Endometriosis Group Care: Piloting an interdisciplinary group care model for endometriosis treatment

NCT05622955

12/20/2022

PROTOCOL SYNOPSIS version dated 12/20/2022

Brief Summary: Endometriosis affects an estimated 10-15% of people assigned female at birth and is one of the most common causes of chronic pelvic pain. The disease impairs overall quality of life, directly affects many domains of physical and emotional functioning, and can be a tremendous economic burden. Endometriosis is responsible for an estimated $69.4 billion per year in excess health expenditures and costs $12,118 per patient per year in the United States. Additionally, people with endometriosis lose an average of 6.3 hours of workplace productivity and 4.9 hours of household productivity per week. The current mainstays of endometriosis treatment often fail leading to patients experiencing recurrent pain and needing re-intervention and repetitive surgeries. The need for implementation of more effective treatments for endometriosis-associated pain is great.

Group care has been effectively used to manage chronic back and neck pain, fibromyalgia, and headaches. Moreover, Chao et al. enrolled 26 people with female chronic pelvic pain into a group care program *Centering Chronic Pelvic Pain (Centering CPP).* The authors reported before-and-after assessments revealing that attendance at ≥4 sessions was associated with fewer unhealthy days per month (24 to 18, $P<0.05$), fewer depressive symptoms (12 to 9, $P<0.05$), and lower symptom severity (4.2 to 3.1, $P<0.01$).

To adapt *Centering Chronic Pelvic Pain* to be specific to patients with endometriosis, I assembled an inter-disciplinary team of collaborators: Dr. Sarah Buday, an expert in chronic pain clinical psychology; Dr. Tracy Spitznagle and Emily Yakel, an expert in women's health physical therapy; and Dr. Kerstin Hoffman, an expert in yoga, physical therapy, and group care. Together we developed Peer-Empowered Endometriosis Pain Support (PEEPS), which integrates three evidence-based approaches. 1) Physical therapy improves the pelvic floor and musculoskeletal components of pain, 2) Mindfulness interventions improve global impression of change, overall quality of life, and anxiety and depression, 3) Yoga reduces pain and improves emotional well-being and sexual function. Given that PEEPS combines an interdisciplinary team approach, an integrative setting, and group care into one program incorporating evidence-based components, it is likely to be an effective strategy to treat patients with endometriosis-associated pain. However, since these evidence-based interventions have not been bundled and delivered in this way before, effectiveness of this approach must be evaluated. Given the urgent need for translation of effective treatments into practice, I will take an implementation science approach to understand the implementation outcomes of PEEPS and the implementation context (or barriers and facilitators) of PEEPS.

Here, I propose to conduct a pilot clinical trial in which 40 patients with endometriosis and chronic pelvic pain attend PEEPS in addition to usual care. Within this trial, I will test the **central hypothesis** that PEEPS will lead to decreased endometriosis-related pain interference, improved quality of life, and decreased pain catastrophizing by pursuing the following **specific aims:**

Aim 1: Measure preliminary effectiveness of PEEPS. I will use validated patient-reported outcomes measures to assess preliminary effects on pain interference and quality of life. I **hypothesize** that patients in PEEPS will show decrease in pain interference in daily activities at program completion and 6-months post-completion than at baseline. With 40 patients attending PEEPS this pilot trial will assess both preliminary effectiveness as well as implementability of PEEPS.

Aim 2: Assess PEEPS implementation factors. 2a. Evaluate barriers and facilitators to PEEPS success. I will use an implementation science approach to expedite translation of PEEPS to the clinical setting. I will use the *Intervention Characteristics* (e.g. relative advantage, complexity, design quality) and *Process* (e.g., Planning, Reflecting and Evaluating) domains from CFIR to identify barriers and facilitators to PEEPS implementation at the patient and provider levels. 2b. Assess implementation outcomes of PEEPS**.** Guided by Proctor et al.'s *Implementation Outcomes Framework* and new guidance for CFIR, I will evaluate acceptability, appropriateness, and feasibility of PEEPS implementation.28,29 These outcomes will be measured through participant attendance, group flow and patient and facilitator feedback on individual sessions and the program as a whole.

APPROACH

Aim 1: Measure preliminary effectiveness of PEEPS

1.1. Patient population and recruitment: This pilot clinical trial will be conducted through the Department of OB/GYN at WUSTL. Forty patients will be recruited to participate in an 8-week curriculum of PEEPS. To equitably recruit a diverse group of participants, including those historically excluded from research, we will recruit from three sites: WUSTL Minimally Invasive Gynecologic Surgery (MIGS) (a sub-specialty referral practice), WUSTL General OB/GYN clinics, and Affinia Healthcare (a Federally Qualified Health Center). If a patient is eligible and elects to participate, written informed consent will be obtained in person while at a clinic visit, or via email or fax when the study is discussed by phone.

Inclusion and exclusion criteria:

Inclusion criteria	Exclusion criteria
• Age 18-48 years • Operative confirmation of endometriosis • Chronic pelvic pain (defined as pain perceived to originate from the pelvis, lasting ≥6 months) • No plan to have surgery in next 12 weeks • Be able to attend eight 2-hour weekly sessions on the WUSTL campus	• Non-English speaking • Currently pregnant • Severe physical impairment • History of hip, back, or spine surgery • Opioid use ≥ 5 days in the past 3 months, other than for the 6-week post-operative period • Current or history of psychiatric disorder with psychosis

1.2. Data collection: Participants will be recruited for sequential 8-week PEEPS cohorts with a goal of 6-10 subjects in each cohort. At baseline, we will collect data on medical and psychosocial history, and prior and current treatments for endometriosis (medications, physical therapy, surgery, counselling, alternative therapies). Participants will complete baseline questionnaires prior to the first session of PEEPS, within one month of PEEPS completion, and at 6-months post-completion. Surveys will be administered in Research Electronic Database Capture (REDCap), and the following measures will be administered:

- PROMIS pain interference SF 8a: validated, 8 questions, assesses pain interference in daily activities[43]
- PROMIS pain intensity: validated, 3 questions, measures pain on a 1-5 scale over the past 7 days[44]
- Endometriosis Health Profile-30: validated, 30 questions, endometriosis-related quality of life measure[45]
- PROMIS Physical Function SF10a: validated, 10 questions, measures physical activities of daily living[46]
- PROMIS Anxiety SF7a: validated, 7 questions related to anxiety in past 7 days[47]
- PROMIS Depression SF8b: validated, 8 questions related to depression in past 7 days[48]
- Female Sexual Function Index: validated, 19 questions[49]
- Pain Catastrophizing Scale: validated, 13 questions[50]
- Patient Global Impression of Change: validated, 1 question, on a 0-10 continuous scale[51]
- Modified Everyday Discrimination Scale: validated, 9 questions, with 10 follow up questions if discrimination ongoing to assess experiences of healthcare discrimination[52]
- Personal goals: I will ask participants to identify three personal goals related to quality of life that they hope to achieve by participating in PEEPS, such as “Be able to go on a hike without pain limiting my activity”.

Patients will receive a unique link to their questionnaires at each of the three time points. Participants who do not respond will be sent three reminder messages and receive up to two completed phone call reminders. The research team will be responsible for day-to-day study supervision and data management. The study statistician will perform monthly data quality control analysis for missing values and data discrepancy and create monthly data reports on screening and recruitment. Data security will be maintained by using dedicated password-protected, encrypted computers with multiple backups.

1.3. Analysis plan: This is a pilot observational trial of a novel intervention where preliminary effect size is unknown. Recommendations for pilot clinical trials suggest using 12-70 subjects.[53] Enrolling 40 subjects will reduce imprecision around the standard deviation estimate and allow for sufficient participants in PEEPS to asses implementation factors. We hypothesize that patients engaging in PEEPS will experience less pain interference after completing PEEPS than at baseline. Descriptive statistics and two-sample t-test will be performed for numeric variables with normal distribution, Wilcoxon Rank Sum test if not normal distribution. Frequency analysis and Fisher exact or Chi-square test for categorical variables will be performed as appropriate. Longitudinal analysis on primary outcomes and secondary outcomes using paired t-test

comparing each time point (completion and 6-months) to baseline. Mixed effects model will be used for fixed effect of PEEPS compared to baseline over time with random effect of intercepts. For categorical outcomes, we will calculate relative risk and 95% confidence intervals.

1.4. Feasibility of recruitment and retention: Patients will receive $25 for completion of the baseline questionnaire and $50 for each of the two other time points (completion and 6- months). Patients who complete all portions of the study will receive a total of $125.

Aim 2: Assess PEEPS implementation factors

2a. Evaluate barriers and facilitators to PEEPS success.

Overview: Given the urgent need for effective endometriosis-related pain treatments, developing an intervention that can be expeditiously translated into clinical practice is just as important as developing an effective intervention. Thus, I will use the *Characteristics of Individuals* and *Process* domains from the CFIR framework to understand the implementation barriers and facilitators of PEEPS. In D&I science, "context" describes the circumstances and unique factors that surround intervention implementation efforts (in this case PEEPS), including barriers and facilitators to intervention success. A thorough understanding of context can help guide intervention adaptations and development of strategies to support intervention implementation.

Consolidated Framework for Implementation Research (CFIR): CFIR is a comprehensive implementation framework[54] that will provide a structured way to approach the multi-level implementation of PEEPS. Guided by constructs in the *Intervention Characteristics* (e.g. relative advantage, complexity, design quality) and *Process* domains (Planning, Executing, Reflecting and Evaluating), I will assess PEEPS taking into consideration that patients and clinicians are active participants, inherently evaluating and developing feelings about the intervention.

2b. Assess implementation outcomes of PEEPS.

Overview: Implementation outcomes are indicators of implementation success and can be used to distinguish implementation effectiveness from treatment effectiveness, a key step necessary to transition from a research protocol to community health.[28] If an intervention is not implemented well, treatment will not be effective. Given PEEPS' inter-disciplinary group care approach, it is important to understand implementation outcomes at both the patient and clinician levels.

Implementation Outcomes Framework (IOF): Proctor et al.'s *Implementation Outcomes Framework* provides a practical structure to measure and determine implementation effectiveness. The three early implementation outcomes of *acceptability*, *appropriateness*, and *feasibility* will guide assessment of PEEPS implementation in this pilot RCT (**Table 2**). These early outcomes are markers of implementability of a future intervention.[29] Details of *acceptability and appropriateness* are described in Table 2. As part of the *Feasibility* evaluation, we will analyze recruitment data, patient demographics, referral locations, referring provider characteristics, reasons for declining participation, and percentage of participants who complete each PEEPS session. This will allow us to determine the recruitment volume needed at each site for the future multi-site trial.

2.1. Data collection: I will administer valid and reliable surveys to PEEPS participants and facilitators weekly during session "Closing" time, and a summative survey at intervention completion (**Table 2**). These surveys contain Likert scale, dichotomous, and open-ended items. Participants will be notified that this feedback will be reviewed at study completion, and that pressing concerns should be addressed with one of the facilitators.

Table 2. Data Collection for implementation barriers and facilitators (i.e. context) and implementation outcomes (Aims 2a and 2b)

Factor	Definition	Level	Sample Type and Analysis	Aim and Framework
Intervention Characteristics				Aim 2a CFIR
Relative advantage	Advantage/disadvantage relative to existing treatments	Patient/ Clinician	· Validated, Quantitative[55]	
Complexity	Perceived difficulty of intervention and disruptiveness to daily life	Patient/ Clinician	· Validated, Quantitative[55] · Future PEEPS timing (summative)	
Design quality	Perceived excellence of intervention, format, and content	Patient/ Clinician	· Validated, Quantitative, Qualitative[55]	
Process				Aim 2a CFIR
Planning	Quality of intervention delivery method	Patient/ Clinician	· Quantitative, Likert scale · Suggestions for improvement, Qualitative	

Program execution	Carrying out intervention according to plan	Patient/ Clinician	· Validated, Quantitative, Qualitative[55]	
Reflecting & Evaluating	Feedback on experience with intervention	Patient	· Most helpful part, Qualitative · Least helpful part, Qualitative	
Acceptability	Stakeholder perception if PEEPS is agreeable/ satisfactory	Patient/ Clinician	· Satisfaction with intervention- Validated, Quantitative, Qualitative[56] · Likelihood of recommending to peer Quantitative, Likert scale	Aim 2b IOF
Appropriateness	Perceived fit, relevance, and compatibility of PEEPS Perceived cultural appropriateness of PEEPS	Patient Clinician	· Appropriateness of material, Validated, Quantitative[56] · Session flow, Validated, Qualitative[57] · Participant engagement, Qualitative · Group dynamics, Qualitative	Aim2b IOF
Feasibility	Extent to which PEEPS can be successfully carried out	Patient	· Administrative data on recruitment, enrollment, retention, Quantitative	Aim 2b IOF

CFIR, Consolidated Framework for Implementation Research; IOF, Proctor's Implementation Outcomes Framework.

2.2. Outcome measures: After completion of all PEEPS sessions, we will use a mixed methods approach that includes descriptive statistics and content analysis. Categorical survey outcome data will be analyzed using chi-square or Fisher's exact tests as appropriate. Ordinal survey outcome data will be analyzed using the Mann-Whitney U test. A p-value of 0.05 will be used to assess significance. Qualitative data from open-ended survey responses will be entered and analyzed in NVivo 12 software. Qualitative data will be analyzed for *a priori* and emerging themes.[58] We will examine satisfaction using sentiment analysis of major and sub-themes. We will then triangulate the quantitative and qualitative data to gain insight on the constructs measured in Table 2. These findings will be used to optimize PEEPS in preparation for the definitive multi-center effectiveness RCT.

PROTECTION OF HUMAN SUBJECTS

1. Risk to Human Subjects

1a. Human Subjects Involvement, Characteristics, and Design. This study is a pilot randomized controlled trial of people with endometriosis-related chronic pelvic pain. Patients meeting inclusion criteria will be enrolled from the outpatient OB/GYN clinic setting. Patients will be recruited for sequential 8-week PEEPS cohorts with a goal of 6-10 subjects participating in each cohort. Enrolled patients will be randomized to PEEPS plus usual care versus usual care alone. Recruitment and randomization will continue until 30 participants in the PEEPS arm attend at least one PEEPS session. Randomization will occur in REDCap with the assistance of the study statistician.

1b. Study Procedures, Materials, and Potential Risks. This study will involve collection of data from two key components.

1) Clinical data collection: Relevant clinical and demographic data will be abstracted from medical records including medical and psychosocial history, and prior and current treatments for endometriosis (medications, physical therapy, surgery, counselling, alternative therapies). This data will be abstracted from the patients medical records. For all subjects, these data will be stored in a secure, password-protected REDCap database anonymized with study identifier only. No private identifiable information will be collected.

2) Survey data collection: Subjects in both arms will complete surveys at baseline (defined as the month leading up to the first PEEPS session for their cohort), PEEPS completion, and 6- and 12-months after completion. The validated patient-reported outcomes measures will assess pain severity, physical function, history of sexual trauma, mood symptoms, other quality of life measures, and experiences of discrimination in healthcare. This survey data will also be collected and stored in the password-protected REDCap database.

The proposed study involves potentially rare risks to the subjects, including loss of confidential health information, musculoskeletal injury to patients while participating in the yoga and physical therapy components, emotional distress in completing validated surveys on mental health, and excessive demands on patients. Patients with endometriosis and chronic pelvic pain have intermittent pain exacerbations, sometimes due to common triggers such as menses, ovulation, or intercourse, but many exacerbations are unpredictable and

sporadic. It is possible that participating in PEEPS might a pain trigger for some participants. Protections against anticipated risks are outlined below under "Adequacy of Protection Against Risk."

2. Adequacy of Protection Against Risks

2a. Informed Consent and Assent. Patients will be referred by their primary women's health clinician from WUSTL Minimally Invasive Gynecologic Surgery, WUSTL OB/GYN, and Affinia Healthcare (a federally qualified health center). Pre-screening for eligibility criteria via medical record review will be conducted, and potential participants will be approached either in clinic by a research assistant or by telephone. None of the data obtained in pre-screening will be saved. The study design, expectations, and risks/benefits will be explained, and potential subjects will be given a written informed consent form by a study team member. Consent will be documented by using a signed consent form. Trained study team members will have sufficient time to explain the study and the informed consent carefully in a private room, and eligible patients may decide to enroll at any time as long as they meet eligibility criteria. Of note, our team has significant experience recruiting patients as part of prior investigations in this population. Adult subjects' capacity to consent will be determined by the primary clinician and their medical assessment of the patient.

2b. Protection Against Risk. PEEPS is a group care intervention comprised of education, yoga, mindfulness, and physical therapy. The intervention will be delivered by a gynecologic surgeon/endometriosis specialist, experienced physical therapist/yoga instructor, and clinical psychologist.

Informed Consent*:* Informed consent will always be obtained before a subject participates in any component of the protocol. For all participants, the consent form will be explained to participants as well as having them read the consent themselves. This consent will contain a detailed description of all study procedures, as well as any possible risks and/or benefits. Patients will be asked to sign the consent form. It will be clearly communicated to the patients during the consent process that their decision to participate will not affect their gynecologic care. A copy of the consent forms will be kept in a locked cabinet in the research office and participants will be given a copy of the consent forms for their own records.

Musculoskeletal injury: The activity components will be explained, and modified according to each persons' ability and comfort. The experience of the facilitator leading yoga classes, group care physical therapy sessions, and one-on-one physical therapy sessions mitigates the risk to participants engaging in activity. Patients will be encouraged to verbalize their experiences with the activities, and to inform the facilitators if discomfort with any activity. Such activity will be modified to a tolerable version or discontinued. We will exclude patients with severe physical impairment or history of hip, back, or spine surgery, as these groups might be at increased risk of injury from the yoga component.

Emotional distress: While it is possible that completing surveys on mood symptoms could cause emotional distress, all surveys we will administer are validated and reliable, which minimizes this risk. All portions of the curriculum have been designed and adapted with a trauma informed approach to minimize risk of re-traumatization from the educational content or delivery. Each session will have components of mindfulness and/or cognitive behavioral therapy components which we anticipate will be helpful to patients in coping with pain and the mood disorders associated with endometriosis-related pain. We will encourage participants at each PEEPS session to reach out to their doctor to discuss any symptom changes or for urgent needs/concerns regarding their health throughout the study period. We will screen for severe depression and suicidality at each questionnaire time point and have developed a triage and referral plan should a participant experience severe depression or suicidality. We will exclude participants with a history of psychiatric disorder with psychosis to minimize psychological risk associated with completing questions on mental health.

Pelvic pain exacerbation: Patients with endometriosis and chronic pelvic pain have intermittent pain exacerbations, sometimes due to common triggers such as menses, ovulation, or intercourse, but many exacerbations are unpredictable and sporadic. It is likely that some participants given their endometriosis-related chronic pelvic pain will have a pelvic pain exacerbation during the course of the intervention, unrelated to PEEPS. Patients will be encouraged at each PEEPS session to reach out to their OB/GYN to discuss any symptom changes or for urgent needs/concerns regarding their health throughout the study period.

Protection of Confidentiality*:* As with any research, there is a risk of accidental loss of privacy and inadvertent release of protected health information, and this can lead to psychological, social, or legal distress. Although these are serious risks for study subjects and their families, the likelihood of adverse effects from these potential risks within this protocol are extremely low when using the system of patient identifiers and unique research code numbers located in different locations and password protected datasets with limited accessibility. Patients will be consented in private rooms and will be notified that their decision to participate will not affect their medical care. Clinical data will be entered into Research Electronic Data Capture (REDCap), a secure, web-based application available through the Clinical and Translational Science Award at WUSM. Our REDCap database is hosted on Unix servers on a secure computer network. Access to our REDCap system is protected by multiple layers of security, running on Unix platforms configured for strict user permission policies. User access is provided via an external secure web server. All web communication between the user web browser and the web server is SSL encrypted. Further protections are provided via strict Unix permission configurations on the servers themselves. Access to the data username/password keys is restricted in accordance with our University's HIPAA policy.

Burden to Patients: The patients will not be charged for any evaluations, nor will they be obligated to continue with the study if they wish to withdraw. Such withdrawal will not affect any programs or services for which they would be otherwise eligible. Parking or public transportation costs will be covered to minimize cost of participation to the subject. Participants will receive $25-50 gift cards to compensate them for the time spent on survey completion.