Novel web-based, self-directed intervention for chronic pelvic pain

IRB approval: 7/16/2024

Protocol Number: HUM00231526

National Clinical Trial (NCT) Identified Number: NCT06352840

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Principal Investigator*: Sara Till, MD, MPH

Sponsor: University of Michigan

Grant Title: An intervention for chronic pelvic pain

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

This trial will be carried out in accordance with the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812) and research best practices. The PI and all study team members who are responsible for the conduct, management, or oversight of this study will complete Human Subjects Protection training and clinical research best practices.

The protocol, informed consent document, recruitment materials, and all participant materials will be submitted to IRBMED for review and approval. Approval of both the protocol and the consent documents will be obtained before any participant is consented. Any amendment to the protocol will be submitted for review and approval by IRBMED before the changes are implemented to the study. All changes to the consent form(s) will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 7/10/24

Name*: Sara Till, MD, MPH

Title*: Principal Investigator, Assistant Professor of Obstetrics and Gynecology

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1 PROTOCOL SUMMARY

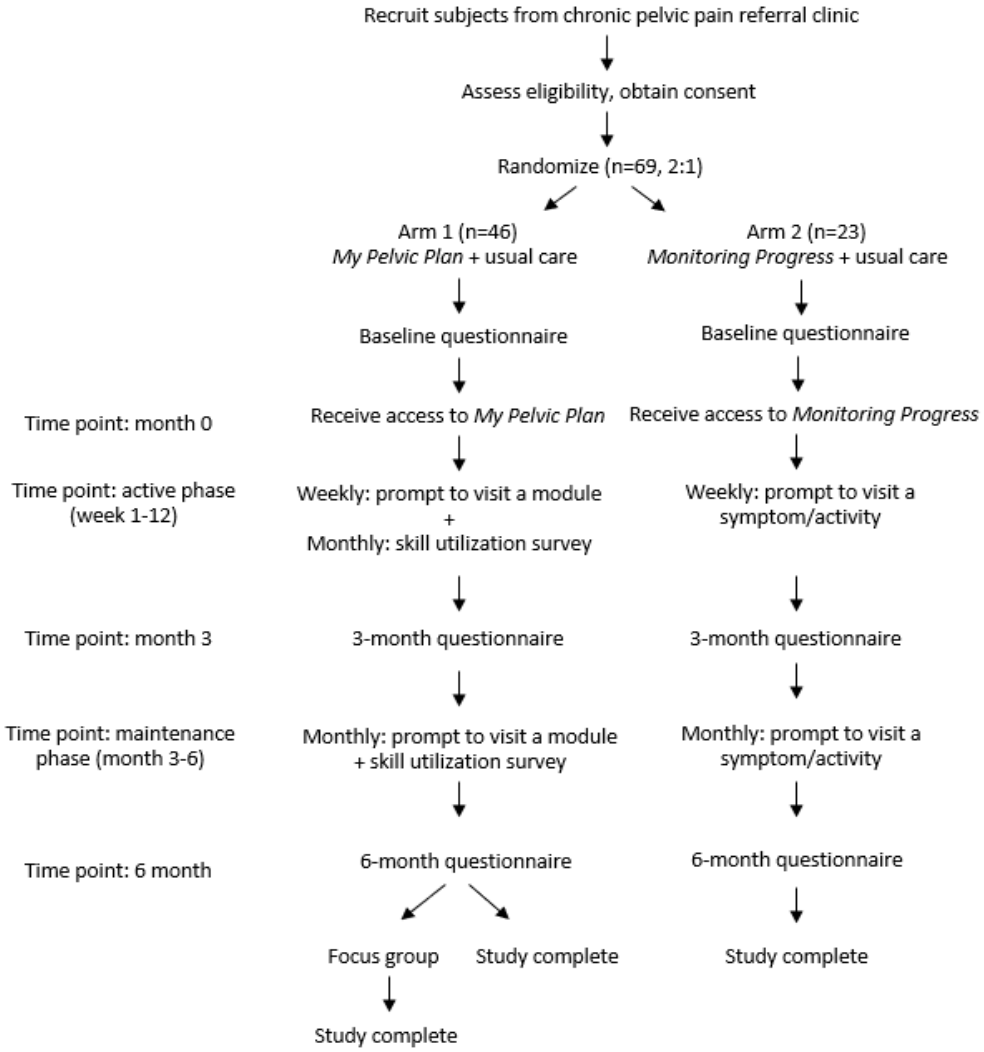
1.1 SYNOPSIS

Title:	Novel web-based, self-directed intervention for chronic pelvic pain
Grant Number:	1K23HD09928301A1
Study Description:	We propose to conduct a pilot randomized controlled trial to evaluate preliminary effectiveness of a web-based, self-management program for patients with CPP and phenotypic factors that predict positive response. Our overall hypothesis is patients with CPP who have access to this novel intervention will demonstrate improved in pain, physical function, and quality of life.
Objectives*:	Primary Objective: - To evaluate effectiveness of the intervention by comparing pain interference among intervention group versus control group following the intervention. Secondary Objectives: - To compare pain intensity among intervention group versus control group. - To compare physical function and health-related self-efficacy among intervention group versus control group.
Endpoints*:	Primary Endpoint: - PROMIS Pain Interference SF 4a at 3 months. Secondary Endpoints: - PROMIS pain intensity from baseline to 3 months. - PROMIS Self Efficacy for Managing Symptoms SF 4a at 3 months
Study Population:	We will recruit 69 women (female sex assigned at birth) with chronic pelvic pain.
Phase* or Stage:	Stage 1 on NIH Stage Model for behavioral interventions
Description of Sites/Facilities Enrolling Participants:	Department of Obstetrics and Gynecology and the Chronic Pain and Fatigue Research Center (CPFRC) at the University of Michigan. Patients will be recruited from the Chronic Pelvic Pain and Endometriosis referral clinic at Michigan Medicine, where our group of specialty-trained gynecologists see approximately 150 patients with CPP every month.

Description of Study Intervention/Experimental Manipulation:	Patients will be randomized (2:1) to participation in a 6-month web-based, integrative self-management program in addition to usual care as determined by the patient's CPP provider (intervention group), or to a web-based symptom monitoring program in addition to usual care (control group). The intervention is comprised of a self-guided program, *My Pelvic Plan*, that combines education on several individual conditions that often contribute to CPP, and will include instruction on cognitive and behavioral restructuring, self-administration of acupressure, engaging in physical activity, and a brief introduction to pelvic floor physical therapy techniques.
Study Duration*:	3 years
Participant Duration:	7 months

1.2 SCHEMA

Flow Diagram



1.3 SCHEDULE OF ACTIVITIES

	Pre-consent	0 month Day 0 ± 14	1 month Day 30 ± 14	2 month Day 60 ± 14	3 month Day 90 ± 14	4 month Day 120 ± 14	5 month Day 150 ± 14	6 month Day 180 ± 14
Review eligibility	x	x						
Consent		x						
Randomization		x			x			
Adverse Event Reporting		x	x	x	x	x	x	x
Intervention								
Access *My Pelvic Plan* (Intervention group)		x	x	x	x	x	x	x
Access *Monitoring Progress* (Control group)		x	x	x	x	x	x	x
Outcome evaluation								
Questionnaire		x			x			x
Current treatment survey		x						x
Utilization survey (Intervention group)			x	x	x	x	x	x
Focus group (n=20, Intervention group)					x			

2 INTRODUCTION

2.1 STUDY RATIONALE

Chronic Pelvic Pain (CPP) is a debilitating problem that afflicts 15-20% of reproductive age women.[1] Pain and suffering often persist despite treatment, and lead to decreased productivity and reduced quality of life.[2,3] The limitations of current surgical and pharmacologic treatments for CPP have been well documented.

One of the most significant clinical challenges in CPP is predicting which treatment is likely to be effective for an individual patient, due in large part to the heterogeneity of CPP. Management of other chronic conditions has improved with development of clinical phenotypes, which help clinicians more quickly match patients with effective treatments. However, clinical phenotypes have not yet been extensively explored in CPP.

We propose to develop a web-based, self-management program for patients with CPP and to conduct a pilot randomized controlled trial to evaluate preliminary effectiveness of the intervention and phenotypic factors that predict positive response. Our overall hypothesis is patients with CPP who receive access to this web-based self-management program, *My Pelvic Plan*, will demonstrate improvements in pain, health-related self-efficacy, physical function, and quality of life with this integrative self-management approach. This project will generate preliminary data to support an R01 application to perform an RCT efficacy trial with a focus on patient phenotyping.

2.2 BACKGROUND

The significant suffering caused by chronic pelvic pain (CPP) leads to multiple surgeries and long-term medical therapies at a cost of $2.8 billion annually.[1] Women with CPP suffer tremendously: they use three times more medications, have four times more gynecologic surgery, and are five times more likely to undergo hysterectomy than women without CPP.[1] Pain and suffering often persist despite these treatments, and lead to decreased productivity, diminished emotional well-being, altered life course trajectory, low work productivity, impaired sexual function and reduced quality of life. Many patients with CPP report hypervigilance and fear around behaviors that may exacerbate symptoms and demonstrate disadvantageous psychological responses to pain such as dissociation, avoidance, and reduced self-efficacy.[4,5]

Non-pharmacologic therapies are increasingly being utilized in other chronic pain conditions with promising results. Cognitive Behavioral Therapy (CBT), acupressure, and physical activity interventions have been shown to be effective in a wide range of chronic pain conditions.[6,7] Among patients with CPP, several small studies have demonstrated efficacy of CBT, acupressure, and physical activity interventions.[8-11]

Cognitive Behavioral Therapy (CBT) is an evidence-based practice that has been widely applied to chronic pain populations.[6] Physical activity interventions have demonstrated significant improvements in pain, quality of life, physical function, depression, anxiety, pain-related self-efficacy, and catastrophizing in patients with fibromyalgia, IBS, low back pain, and osteoarthritis.[12-14] Acupuncture and acupressure interventions have demonstrated improvements in pain, physical function, and fatigue in patients with fibromyalgia and low back pain.[15,16] Many patients have difficulty participating in these CBT interventions due to limited availability of providers, particularly in rural or underserved areas, lack of insurance coverage, and high out-of-pocket costs. Web-based self-management programs help to reduce barriers to access, and many have been shown to be as effective as traditional face-to-face interventions.[9,17]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Breach of confidentiality: Participation in this study poses a risk for breach of confidentiality. Several measures have been taken to reduce the risk of breach of confidentiality. These include training of study team members, electronic and physical security measures for data capture and storage and collecting a minimum of identifiable information for each individual project. Breach of confidentiality will be considered a "definitely related" Serious Adverse Event. As such, it will be reported to the University of Michigan IRB within 7 days of occurrence, and a remediation plan will be put in place immediately.

Discomfort associated with being asked personal questions about health history and the completion of questionnaires: Any participant becoming distressed while completing questionnaires will be encouraged to seek clarification of any questions that they find to be unclear or troubling. All participants are told that they have the option to terminate participation without penalty and/or will be assisted in arranging medical/ psychiatric help including, if necessary, emergency treatment if needed.

Symptom exacerbation: We do not anticipate that the *My Pelvic Plan* program is likely to place patients at an increased risk of symptom exacerbations. Cognitive and behavioral programs have been shown to be low risk for adverse events.[18] However, we will discuss that new activities, such as physical therapy and exercise, sometimes precipitate a temporary increase in myofascial pain, and will offer basic anticipatory guidance. This is a well-described phenomenon and is not unique to this program. Our CPP provider have extensive expertise in determining whether exacerbations are typical given possible triggers and can offer individual guidance on whether additional evaluation is warranted.

During the study period, all patients will receive usual care as determined by their CPP provider and PCP. While we will not enroll patients who are planning to undergo surgery during the study period, patients will be able to proceed with any intervention determined to be necessary by their medical providers, including surgery and medication changes, without being excluded from our analysis. We will collect data on interim surgery or medication changes at the 3 and 6-month follow up periods.

Patients with chronic pelvic pain have episodic symptom exacerbations, which can sometimes be predicted or explained by known triggers such as menses, but often appear idiopathic and unpredictable. While the *My Pelvic Plan* program will contain information and skills to help manage exacerbations, the program will repeatedly clarify that this is not a replacement for professional medical

advice, and they should contact their provider if they have urgent concerns. They will maintain the same level of access to their providers as any other patient, which they can utilize should they have a symptom exacerbation during the study period.

Patients with chronic pelvic pain have higher rates of depression compared to patients without chronic pain conditions. While we do not anticipate that the *My Pelvic Plan* program is likely to exacerbate symptoms of depression, we want to ensure that patients who are suffering from severe depression receive appropriate treatment. Therefore, PROMIS Depression SF 8b will be scored immediately. If a patient receives a score $\geq$ 70, consistent with severe depression, they will receive a call from a study member who will complete a brief screen for suicidal ideation. If positive, the patient will be referred to the University of Michigan Psychiatric Emergency Service. If no suicidal ideation, we will offer referral to University of Michigan Depression Center or offer to contact the patient's PCP to help facilitate evaluation and treatment.

2.3.2 KNOWN POTENTIAL BENEFITS

Based on data from similar interventions in patients with other chronic pain conditions, we anticipate that patients in the intervention group will see modest improvement in pain interference, physical function, and health-related self-efficacy associated with participation in this study (immediate and short-term potential benefits).

We also anticipate that the information gathered from this pilot study will allow us to refine the program to best meet the needs of similar patients with chronic pelvic pain. The long-term potential benefits include assisting with the refinement of an accessible intervention that will eventually be made publicly available at no cost to patients.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The anticipated risks to study participants are reasonable given the nature of the study. There are few reasonable alternatives to gathering detailed symptom and quality of life information outside of these validated questionnaires. The proposed benefits of the study outweigh the anticipated risks of study participation.

At any time, the participants may withdraw from the study. Participants may refuse to answer any questions that may be uncomfortable. This message is conveyed in all during the informed consent process and during instructions to participants. To minimize any risk of a breach in confidentiality, all study staff will be trained, physical security measures for data capture and storage will be used and we will only collect a minimum of identifiable information. Records will be kept confidential to the extent provided by Federal, State, and local law. Nevertheless, subjects are informed that the sponsor and the Institutional Review Board for the use of human subjects in research may inspect the records of this investigation.

3 OBJECTIVES AND ENDPOINTS

Outcome type	Measure description title	Specific measurement	Timeframe
Primary outcome	To evaluate effectiveness of the intervention by comparing	PROMIS Pain Interference SF 4a	3 months (primary endpoint) and 6

	pain interference among intervention group versus control group following the intervention.		months (secondary endpoint).
Secondary outcomes	To compare pain intensity among intervention group versus control group.	PROMIS pain intensity 1a	3 months (primary endpoint) and 6 months (secondary endpoint).
	To compare health-related self-efficacy among intervention group versus control group.	PROMIS Self Efficacy for Managing Symptoms SF 4a	3 months (primary endpoint) and 6 months (secondary endpoint).
Tertiary outcomes	To explore additional pain characteristics among intervention group versus usual care group.	painDETECT Fibromyalgia Survey Score	3 months (primary endpoint) and 6 months (secondary endpoint).
	To explore quality-of-life measures among intervention group versus control group	PROMIS Physical Function SF 4a PROMIS Anxiety SF 4a PROMIS Depression SF 4a PROMIS Fatigue SF 4a PROMIS Sleep Disturbance SF 4a PROMIS Sleep-related impairment SF 4a PROMIS Ability to participate in social roles and activities SF 4a PROMIS cognitive function – abilities PROMIS emotional support Pain Catastrophizing Scale Female Sexual Function Index Patient Global Impression of Change Complex Multiple Symptom Inventory Chronic overlapping pain condition screener Connor-Davidson Resilience Scale Relationship Assessment Scale CPP self-report opioid benzo assessment	3 months (primary endpoint) and 6 months (secondary endpoint).

		Cannabis use survey	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This Stage 1 intervention will conduct a pilot randomized controlled trial to evaluate preliminary effectiveness of a web-based, self-management program for patients with CPP and phenotypic factors that predict positive response. Our overall hypothesis is patients with CPP who have access to this intervention will demonstrate improved in pain, physical function, and quality of life.

This trial will be conducted at Michigan Medicine (single site) and all patients will recruited from the Chronic Pelvic Pain and Endometriosis referral clinic.

Random allocation will occur in 2:1 ratio (intervention:control) utilizing permuted blocks of 4 without stratification. Allocation concealment will be ensured using computer generated central randomization and will occur after patient has signed the consent form. The study team member who generates random allocation sequence will not be involved in recruitment or enrollment. Patients will be blinded to their group assignment. Study team members involved in outcome assessment will be blinded to group assignment. The patient's CPP provider who will continue to provide usual care for pelvic pain will also be blinded from group assignment.

Patients will be randomized to participation in a 6-month web-based, integrative self-management program (*https://www.mypelvicplan.com/*) in addition to usual care as determined by the patient's CPP provider (intervention group), or to a web-based symptom monitoring program (*https://monitoringprogress.org/*) in addition to usual care (control group). The intervention is comprised of a self-guided program that combines education on several individual conditions that often contribute to CPP, and will include instruction on cognitive and behavioral restructuring, self-administration of acupressure, engaging in physical activity, and a brief introduction to pelvic floor physical therapy techniques.

Following enrollment, patients will complete online baseline questionnaires, which will include relevant medical and gynecologic history, pain symptoms, quality of life measures, and current treatments for pelvic pain symptoms (medications, physical therapy, etc.). After completing questionnaires, patients in the intervention group will receive access to the intervention website and those in the control group will receive access to the symptom monitoring website. Patients will be instructed to continue routine follow up and usual care with their established CPP provider throughout the study.

Patients will receive a questionnaire to evaluate pain symptoms and quality of life measures at 3-month interval (primary endpoint) and 6-month interval (secondary endpoint). After completion of 3-month questionnaire battery, we will be performing focus groups for approximately one-half of the patients in the intervention group (n=20) in order to obtain in-depth feedback regarding the program.

A participant is considered to have completed the study if they have completed the baseline questionnaire and at least the 3-month questionnaire. Patients in the intervention group may decline this invitation to participate in the focus groups and still be considered to have completed the study.

The study will conclude once all patients have completed the final 6-month questionnaires. Patients may choose to withdraw from the study at any time. If a patient withdraws before the 3-month questionnaire is sent, we will attempt to replace them with another eligible patient.

4.2 SCIENTIFIC RATIONAL FOR STUDY DESIGN

Non-pharmacologic therapies are increasingly being utilized in other chronic pain conditions with promising results. The *My Pelvic Plan* program includes multiple non-pharmacologic therapies, including cognitive behavioral techniques, acupressure, and physical activity.

Cognitive Behavioral Therapy (CBT) is an evidence-based practice that has been widely applied to chronic pain populations including fibromyalgia,[19] low back pain,[20] and irritable bowel syndrome (IBS).[7] Among patients with CPP, several small studies have demonstrated efficacy of CBT interventions.[8,21]

Physical activity interventions have demonstrated significant improvements in pain, quality of life, physical function, depression, anxiety, pain-related self-efficacy, and catastrophizing in patients with fibromyalgia, IBS, low back pain, and osteoarthritis.[12,13,22] Among patients with CPP, several small studies have demonstrated efficacy of physical activity interventions.[10,11]

Acupuncture and acupressure interventions have demonstrated improvements in pain, physical function, and fatigue in patients with fibromyalgia and low back pain.[15,16] Among patients with CPP, several small studies have demonstrated efficacy acupressure interventions.[9,23]

Many patients have difficulty participating in these non-pharmacologic interventions due to limited availability of providers, particularly in rural or underserved areas, lack of insurance coverage, and high out-of-pocket costs. Web-based self-management programs help to reduce these barriers, and many have been shown to be as effective as traditional face-to-face interventions. By creating a web-based program that integrates the above nonpharmacologic interventions, we aimed to address gaps in availability and access for a patient population that is likely to greatly benefit from an integrative treatment approach.

Because CPP is a heterogeneous condition, we hypothesize that there will not be one version of an intervention that it effective for all patients. Our goal is to expose patients to several treatment modalities and allow them to build a program that meets their specific needs. As this is an exploratory study, we will incorporate several types of treatment modalities – cognitive/behavioral, acupressure, physical therapy, and physical activity – and allow patients to utilize each as they wish. Evaluating utilization and preliminary effectiveness of each of the modalities will inform how we adapt the intervention for future studies. Effect sizes of individual non-pharmacologic interventions are typically small (0.15-0.3).[18,24] However, interventions that integrate several of these modalities appear to have substantially improved efficacy (0.3-0.8),[25-27] indicating possible synergistic rather than additive effects. Effect sizes for pharmacologic treatments for chronic pain conditions are similarly modest.[28]

Limited effects of both pharmacologic and non-pharmacologic therapies seem to be due to the fact that response is often bimodal, with patients typically responding either minimally or robustly, in which case the average effect appears quite modest. Therefore, experts in chronic pain research have advocated for a shift toward identifying responders when investigating treatments, which can better inform development of personalized treatment strategies. For this reason, we will gather preliminary information about patient phenotyping – whether certain factors predict which patients tend to respond most robustly to various treatments. We will be performing an exploratory analysis focused on development of phenotypes within chronic pelvic pain. We will compare overall responders versus non-responders and will also explore response to specific skills within the program. We intend to focus more on this patient phenotyping exploration in future studies.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Woman (female sex assigned at birth, may include cis-gender, trans-gender, nonbinary)
- At least 18 years old
- have chronic pelvic pain, defined as moderate to severe pelvic pain that is ≥ 4 on a 0-10 numeric rating scale (worst pain during the day) for ≥ 6-month duration, and is non-cyclic, occurring for at least 14 days of each month.
- must be currently receiving care within Department of Obstetrics and Gynecology at the University of Michigan for treatment of chronic pelvic pain.
- Access to internet via computer or smartphone
- English-language proficiency (current version of the website is in English)
- We will attempt to recruit a diverse group of patients, with attention to diversity in race, ethnicity, education level, rural vs urban locality, sexual orientation, and gender identification.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- underwent gynecologic surgery within 3 months of screening visit
- plan to undergo gynecologic surgery within 6 months following screening visit
- pregnant (self-reported) at time of screening visit. Will not exclude patients who become pregnant during the course of the study.

- severe physical impairment precluding participating in internet-based program (for example, complete blindness or deafness)
- current psychiatric disorder with history of psychosis (for example, schizophrenia, schizoaffective disorder, delusional disorder),
- current suicidal ideation or suicide attempt within 2 years of screening visit. We will screen for severe depression and suicidality at each questionnaire time point and have developed a robust triage and referral plan.

5.3 SCREEN FAILURES

Screen failures are defined as participants who go through screening process for eligibility but are not subsequently entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) at time of screening because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include pain that does not meet intensity or frequency threshold, recent or planned surgery outside of defined threshold, and currently undergoing cognitive behavioral therapy at time of screening visit. Rescreened participants will be assigned the same participant number as for the initial screening.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

We will be using thoughtful recruitment and allocation methods to minimize bias. We will attempt to include a diverse group of participants for this study, with intentional recruitment to reflect diversity in age, race, geographic location and pelvic pain conditions.

We will contact both intervention and control patients with text or email prompts to visit their respective website on prespecified basis with goal of increasing program utilization and study retention. In the first 12 weeks of the study (active phase), participants will receive a weekly text or email prompt directing them to a specific module or portion of their respective website. During the remaining time in the study (maintenance phase), all participants will receive monthly text or email prompts to visit their respective website. Details of the prompts for the intervention and control groups are included in 8.2 Study evaluation and procedures.

We are unable to track website utilization for specific users. However, we will send an email link to a survey once per month which will ask which skills (from the *Managing Symptoms* section of the website) they used in the last month regardless of whether they visited that module in the site. We assume that some patients will need repeated exposure to skills to gain mastery and incorporate into their routine, whereas other patients may visit a module once and be able to incorporate it into regular practice.

Patients will receive a questionnaire battery at 3-month interval (primary endpoint) and 6-month interval (secondary endpoint). Patients will receive a reminder email if they have not completed the survey or questionnaire within 4 days, 7 days, and 14 days. Only three reminders will be sent per survey/questionnaire, with the exception of the 6-month survey, for which patients may receive one additional reminder at 21 days.

5.5 COMPENSATION

All patients will receive $50 for completion of each of the three questionnaires (baseline, 3-month, 6-month). Patients in control group who complete all portions of the study will receive a total of $150.

In addition, intervention patients will receive $5 for each of the six utilization surveys completed. Intervention patients who participate in a focus group at 3-months will receive $100. Therefore, patients in intervention group who complete all portions of the study will receive a total of $180-280, depending on focus group participation.

All compensation will be managed by a study team member in conjunction with the University of Michigan Human Subjects Incentive Program (HSIP). Patients will be sent a gift card at time of completion of the baseline questionnaire. Additional compensation payments will be virtually loaded to the gift card upon completion of additional questionnaires.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

As this is an exploratory study, we will incorporate several types of treatment modalities – cognitive/behavioral, acupressure, physical therapy, and physical activity – and allow patients to utilize each as they wish. However, we will utilize an established tailoring program to direct participants to particular modules or skills that are likely to be most relevant for their individual symptoms and characteristics. This tailoring program utilizes the baseline patient reported outcome measures (PROMIS 29+2). Responses to each of these measures will be scored to obtain a T-score, which will then be ranked in order of divergence from population mean to represent relative burden of each factor. All patients will receive prompts to the same modules during the first four weeks of the active phase. However, prompts during the next 8 weeks of the active phase will correspond to the rank order of the baseline measure T-scores, directing patients to modules that address each of these factors. During the maintenance phase of the study, all patients will receive the same monthly prompt to visit the Monitoring Progress symptom tracker subpage of the website.

Evaluating preliminary effectiveness of the program will inform how we might adapt the intervention for future studies. This will also help explore preliminary information about patient phenotyping – whether certain factors predict which patients tend to respond most robustly to various treatments.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

There is no variability in this program itself as all intervention patients have access to the same web-based program. While patients will receive tailored or curated prompts to visit specific modules in the program based on their individual symptom burden, the website itself is static.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Random allocation will occur in 2:1 ratio (intervention:control) utilizing permuted blocks of 4 without stratification. Allocation concealment will be ensured using computer generated central randomization and will occur after patient has signed the consent form. . Enrollment will occur on a rolling basis until 69 patients have been enrolled. The study team member who generates random allocation sequence will not be involved in recruitment or enrollment.

Both patients and outcome assessors will be blinded to study group assignment. During recruitment, we will state that we are testing two different web-based approaches for self-management for chronic pelvic pain, so patients will not be aware of which study group they are enrolled in. Patients will be contact at essentially the same intervals throughout the study period to further maintain blinding. We will attempt to blind the patient's CPP provider as to their group status but are unable to control the possibility that a patient mentions the intervention to their provider. We will ask providers not to comment about group status or discuss the intervention in detail with patients to maintain patient blinding to as great an extent as possible.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Each month, we will ask intervention group participants to indicate which skills they have utilized in the past month. However, we are unable to track website utilization for individual patients based on the current website design.

Relative to questionnaires, we will require completion of baseline questionnaires in order to participate in the study. We will not dismiss patients from participating if they do not complete questionnaires but will send multiple reminders and monetary incentives for participating.

6.5 CONCOMITANT THERAPY

All patients will receive usual care as recommended by their CPP provider throughout the study. Our group of CPP providers utilize a fairly similar, multimodal approach for managing chronic pelvic pain. This commonly includes hormonal suppression, physical therapy, muscle relaxants, and centrally acting neuropathic medications. The specific strategies are highly dependent on the conditions contributing to pain symptoms in an individual patient. Of note, we utilize shared decision-making with patients, which means that some patients choose not to utilize a treatment that we may typically recommend as first-line therapy for a particular condition. Therefore, we anticipate that there will be variability in treatments

utilized across patients. We will assess treatments utilized at each questionnaire time point and will perform exploratory analyses to assess impact on primary and secondary outcomes.

While we will exclude patients who have undergone gynecologic surgery within 3 months of screening visit, plan to undergo gynecologic surgery within 6 months following screening visit, are currently pregnant, at time of screening visit, patients will be able to proceed with any intervention determined to be necessary by their medical providers, including surgery and medication changes, without being excluded from our analysis. We also will not exclude patients who become pregnant during the study. We will collect data on interim surgery or medication changes at the 6-month follow up period.

6.5.1 RESCUE THERAPY

Patients may use rescue therapies as recommended by their CPP provider or other physician as part of usual care. The only additional rescue intervention to be initiated directly by the study team is to assess for severe depression at time of questionnaire submission (baseline, 3-month, 6-month). If a patient screens positive for severe depression (defined by score >70 on PROMIS Depression SF 8b), they will receive a call from a study member who will complete a brief screen for suicidal ideation. If positive, the patient will be referred to the University of Michigan Psychiatric Emergency Service. If no suicidal ideation, we will offer referral to University of Michigan Depression Center or offer to contact the patient's PCP to help facilitate evaluation and treatment.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

After patients are randomized to group and complete baseline questionnaire, we will not discontinue access to the intervention for the duration of the 6-month study period, despite new medical/psychiatric diagnoses including pregnancy or undergoing gynecologic surgery. Patients may elect to withdraw from the study as described below.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patients may choose to withdraw from the study at any time. If a patient withdraws before the 3-month questionnaire is sent, we will attempt to replace them with another eligible patient

7.3 LOST TO FOLLOW-UP

Patients will receive an email with a link to questionnaires and utilizations surveys at each time point specified above. If questionnaires are not completed within 4 days, an automatic reminder email will be

sent. If questionnaires are not completed within 7 days, a study member will call with a reminder. If questionnaire is not completed with 14 days, a study member will call with another reminder. Patient will be considered lost to follow up if they fail to complete the 6-month questionnaire within 21 days after survey invitation.

We will not exclude or dismiss patients based on completion of 6-month questionnaire or monthly utilization survey as these are not essential for the primary outcome.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCREENING PROCEDURES

We will be using thoughtful recruitment and allocation methods to minimize bias**.** Our group of specialty-trained gynecologists see approximately 150 patients per month in this referral clinic. Each returning patient will receive a brochure containing a brief description of the study and an interest sheet during their check-in. A physician may assess interest if they feel that the patient may be an appropriate candidate. A study team member will also screen patients scheduled for return visits in the clinic and contact potentially eligible patients via text or email to inform them that they may be eligible for the study. We will not recruit new patients during this pilot study as patients often initiate a number of new treatments following the initial visit and we suspect that it might be more challenging to differentiate effect of the intervention versus treatment plan in this population.

A study team member will contact interested patients to assess eligibility and confirm interest and obtain consent (electronic). Potential subjects will be contacted up to seven times (by telephone, text, portal message, or email) in order to establish contact. Entry as a subject requires passing a telephone screen to confirm eligibility.

8.2 STUDY EVALUATION AND PROCEDURES

Once eligibility and interest are confirmed, the study team member will send an email link to an electronic version of the consent form. The study team member and patient will review study consent verbally over the telephone and answer any questions. Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant. Consent forms will be signed and stored electronically. We have elected to perform this combination of verbal and online consent as opposed to a face-to-face consent as the majority of patients from our referral clinic travel between 1-4 hours to reach our clinic. One of goals of this intervention is to expand access and limit barriers related to travel that our patients typically encounter. Therefore, we felt that requiring subjects to return for a visit specifically for a face-to-face consent would impose too great a burden for many participants, and that this approach was reasonable given the remote contact utilized in other aspects of this study.

Random allocation will occur in 2:1 ratio (intervention:control) utilizing permuted blocks of 4 without stratification. Allocation concealment will be ensured using computer generated central randomization and will occur after patient has signed the consent form. The study team member who generates random allocation sequence will not be involved in recruitment or enrollment. Patients will be blinded to their group assignment. Study team members involved in outcome assessment will be blinded to

group assignment. The patient's specialty gynecologist who will continue to provide usual care for pelvic pain will also be blinded to group assignment.

Enrollment will occur on a rolling basis until 69 patients have been enrolled. We anticipate that we will likely need to screen approximately 200 patients in order to enroll 69 participants over an 18-month period. We will attempt to recruit a diverse group of patients, with attention to diversity in race, ethnicity, age, education level, rural vs urban locality, sexual orientation, and gender identification.

Following enrollment, patients will complete online baseline questionnaires, which will include current treatments for pelvic pain symptoms (medications, physical therapy, etc.). After completing questionnaires, patients in the intervention group will receive access to the intervention website and those in the control group will receive access to the symptom monitoring website.

Intervention group

Patients in the intervention group will receive access to the *My Pelvic Plan* website (*https://www.mypelvicplan.com/*), which is a self-directed program which integrates patient education about conditions that frequently contribute to pelvic pain, as well as instruction on cognitive and behavioral restructuring, self-administration of acupressure, engaging in physical activity, and a brief introduction to pelvic floor physical therapy techniques. They will have open access to the program over the 6-month intervention period**.** The intervention will be comprised of an active (12-week) phase and a maintenance (3-month) phase. During the active phase, we will use an established tailoring program to direct participants to particular modules or skills that are likely to be most relevant for their individual symptoms and characteristics. All intervention participants will receive a weekly text or email prompt directing them to a specific module. All participants will receive prompts to the same modules for the first four weeks of the study. During the next 8 weeks, participants will receive prompts to modules that corresponded to their most impactful symptoms on their baseline questionnaires. Following the 12-week active phase, all participants will enter the maintenance phase, during which they will receive monthly prompts to Monitoring Progress symptom tracker module.

Patients will have open access to the program over the 6-month intervention period. While they will receive text or email prompts to visit specific modules, they will ultimately choose how they navigate and utilize the program and we will not prescribe a specific schedule or utilization frequency.

We are unable to track website utilization for specific users. However, we will send an email link to a survey once per month which will ask which skills (from the *Managing Symptoms* section of the website) they used in the last month regardless of whether they visited that module in the site. We assume that some patients will need repeated exposure to skills to gain mastery and incorporate into their routine, whereas other patients may visit a module once and be able to incorporate it into regular practice.

Patients will receive a questionnaire battery at 3-month interval (primary endpoint) and 6-month interval (secondary endpoint). Patients will receive an email with a link to questionnaires at 3 months and again at 6 months. The 6-month questionnaire will also include questions regarding current treatments for pelvic pain symptoms, including interval surgery.

After completion of 3-month questionnaire battery, we will be performing focus groups for approximately one-half of the patients in the intervention group (n=20) in order to obtain in-depth feedback regarding the program. We will attempt to include an intentionally diverse group of

participants for these focus groups, with intentional recruitment to reflect diversity in age, race, geographic location and pelvic pain conditions. These sessions will focus on skills and modules that were most impactful and whether participants believe that combining the intervention with an individual coach or an online community might be beneficial.

Control group
Patients in the control group will undergo an active control intervention in which they receive open access to a separate website (*https://monitoringprogress.org/*) that contains only the Monitoring Progress symptom tracker subpage over the 6-month study period. Control group participation will also be divided into an active (12-week) phase and a maintenance (3-month) phase. Similar to the intervention group, the control group will receive a weekly text or email prompt directing them to track a specific symptom or activity during the active phase of that study. During the maintenance phase of the study, they will receive monthly prompts to the Monitoring Progress subpage (without prompting to a specific symptom or activity).

Control participants will receive a questionnaire battery at 3-month interval (primary endpoint) and 6-month interval (secondary endpoint).

Both patients in the intervention and control groups will receive contact from the study team at the same intervals throughout the study. If questionnaires are not completed within 4 days, an automatic reminder email will be sent. If questionnaires are not completed within 7 days, a study member will call with a reminder. If questionnaire is not completed with 14 days, a study member will call with another reminder. Patient will be considered lost to follow up if they fail to complete the 6-month questionnaire within 21 days after survey invitation. Both intervention and control groups will continue to follow with their specialty gynecologist and will receive usual care throughout the study period. On average, patients follow up every 3-4 months in this clinic per their physician recommendation and we will not recommend any specific changes to usual care follow up as part of this study.

A participant is considered to have completed the study if they have completed the baseline questionnaire and the 3-month questionnaire.

After completion of 3-month questionnaire, we will be performing focus groups for approximately one-half of the patients in the intervention group (n=20) in order to obtain in-depth feedback regarding the program and potential adjunct therapies for future studies. Patients in the intervention group may decline this invitation and still be considered to have completed the study.

The study will conclude once all patients have completed the final 6-month questionnaires. Patients may choose to withdraw from the study at any time. If a patient withdraws before the 3-month questionnaire is sent, we will attempt to replace them with another eligible patient.

8.3 SAFETY ASSESSMENTS

The study team will assess for severe depression at time of questionnaire submission (baseline, 3-month, 6-month). If a patient screens positive for severe depression (defined by score >70 on PROMIS Depression SF 4b), they will receive a call from a study member who will complete a brief screen for suicidal ideation. If positive, the patient will be referred to the University of Michigan Psychiatric

Emergency Service. If no suicidal ideation, we will offer referral to University of Michigan Depression Center or offer to contact the patient's PCP to help facilitate evaluation and treatment.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.4.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention related***.

This intervention is considered to carry low risk to subjects. Patients with chronic pelvic pain have episodic symptom exacerbations, which can sometimes be related to known triggers such as menses or intercourse, but often appear idiopathic or unpredictable. Additionally, patients with chronic pain conditions have higher rates of depression compared to their peers and we want to ensure that patients suffering from severe depression receive appropriate treatment.

Therefore, we will consider the following to be adverse events:
- Pain exacerbation prompting evaluation in emergency department
- Pain exacerbation prompting scheduled gynecologic surgery
- Screen positive for suicidal ideation in discussion with study team member following up on screen for severe depression

8.4.2 DEFINITION OF SERIOUS ADVERSE EVENTS

We will consider the following to be serious adverse events:
- Pain exacerbation prompting inpatient hospitalization
- Pain exacerbation prompting urgent or emergent surgical evaluation
- Suicide attempt or significant deterioriation of psychiatric conditions resulting in inpatient psychiatric hospitalization

8.4.3 CLASSIFICATION OF AN ADVERSE EVENT

8.4.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **0 – No AE**
- **1 - Mild AE** – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- **2 – Moderate AE** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **3 – Severe AE** – 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 too "serious".
- **4** – Life threatening or disabiling AE
- **5** – Fatal AE

8.4.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **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 procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **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 procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). 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 procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) 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 procedures 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.

8.4.3.3 EXPECTEDNESS

A clinician with appropriate expertise in chronic pelvic pain 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 procedures.

8.4.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

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.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric 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. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

Study coordinator will record 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. We will primarily rely on patient self-report of adverse events and will not proatively search internal or external medical record systems to identify these. Events will be followed for outcome information until resolution or stabilization.

8.4.5 ADVERSE EVENT REPORTING

AEs will be reported to the University of Michigan IRBMED as required and to NIH annually.

8.4.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to NIH and the

reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.4.7 REPORTING EVENTS TO PARTICIPANTS

Serious adverse events that have been deems probably or definitely related to the intervention will be reported to patients within 60 days of the incident. All other adverse events, serious adverse events, and incidental findings will be communicated to participants along with study-related results by email or preferred method of communication within one year following the end of the study.

8.5 UNANTICIPATED PROBLEMS

8.5.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to 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.

8.5.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). 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 to NIH as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.
- Any other UP will be reported to the IRB and NIH annually.
- 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) annually.

8.5.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unanticipated problems will be reported to participants along with adverse events, serious adverse events, incidental findings and study-related results by email or preferred method of communication within one year following the end of the study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint:

We hypothesize that patients who receive the *My Pelvic Plan* intervention in addition to usual care will demonstrate improvement on PROMIS Pain Interference SF 4a from baseline to 3-month follow-up. Alternatively, our null hypothesis is that there will be no difference in Pain Interference from baseline to 3-month follow up. As this is a pilot study, we will be evaluating preliminary program effectiveness by comparing the intervention group to an active control group and will use this information to generate effect size for a trial to evaluate efficacy.

- Secondary Endpoints:

We hypothesize that patients who receive the *My Pelvic Plan* intervention in addition to usual care + symptom tracker will demonstrate improvements on PROMIS Pain Intensity and PROMIS Self Efficacy for Managing Symptoms SF 4a from baseline to 3-month follow-up. Alternatively, our null hypothesis is that there will be no difference in Pain Intensity and Self-Efficacy from baseline to 3-month follow up.

9.2 SAMPLE SIZE DETERMINATION

As this is a pilot study, we have chosen to recruit a sample of 69 patients so that we can assess the feasibility of the project and to derive important effect size estimates for the definitive clinical trial that

will be conducted in a future R01 application. We are not attempting to power the analyses to detect a difference in our primary outcome (pain interference).

In addition to pain interference, we will also examine pain intensity and health-related self-efficacy to assess whether these outcomes might be more appropriate primary outcomes in an efficacy trial.

9.3 POPULATIONS FOR ANALYSES

We will use an intent to treat analysis. Primary outcome (pain interference) will be assessed at 3-months and 6-month data will only contribute to secondary outcomes. Given this, we will plan carry the last observation forward (either 3-month or baseline) for patients who are lost to follow up at 6-months.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

For descriptive statistics, continuous variables will be presented using means with standard deviation. Categorical variables will be presented using percentages with 95% confidence intervals. All tests will be two sided at 5% significance level. Normality will be assessed, and nonparametric tests used where appropriate.

We will prespecify several covariates for regression models with special attention to emerging constructs in the pain literature, specifically FM survey score and PainDETECT, that may be associated with treatment response. However, we will also perform exploratory analyses given our focus on hypothesis generation.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary outcome (PROMIS Pain Interference) is a continuous measure and utilizes a standardized, publicly available scoring system. We will report mean and standard deviation for each group.

Given pilot RCT design, we will use a simple posttreatment comparison of pain interference at 3-months. We will compare means with t-test. All tests will be two-sided at 5% significance level. Of note, data collected at 6-month interval will be analyzed as an exploratory outcome.

We will estimate effect size by calculating Hedges' *g* (rather than Cohen's *d* because groups are different sizes) for pain interference at 3-months, which we will use in planning for future efficacy trial.

As part of our exploratory analyses, we plan to categorize patients as "responders" vs "non-responders." "Responder" will be defined as an improvement of at least 2.5 on PROMIS Pain Interference from baseline to 3-months. We will compare differences in contributing pain conditions, pain characteristics such as Fibromyalgia Survey Score or PainDETECT, and comorbid mental health factors that may be associated responder status. We tentatively plan to use logistic regression to compare factors associated with responder status. We will use these exploratory analyses to inform structure of our future efficacy trial.

We will be using an intent to treat analysis. Patients may elect to skip questions on the questionnaire and therefore it is possible that we encounter some missing data or incomplete questionnaires. We will report the proportion of missing outcome per group and characteristics of patients with missing data. If we encounter more than 5% missing data, we plan to conduct sensitivity analyses to assess effect of missingness on results.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary outcomes (PROMIS Pain Intensity and PROMIS Self-Efficacy) are also continuous measures and utilize a standardized, publicly available scoring system. We will use a simple posttreatment comparison of pain interference at 3-months. All tests will be two-sided at 5% significance level. Of note, data collected at 6-month interval will be analyzed as an exploratory outcome.

We will be using an intent to treat analysis. Patients may elect to skip questions on the questionnaire and therefore it is possible that we encounter some missing data or incomplete questionnaires. We will report the proportion of missing outcome per group and characteristics of patients with missing data. If we encounter more than 5% missing data, we plan to conduct sensitivity analyses to assess effect of missingness on results.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics of the intervention and control groups will be compared using descriptive statistics, using independent samples t-test for continuous variables and chi-square/Fisher's exact test for categorical variables. All tests will be two sided with 5% significance level. Planned analyses include demographic information, medical and surgical history, chronic pain diagnoses (endometriosis, pelvic myofascial pain, irritable bowel syndrome, etc.), and current category of treatments (hormonal suppression, pelvic physical therapy, etc.).

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

We will explore preliminary phenotyping hypotheses based on demographic factors, baseline symptoms, comorbid conditions, and outcome predictors. We will primarily focus on changes in pain interference but will explore additional outcomes. We will define "responder" as a patient who demonstrates a minimally important difference (MID) of 2.5 on pain interference and will explore phenotypic differences between responders and non-responders.

While we will explore a broad array patient-level factors including demographics, pain characteristics, comorbid conditions, and psychological/cognitive factors, we plan to devote special attention to emerging constructs in literature that are associated with response to treatment. Constructs may include the Fibromyalgia Survey Score, presence of endometriosis or myofascial pain diagnoses, duration of chronic pelvic pain, comorbid pain disorders, catastrophizing, depression, anxiety, and psychosocial factors. We will also correlate characteristics with utilization of overall program and of individual modules (i.e., did patients with higher depression scores utilize the CBT modules more frequently). Given that the program is in an early phase of development, we are not ready to direct patients to specific modules based on individual characteristics. But we hope to gather preliminary information in order to guide patients to particular skills in a later study.

Baseline phenotypic differences between responders/non-responders will be conducted with ANOVA for continuous variables and chi-square testing/Fisher's exact test for categorical variables. General Linear Models will be used for multivariable analyses of responder status.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and NIH, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable

- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and NIH, or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

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

The study monitor, other authorized representatives of the NIH and representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

The study participant's contact information will be securely stored at the clinical 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, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the University of Michigan within the Department of Obstetrics and Gynecology. 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 by clinical sites and by University of Michigan research staff will be secured, and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Michigan.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subject's research is required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

All participant data will be securely stored throughout the duration of the study and during the analysis phase of the study.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Sara Till, MD, MPH Assistant Professor
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10.1.5 SAFETY OVERSIGHT

Because of the small size of the study and fairly low potential risks, the Primary Investigator (Dr. Till) and Primary Mentor (Dr. Clauw) (PIs) will be responsible for monitoring patient safety and protocol adherence.

10.1.6 CLINICAL MONITORING

N/A

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.8, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff under the supervision of the primary investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the screening phone visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. All other study materials will be collected and recorded electronically. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Qualtrics, a 21 CFR Part 11-compliant data capture system provided by the University of Michigan. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years after study completion.

10.1.9 PROTOCOL DEVIATIONS

The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern. We will not classify missed questions on surveys or missing surveys (other than the primary outcome) as protocol deviations.

It will be the responsibility of the primary investigator to use continuous vigilance to identify and report deviations within 30 working days of identification of the protocol deviation, or within 15 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to NICHD Program Official. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of

the primary endpoint by contacting the primary investigator. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.2.

10.1.11 CONFLICT OF INTEREST POLICY

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 design and conduct of this trial. The study leadership in conjunction with the NICHD 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.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
CFR	Code of Federal Regulations
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IRB	Institutional Review Board
ITT	Intention-To-Treat
MOP	Manual of Procedures
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UP	Unanticipated Problem
US	United States

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