (n=4). We didn't find any published study on the use of VR for diffuse amplified musculoskeletal pain in children or adolescents.

2.1.6 Distraction as a potential mechanism of action for acute pain relief:
Our understanding of the potential mechanism of analgesia produced by VR is considered as key to its utilization for chronic pain (18, 53, 54, 55). The most well studied mechanism for acute pain management is active distraction. VR is thought to be more effective than traditional methods of distraction because of the qualities of immersion and presence in engaging central attention resources. 'Immersion' is an objective term that describes the amount of sensory input the VR system creates. 'Presence' is a subjective value of the illusion one experiences when using the system. While separate values, an increase in immersion often leads to an increase in presence felt by the user (17, 56, 57). Strong evidence has also shown that the quality of VR, the amount of immersion, and interactivity directly correlates with the measured quantity of analgesic effect (17, 40, 48, 58, 59). What remains unknown to date is whether VR-induced distraction is effective for pediatric AMPS patients even transiently.

2.1.7 Impact of Virtual Reality at point of care for AMPS patients via distraction:
AMPS can be a very painful condition and the mean pain score has been reported as high as 6.5 on a 0-10 visual analog scale in this population (36). Patients experience periods of extreme discomfort and disability, which has psychological and economic consequences for both patients and parents. AMPS patients presenting to primary care and pediatric emergency department with extreme body pain and inability to walk often leads to hospitalizations. If VR is shown to be an effective analgesic modality leading to immediate improvement in perceived pain in this population, its implications at the point of care could be far-reaching. In addition, it could be utilized as an adjunct to the often painful desensitization physical therapy. Repeated VR sessions in which a person with persistent pain is exposed to a highly engaging virtual environment has been suggested to build confidence in one's ability to use

distraction for pain (54). It might also provide a novel option for AMPS patients who fail to respond to conventional treatment such as CBT (54).

2.1.8 Non-Distraction mechanisms for VR: Innovation and potential for improvement with research:
Evidence around non-distraction mechanisms for application of VR for chronic pain is in its infancy. The hope is that it will produce lasting benefits on pain control even when the patient is not actively using a VR device. These hypothesized mechanisms include self-control over pain (35, 51), targeting catastrophizing via exposure (26, 27), mirror visual feedback (21, 25), and promoting motivation for movement and positive emotions (28, 29, 30).

Pain catastrophizing is a cognitive strategy broadly defined as "an exaggerated negative orientation towards actual or anticipated pain experiences that significantly contributes to the maintenance of pain" (26). The ability to transition from visuals representing feelings of pain in the virtual world to visuals representing feelings of calm, comfort and happiness has been shown to enhance self-efficacy in controlling pain and decrease pain catastrophism as compared to distraction only (35).

It is worth noting that greater perceived coping efficacy and less catastrophizing to cope with pain is associated with better health outcomes in pediatric AMPS patients with lower levels of pain, functional disability, and psychological impairment (60). Pain catastrophizing has been suggested as a potential target in fibromyalgia patients by the use of VR exposure therapy similar to its use for phobias of spiders and flying (61, 62, 63). It is hypothesized that reducing catastrophizing will lead to reduced fear of movement and increased compliance with exercise therapy. Along these lines, Gromala et al. (65) and Arceneaux et al. (64) have used VR to help patients cope with pain that can occur during walking.

In Conversion Disorder a person experiences blindness, paralysis, or other symptoms affecting the nervous system that cannot be explained solely by a physical illness or injury. Conversion symptoms can be seen in AMPS patients. VR technology has been shown to simulate movement of specific body parts that the patient is unable to control or avoids using (66). AMPS patients with conversion gaits and limb paralysis could potentially benefit from this VR functionality.

Finally, VR has been reported as a means to promote positive emotions, motivation and education (28, 29, 30). It is a strategy not meant to treat pain directly, but instead to overcome one of the obstacles that can hurt the treatment effectiveness of patients with chronic pain syndromes. It is known that the optimal outcomes in AMPS patients is often contingent in large part on the degree to which patients understand and implement appropriate self-management strategies (12). VR has been envisioned as a "pain-coach" standardizing the presentation of information and education around pain processing and behavior in form of providing a common application using images, instructions, and sounds (54). Once patients have achieved enhanced pain control via a combined VR-behavioral intervention protocol, they may be more motivated and more successful with practicing the behavioral intervention on its own in their home environment (54).

What remains unknown is whether immersive VR would reduce pain in adolescents with a chronic pain disorder like AMPS via one or a combination of these mechanisms. Although studying the impact of VR delivered over multiple sessions and collecting cognitive pain measures in pediatric AMPS patients to demonstrate a lasting improvement should be the ultimate goal, the first step is to study the feasibility and acceptability of VR in pediatric AMPS patients. Informed by the emerging evidence for potential mechanism of action of VR for chronic pain, we propose this pilot trial using a VR application that is immersive and would promote positive emotions in AMPS patients.

2.1.9 Choice of VR Intervention for a pilot trial in AMPS subjects:
It is important to realize that children and adolescents with AMPS are characterized by being in chronic disabling pain with a significant impact on their emotional, physical and social wellness. The use of a novel application like VR warrants a delicate balance between sufficient level of immersion without any risk of creating negative emotions in this patient population. Gromala has published a series of recommended best-practices laying out a framework for adoption of VR in clinical practice, creating therapy applications or technology (67). Extrapolating from these

guidelines, we did a search of publicly and commercially available VR applications and found most of them unfit for the pediatric population with AMPS. Some of the reasons were being non-immersive (projector-based VR), posing a risk of creating negative emotions such as over stimulation, nausea, or a sense of failure, and finally being hard to learn, requiring too much setup (hand, head trackers) or complex interactions not likely tolerated by an adolescent in pain.

We found Happy Place to be the only publicly available application with an explicit intent to be used for chronic pain patients (68). It distracts the user from real world and real body by maximizing presence but has a low risk of inducing negative emotion. In fact, it is intended to promote positive effects such as relaxation, calmness and feeling of awe and wonder. It is easy to use and has a flat version for screen use.

2.2 Risks to Subjects:

Immersive VR has been found to be very safe in randomized controlled trials for acute pain in children. Usually, there are no side-effects. Potential side effects may include nausea, vomiting and dizziness. Attached with the protocol is a table summarizing the adverse events in the eight RCTs studying immersive VR in the pediatric population published till date. In 6 out of these 8 trials there were no side effects reported. In 2 studies, 5% and 16% of the subjects experienced mild nausea. Apart from nausea there are no other side-effects reported from a brief use of immersive VR in the under 18-year-old age group in the published literature.

The safety manual of the device Oculus GO which we will use for this trial, mentions that 1 in 4000 children may have seizures, eye or muscle twitching or blackouts triggered by light flashes or patterns, even if they did not have a history of seizure-disorder. Thus, subjects with history of seizures, motion sickness, severe headaches with contraindication to the use of visual exposures to stimuli will be excluded.

2.3 Potential Benefits to Subjects:

There is no direct benefit from participation in this study. AMPS subjects participating in this study might experience pain relief for a variable period of time from the use of immersive VR. It might enhance their pain coping skills, improve self-efficacy to manage pain and reduce pain catastrophizing.

If VR is shown to reduce chronic pain in the immediate period, the implications for the AMPS population could be far-reaching. It might provide transient analgesia for AMPS patients during desensitization physical therapy and also in the emergency room when they present with chronic pain exacerbation. The integration of VR as a non-pharmacological intervention in the management of AMPS patients could help avoid unnecessary and potentially harmful opioids and provide another treatment option for non-responders to standard of care. Finally, if VR is shown to enhance self-efficacy in managing pain, AMPS patients can be more successful in self managing their pain in their home environment.

2.4 Alternatives

Participation in this research study is completely voluntary. If the subjects choose not to participate, they will continue to get standard of care treatment for AMPS. Non-participation in the study will not affect their management in any way.

Standard of care for AMPS includes desensitization physical therapy, cognitive behavioral therapy, aerobic exercise and sleep hygiene.

The VR device, Oculus GO and the application ‘Happy Place’ are available outside the research setting as well if the subjects wish to continue using them after participation in the study. Oculus GO costs $199 at the time of writing this protocol, and ‘Happy Place’ is a free application.

3 Objectives:

The overarching research aim for this pilot trial is to collect feasibility data and other clinical estimates in preparation for a full scale adequately powered RCT to determine the effect of Virtual Reality on pediatric AMPS. As a pilot trial, the purpose is to evaluate the feasibility of trial processes, establish realistic milestones for completing trial enrollment, and estimate unknown parameters needed to design the large trial. We propose this pilot trial to address whether conducting a definitive RCT using Virtual Reality for pediatric AMPS is an appropriate trial design and whether it is feasible with regard to 1) subject recruitment and data collection, 2) subject and parent acceptability of the intervention and control arms, 3) adherence to protocol. In addition, we wish to obtain estimates of the variance of the primary and secondary outcomes in the intervention and control arms required to design a definitive RCT.

The primary objectives of this trial are as follows:

1. **To assess recruitment potential:** how many pediatric AMPS subjects were found eligible out of those screened within the trial period (eligibility rate) and out of these eligible subjects how many choose to participate in the trial (consent rate).

2. **To investigate the acceptability of intervention (Virtual Reality) and control (iPad) to pediatric AMPS subjects and their parents** by using a mixed-method questionnaire (both quantitative and qualitative questions).

3. **To measure key outcome domains** for completion rates, missing data, estimates, variance (means, standard deviation and 95% confidence intervals for the differences between the intervention and control groups) for primary and secondary outcome measures for pediatric AMPS subjects (this data synthesis will inform the sample size of a definitive trial).

    - The primary outcome of a definitive RCT will be subject pain intensity reported on the Visual Analog Scale (VAS) (73). The secondary outcomes include pain catastrophizing reported on Pain Catastrophizing Scale - Children (PCS-C) (71) and subject's self-efficacy to manage pain reported on the Self-Efficacy Scale for Child Functioning (SES-C) (72).

The secondary objectives of the trial are as follows:

1. **To assess eligibility criteria** by determining whether the eligibility criteria for inclusion in the trial are too open or too restrictive by estimating feasible eligibility (number of pediatric AMPS patients not eligible) and the reasons for ineligibility.

2. **To assess response of subjects** by estimating the completion rate of outcome measure questionnaires on day 2 after the study visit in the intervention and control groups.

3. **To explore the trial design** by studying the logistics of blinding, randomization, adherence to protocol and data collection on REDCap.

We hope that the results of this pilot trial will help address these areas of uncertainty before a future definitive RCT can take place. The decision to proceed with a future definitive trial is dependent on successful recruitment, randomization within the planned time window, successful use of Virtual Reality and an adequate response rate from AMPS subjects. This proposal is informed by and based on the CONSORT 2010 statement: extension to randomized pilot and feasibility trials (reference). Thus, the primary focus of this pilot trial is not hypothesis-driven testing of efficacy or effectiveness but to assess feasibility of conducting a future definitive RCT.

This proposal is innovative because it explores a new non-pharmacological intervention for AMPS. It is significant because the results of a future larger RCT based on this pilot trial has the potential to change clinical practice for patients with AMPS. It is necessary because there are no other studies studying Virtual Reality to reduce pain in pediatric AMPS population.

4 Enrollment and Withdrawal

4.1 Inclusion Criteria

1. Age between 13 years and 17 years old (inclusive) at the time of consent.
    - Younger children's heads will likely be too small to use the VR headset (70) and 17 is the upper age limit for the definition of pediatric population.
2. A primary diagnosis of AMPS including CRPS (complex regional pain syndrome), or localized or diffuse amplified pain syndrome (as determined by the investigating pediatric rheumatologist).

4.2 Exclusion Criteria

1. An underlying organic cause can explain the pain including inflammatory, infectious, traumatic or malignant etiologies.
2. A history of motion sickness, underlying epilepsy, severe headaches or other conditions where the use of visual exposures to stimuli is contraindicated.
3. Inability to report a pain score and/or incapacity to give assent due to intellectual deficit.
4. Blind subjects.
5. Non-English-speaking subjects will be excluded due to the unavailability of the content of the VR application used in this study in languages other than English.
6. Any other condition that the investigators think can compromise the integrity of the study or subject safety.

- Study subjects may participate in another research study while participating in this research study.

4.3 Withdrawal of Subjects

- If a subject develops severe nausea or vomiting or severe headache or dizziness, he or she will be withdrawn from the research without their consent.

4.4 Recruitment and Retention

4.4.1 Local Recruitment Methods

4.4.1.1 Study Sites:

The study will be carried out in the pediatric rheumatology clinic situated at the 4th Floor of Floating Hospital for Children and Tufts affiliated pediatric rheumatology satellite clinics in Woburn, Lawrence, Brockton and Chelmsford. The setting of these interventions will be in a private clinic room at one of the sites.

For the Tufts affiliated satellite clinics, the pediatric rheumatology clinic space will be used for the purpose of this study. These institutions will not be engaged in research or data transfer.

4.4.1.2 Recruitment Sites:

Subjects will be recruited from the pediatric AMPS population seeking care at Tufts Medical Center. Subjects will be identified through recruitment strategies employed at the pediatric rheumatology clinic in Boston and the Tufts affiliated pediatric rheumatology satellite clinics in Woburn, Lawrence, Brockton and Chelmsford.

4.4.1.3 Recruitment Strategies:

Subjects will be recruited during clinic interactions and through identification in the EMR by ICD searches.

4.4.1.3.1 Clinic interactions:

A screening sheet will be designed to assess eligibility as determined by the inclusion and exclusion criteria (see appendix). This will be used by the investigators (TD, YZ, SJ) to identify eligible subjects during

routine clinic interactions. The investigators will use a study introduction sheet to explain the purpose of the trial briefly to potential subjects and their parents.

Medical record numbers of eligible and interested subjects will be shared with one of the investigators (SJ) during the weekly departmental meetings (every Wednesday and alternate Fridays).

This co-investigator (SJ) will then follow up with these eligible and interested subjects by telephone or email. A pre-defined script will be used for email and voicemail (see appendix). For over the phone conversation, we will use the study introduction sheet (see appendix). Attempts to contact potential subjects via email and telephone will be limited to a total of three attempts one week apart.

4.4.1.3.2 EMR ICD Search:
We will utilize the CTSI's HER Chart Abstract Services to identify eligible subjects with the following ICD-10 codes (G89.0, G89.4, G90.50, G90.59, G90.511, G90.512, G90.513, G90.519, G90.521, G90.522, G90.523, G90.529). This search would be limited to identifying potential subjects seen at Tufts or Tufts affiliated pediatric rheumatology clinic one year prior to trial commencement. All eligible subjects will be approached telephonically or via email if available and invited to participate in the study. Once again, the study introduction sheet will be used to explain the purpose of this research.

4.4.1.3.3 Screening Log:
A screening log will be maintained tracking all the pediatric AMPS patients who are screened and those who were found eligible. For ineligible subjects, the reason for ineligibility will be reported. The screen failure data will only be retained until the manuscript is written (~March 2020). This data will be used to assess the eligibility rate. In addition, this log will maintain a list of consented subjects.

4.4.1.4 Scheduling the Study Visit:
Subjects will be able to choose a date for the study visit in advance. For practical considerations, we will offer the subjects and their families to choose a study visit day from three working days of a week (Tuesday, Thursday or Friday). The only exception will be eligible subjects presenting to Boston clinic on Thursday. If they agree to participate in the study the same day, they will be allowed to do that. One of the co-investigators (SJ) will travel to the satellite clinics for consenting and study interventions if subjects are not able to travel to the study site in Boston.

4.4.2 Study-Wide Recruitment Methods

Is this a multicenter study where subjects will be recruited by methods not under the control of the local Tufts site (e.g., call centers, national advertisements)?

NO

4.4.3 Payment

Will subjects receive money, gifts, or any other incentive for participating in this study?
This does not include reimbursement for expenses, which is considered in the next section.
NO

4.4.4 Reimbursement

Will subjects be reimbursed for their expenses, such as travel, parking, meals, or any other study related costs?
NO

5 Study Design

5.1 Study Timelines

The study will run from April 2018 (panning phase) to March 2020 (appendix) with the data collection to commence in ~January 2019 and be completed by ~December 2019.

5.2 Procedures

The proposed project is a Randomized Controlled Pilot Trial using VR as an intervention for perceived pain in AMPS patients in the immediate period. There are two arms in this study. The subjects in the intervention arm will be using a brief immersive VR experience "Happy Place" (68) delivered via a stand-alone head mounted device, Oculus GO (69). The control subject will watch the same content without the immersive VR on an Apple Tablet (iPad) for the same duration.

5.2.1 Study Procedure and Self-reported Forms:

One co-investigator (SJ) will be responsible for study procedures. Following informed consent, questions assessing baseline characteristics and pre-intervention pain measures (VAS, PCS-C, SES-C) will be administered to each participant (please see appendix: Data Capture and Data Capture 2). After these baseline characteristics have been obtained, the participants will be randomized to the intervention (VR) and control (iPad) groups. The participants in the intervention arm will receive an immersive VR experience "Happy Place" promoting positive emotions delivered via a stand-alone head mounted devise, Oculus GO for a total duration of 10 minutes. The participants in the control group will watch the same experience on an Apple Tablet for the same duration. The participant may only be accompanied by the parents. The participant in the VR arm will be given some time to get familiar with the equipment before starting the intervention. *Pain measures (namely the VAS, PCS-C and SES-C) will then be administered after the relaxation session for each participant (please see appendix, Data Capture 2). In addition, the participants will get quantitative and qualitative questionnaires assessing feasibility and acceptability (Data Capture 3). Finally, participants would be asked to report VAS, PCS-C and SES-C measures two days after the study day in both groups via an email sent using REDCap (Data Capture 2).*

5.2.2 The Equipment:

Oculus GO will be used as the VR equipment which is a stand-alone consumer-grade head-mount display (HMD). The HMD is placed on the head of the user, blocking off the surrounding environment. The visuals and audio are relayed through the HMD in a virtual space. An Apple iPad will be used for controls.

5.2.3 The VR/iPad Content:

The content will be the application Happy Place created by agency Wenderfalck as a joint venture between Sweden's largest private pharmacy, Apotek Hjärtat and VR therapy startup Mimerse. It aims to distract subjects from their pain with a peaceful and interactive environment. The scene is a serene lakeside campground, and guided relaxation and soothing music is optional. Although MPAA rating for this content is not available it is estimated to be rated "G". Happy Place is a publicly available application with an explicit intent to be used for chronic pain subjects. It distracts the user from real world and real body by maximizing presence but has a low risk of inducing negative emotion. In fact, it is intended to promote positive effects such as relaxation, calmness and feeling of awe and won-der. It is easy to use in the immersive VR environment and on the flat screen. Happy Place uses an innovative 'gaze-based interaction' with the virtual world. Around 50 "gaze objects" are placed around the scene and gazing at them would enable a timer following which an event is triggered. It is up to the user to figure out and explore through trial and error which objects trigger events.

The control subjects will watch the same content for the same duration on an iPad screen. This experience will be different from the intervention subjects in two ways: 1) Lack of an immersive environment, 2) Lack of interactivity with the environment.

5.2.4 Duration of Content:

The entire duration of the experience can be adjusted by running the application as a loop but will be kept at 10 mins for the purpose of this study in both the groups. This is based on previous studies using HMD immersive VR for chronic pain subjects (32, 67) and also the mean duration of use of this application in the chronic pain population reported by the developers.

5.3 Evaluations

Will you perform any laboratory tests for this study?

NO

5.4 Collection and Storage of Human Biological Specimens (Tissue Banking)

Will biological specimens be stored for **future, unspecified**, research?

NO

6 Ethics and Protection of Human Subjects

6.1 Informed Consent Process

Will subjects be required to provide informed consent?

☑ **Yes** ☐ **No**

- After eligibility is determined, informed consent from the parents or legally authorized caregivers and assent from the child will be obtained (see appendix).
- One co-investigator (SJ) will be responsible for consenting eligible subjects.
- Consent and assent will be obtained in a private clinic room.
- We will follow the SOP: Informed Consent Process for Research (HRP-090).
- We will follow SOP: Written Documentation of Consent (HRP-091)
- We will exclude Non-English-speaking subjects due to the lack of availability of the content of the intervention in languages others than English.

6.2 Waiver or Alteration of Consent Process

This applies for studies where informed consent will not be obtained, required information will not be disclosed, or the research involves deception.

- Is a waiver or alteration of the consent process being requested for this study?
  Yes. Waiver of consent is needed for the access of medical record for screening prior to signing the ICF.
- Is a waiver of the consent process being requested for parents for research involving children?

  NO
- Is a waiver of the consent process for planned emergency research being requested?
  No

6.3 International Research N/A

6.4 Confidentiality

The co-investigators will code all subject samples with a unique study id number. Only three co-investigators (TD, YZ, SJ) screening patients in the clinics will access to this list saved as an Excel sheet and be able to link code number to subject name. This Excel sheet will be stored on a TMC drive in a folder protected behind TMC Firewall and accessible only to these three co-investigators via a secure TMC login.

Study data are to be collected and managed using the Research Electronic Data Capture (REDCap) electronic data capture system. Participants will be entering their own data. This will be achieved using REDCap's functionality to send a clickable link to subject's email address, which will open up the questionnaires. On submission of the questionnaires, the data will be sent and securely saved in REDCap.

For those who choose to answer the qualitative questionnaires on paper, one of the co-investigators (SJ) will subsequently enter the data into REDCap. HIPAA identifiers collected through REDCap will be limited to email address and date of birth.

Consent / assent forms and paper qualitative questionnaires will be stored in a locked cabinet in a locked office (pediatric rheumatology fellow's office). Data will be exported from REDCap database into statistical software for analysis. Additionally, REDCap has an audit trail that records every time changes are made to any data entered on the website.

The signed and dated ICFs, child-assent forms and research data collected in this study will be maintained for a minimum of 7 years after the study has been closed out in the IRB office. The screen failure data will only be maintained until the end of the study (~March, 2020).

6.5 Provisions to Protect the Privacy Interests of Subjects

- Only one co-investigator will be responsible for obtaining informed consent, assent and carrying out the study procedures. This will limit the number of individuals obtaining private information.

6.6 Provisions to Monitor the Study to Ensure the Safety of Subjects

Immersive virtual reality is very safe and typically does not result in any adverse events. The investigators will monitor the subjects for known side effects like nausea, headache and dizziness during the intervention. The intervention will be stopped in the setting of severe nausea, vomiting, severe headache or dizziness.

6.7 Compensation for Research-Related Injury

Does the research involve greater than minimal risk to subjects? (or if minimal risk, is there potential risk of research-related injury?):

NO

6.8 Economic Burden to Subjects

Does the research involve any costs to subjects?
NO

6.10 Vulnerable Populations

If the research involves individuals who are vulnerable to coercion or undue influence, describe the rationale for their inclusion and the additional safeguards included to protect their rights and welfare.

Will pregnant women be enrolled?
NO

Will the research involve neonates of uncertain viability or non-viable neonates?
NO

Will subjects who are not yet adults (neonates, children, teenagers) be enrolled?
YES.

We would use an informed-consent form for the parents or legal guardians.
Eligible subjects contacted over the phone or email will have adequate time to between study introduction and obtaining the assent.
Subjects found eligible in clinic will be explained the study on the same day. If they are interested, they will have the option to participate the same day or return at a later date.
Since it is a one-time intervention with a brief follow up survey on day 2 after the procedures, we believe the assent obtained at the start of the study should suffice.
Children enrolled as subjects will participate on the day of the intervention and then fill up a survey on day 2 after the participation.
We will ensure to emphasize in an age appropriate language that the participation in the study is entirely optional and will in no way affect the medical care (please see assent attached).

Will minors who are:

i) married, widowed, divorced; or
ii) the parent of a child; or
iii) a member of any of the armed forces; or
iv) pregnant or believes herself to be pregnant; or
v) living separate and apart from his/her parent or legal guardian, and is managing his/her own financial affairs

be approached for study participation for either themselves or their child?
NO

Will wards of the state and/or children at risk of becoming wards of the state be enrolled (this includes foster children or any child that is in state custody)?
NO

Will cognitively impaired adults (adults with impaired-decision making capacity) or adults who may lose the capacity to consent be enrolled?
NO

Will prisoners be enrolled?
NO

Will students and/or employees be enrolled in this research?
NO

7 Adverse Event Monitoring

7.1 Definitions:

- Following would be considered as adverse events (AEs), for the purpose of this study:
  - Severe nausea: reported by the subject as greater than equal to 70 on a 0 -100
  - Vomiting
  - Severe headaches: reported by the subject as greater than equal to 70 on a 0 -100
  - Severe dizziness: reported by the subject as greater than equal to 70 on a 0 -100

7.2 Reporting Procedures:

All unanticipated AEs will be reported to IRB under Title 21 of the Code of Federal Regulations (21 CFR) part 56 (Institutional Review Boards).

7.3 Reportable New Information:

Reportable new information will be reported to the IRB per the Tufts Health Sciences IRB's Reportable New Information Policy.

8 Statistical Considerations

8.1 Study Endpoints

8.1.2 Description of study outcome for primary and secondary objectives:

The overarching research aim of this pilot trial is to assess feasibility and determine estimates for a future definitive RCT. **We will perform the following measurements to achieve our primary objectives:**

1. **To assess recruitment potential,** we will calculate the following:

- Out of the screened patients, how many eligible subjects were found within the trial period (eligibility rate)
- Out of the eligible subjects, how many choose to participate in the trial (consent rate)

2. **To investigate the acceptability of intervention (Virtual Reality) and control (iPad) to pediatric AMPS subjects and their parents** we will use a mixed-method questionnaire (including both quantitative and qualitative questions, see appendix) after the interventions.

   Quantitative questionnaires in REDCap will assess the following:
   - Prior use of VR, iPad and Happy Place,
   - Degree of immersion and fun experienced during the interventions
   - Side effects (dizziness, nausea, headache) experienced during the interventions

   Qualitative questionnaire will also be REDCap based. Subjects and their parents will be given an option to write their responses on a paper-based questionnaire if they chose otherwise. Questions will be open ended assessing preferences of subjects about their VR or iPad experience, their suggestions for improvement, and willingness to try it in the future in the clinic. The parent/caregiver questionnaire is limited to only two questions (see appendix, 'Data Capture 3'), firstly if they are willing to allow their child to try this technology in the future in the clinic and secondly, if they have any comments on the relaxation session.

3. **To measure key outcome domains for the definitive RCT,** we will calculate completion rates, missing data, rates, variance (means, standard deviation and 95% confidence intervals for the differences between

the intervention and control groups) for primary and secondary outcome measures for pediatric AMPS subjects. This data synthesis will inform the sample size of the definitive trial.

- The primary outcome of a definitive RCT will be subject pain intensity reported on the Visual Analog Scale (VAS) (73). The secondary outcomes include pain catastrophizing reported on Pain Catastrophizing Scale - Children (PCS-C) (71) and subject's self-efficacy to manage pain reported on the Self-Efficacy Scale for Child Functioning (SES-C) (72). These outcomes are described in detail in the next section.
- These three self-reported outcomes are previously validated scales for pain in the adolescent population. They will be administered before and after the intervention or control session for each participant. In addition, these outcome measure will be collected via online questionnaires on day 2 after the study visit in the intervention and control groups.

To assess the secondary objectives, we will measure the following:

1. **To assess eligibility criteria,** we will determine whether the eligibility criteria for inclusion in the trial are too open or too restrictive by estimating feasible eligibility. To measure this, we will calculate the number of pediatric AMPS patients screened but not found eligible for the study, and the reasons for ineligibility.
2. **To assess response rate of subjects** we will estimate the completion rate of outcome measure (VAS, PCS-C and SES-C) questionnaires on day 2 after the study visit in the intervention and control groups.
3. **To explore the trial design,** we will assess the logistics of blinding, randomization, adherence to protocol, potential sources of bias, and data collection on REDCap.

8.2 Statistical Analysis

We will report the results using the template for a CONSORT flow diagram for pilot trials. This would include numbers identified, approached, and recruited. For each group, losses and exclusions after randomization, and numbers analyzed, together with reasons (e.g., subjects' unwillingness to use iPad) will be reported.

A table showing baseline demographics and clinical characteristics of each group will be generated including active medications, psychological co-morbidities, and quality of life score.

Quantitative Data:
The quantitative questions assessing acceptability and feasibility will be described using means and percentages. These would include recruitment rate (consisting of eligibility and consent rates), response rate for questionnaire completion at day 2 after the study, immersion and fun scores, and questions assessing side effects.

Qualitative Data:
The feasibility and acceptability outcomes will also be reported descriptively and narratively in the open-ended questionnaires. The data will be qualitatively analyzed by identification of emerging themes, and reporting subject and parent's quotes verbatim.

Sub-group Analysis and Definitive Trial Sample Size Calculation:
To measure key outcome domains for the definitive RCT, we will report descriptive statistics. This would include calculation of missing data, rates, means, standard deviation and 95% confidence intervals for the differences between the intervention and control groups for primary and secondary outcome measures. There will also be a sub-group analysis for the same domains including only the strata with VAS of more than equal to 4 out of 10. This data synthesis will be more representative of active AMPS and will inform the sample size of the definitive trial.

8.3 Number of Subjects

Since this is a pilot trial, a formal sample size calculation is not performed. We aim to recruit up to 40 participants in order to have a total of 30 subjects to complete the study (15 subjects in each arm). This is based on the estimate of how many subjects the authors can practically enroll within the timeframe of this trial. Cocks (79) have reported a table of recommendations for sample size calculations for pilot trials with a range of 20 (10 subjects per arm) to 55 subjects in total. Our sample size of 30 is within this range.

8.4 Data Management

- Study data are to be collected and managed using the Research Electronic Data Capture (REDCap) electronic data capture system. Participants will be entering their own data. This will be achieved using REDCap's functionality to send a clickable link to subject's email address which will open up the questionnaire (see appendix, 'Script for follow-up survey email'). On submission of the questionnaires, the data will be sent and securely saved in REDCap.
- For those who choose to answer the qualitative questionnaires on paper, one of the co-investigators (SJ) will subsequently enter the data into REDCap. HIPAA identifiers collected through REDCap will be limited to email address and date of birth. Data will be exported from REDCap database into statistical software R Studio for analysis.
- Consent / assent forms and paper qualitative questionnaires will be stored in a locked cabinet in a locked office (pediatric rheumatology fellow's office). Data will be exported from REDCap database into statistical software for analysis. Additionally, REDCap has an audit trail that records every time changes are made to any data entered on the website.

8.5 Randomization

Will subjects be randomized?

YES

Randomization and Allocation Concealment:

We propose a parallel-group randomized controlled pilot-trial with a stratified randomization and an equal allocation ratio of 1:1. After a child-assent and a parent or legal guardian consent has been obtained, the subjects will be randomly allocated into Group A (VR group/intervention group) or Group B (iPad group/control group) using a computer-generated random number sequence constructed by a biostatistician. This allocation will be deployed using standard opaque envelopes containing a pre-generated allocation sequence which is unveiled to the investigator just prior to the intervention. The investigator performing the interventions will not have access to allocation codes.

The randomization will be stratified on the basis of pain score on the day of intervention. Subjects with a pain score of 4 or higher on the 0-10 Visual Analog Scale (VAS) on the day of participation will belong to a stratum and will be subjected to a separate randomization scheme than those who have a score of less than 4. This is based on the mean pain score of 6.5 reported in pediatric AMPS population (1, 36) with the IQR (difference between 75th and 25th percentile) of 4 and 8.5 on a Visual Analog Scale of 0-10. This is to ensure that outcome domains representative of active AMPS are captured to inform the sample size of a future trial at the same time maximizing the benefit of this pilot trial to all interested AMPS subjects.

Blinding:

- In this pilot trial blinding of the subjects completely is not possible as subjects will know the intervention they receive. In order to minimize the subject bias, we will introduce the study as

comparison of two audio-visual relaxation techniques, without using the terms "Virtual Reality" or "iPad". The subjects would not know the modality of use in the other group.

- It is not possible to blind the test administrator either as one of the co-investigators (SJ) will perform the trial interventions. We plan to minimize this bias by having the subjects directly entering the outcomes as digital data in REDCap proof to tempering by the investigators. Only the qualitative questionnaires assessing acceptability and feasibility will be paper-based, if subjects choose that option.
- Finally, the data analyzer (SJ) will be the same co-investigator performing the intervention and thus not blinded to the groups.

9 Drugs or Devices

Will the research involve drugs?

NO

Will the research involve devices?

YES

10 Study Administration

10.1 Setting

The study will be carried out in the pediatric rheumatology clinic situated at the 4th Floor of Floating Hospital for Children and Tufts affiliated pediatric rheumatology satellite clinics in Woburn, Lawrence, Brockton and Chelmsford. The setting of these interventions will be in a private clinic room at one of the sites.

10.2 Registration

A screening sheet will be designed to assess eligibility as determined by the inclusion and exclusion criteria (see appendix). This will be used by the co-investigators (TD, YZ, SJ) to identify eligible subjects during routine clinic interactions. The co-investigators will use a study introduction sheet to explain the purpose of the trial briefly to potential subjects and their parents. The same introduction sheet will be used as a script to introduce the study over the phone for subjects identified through ICD-10 searches.

A screening log (see appendix) will be maintained tracking all the pediatric AMPS patients who are screened and those who were found eligible. For ineligible subjects, the reason for ineligibility will be reported. In addition, this log will maintain a list of consented subjects.

10.3 Resources Available

- Trevor Davis, Yujuan Zhang and Saumya Joshi will be responsible for screening patients presenting to pediatric rheumatology clinics.
- Saumya Joshi will be responsible for screening and contacting patients through ICD-10 searches.
- Saumya Joshi will be responsible for obtaining informed consent, assent and performing the study procedures. He has adequate training and expertise for consenting participants.

- At the pediatric rheumatology clinic at TMC, Boston, we see two new AMPS patients every week on average in addition to follow up visits from AMPS patients. We believe recruiting 30 AMPS patients in one-year period should be feasible.
- We have purchased the VR device for the purpose of the study.
- We have a secure departmental iPad which we plan to use for controls and collection of data on RECDap.
- The pediatric rheumatology departmental weekly meetings (every Wednesday and alternate Fridays) will be used to ensure adequate oversight of the informed consent and assent process, adherence to the study protocol and procedures in addition to reminding all members of the research team about their roles and responsibilities and discussing any emerging side effects.

10.4 IRB Review

- Tufts IRB registered with the OHRP will review and approve this study.
- Any amendments to the protocol or informed consent documents will be reviewed and approved by the IRB prior to use, unless required to eliminate an apparent immediate hazard to subjects.

10.5 Multi-Site Research

Is this a multi-site study where Tufts is the sponsor, primary grant recipient, or coordinating site?:

NO

10.6 Community-Based Participatory Research

Will this study involve community-based participatory research?

NO

10.7 Sharing Results with Subjects

NO

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