PennState

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

A randomized double-blind placebo-controlled trial to assess the effectiveness of low-dose naltrexone in combination with standard treatment in women with chronic pelvic pain secondary to endometriosis.

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1.0 Objectives

1.1 Study Objectives

The central hypothesis of the research study is that low dose naltrexone (LDN), in combination with hormonal suppression of endometriosis (standard of care), will lead to significant improvement of endometriosis-related pain. The proposal seeks to: 1) determine if the addition of LDN to standard endometriosis treatments will improve patient- reported endometriosis associated pain using daily 100-point Visual Analogue Scale (VAS) scores and 2) measure the impact of treatment on quality of life as measured by questionnaires including the Endometriosis Health Profile-30 (EHP30) and the Patient's Global Impression of Change (PGIC), and Patient Global Assessments (PGA) specific to pain, dysmenorrhea, and non-menstrual pelvic pain. We propose a double-blind placebo-controlled randomized clinical trial to achieve the following aims:

Aim 1: Identify the impact of LDN on daily endometriosis associated pain. We hypothesize that LDN in combination with standard hormonal suppression of endometriosis will decrease endometriosis associated pain reported using the VAS as compared with hormonal suppression alone.

Aim 2: Identify the impact of LDN on quality of life among women with endometriosis. The EHP30 and PGIC are surveys used to measure quality of life outcomes. We hypothesize that LDN in combination with standard hormonal suppression of endometriosis will improve quality of life as compared with hormonal suppression alone

1.2 Primary Study Endpoints

The primary study endpoint is the difference in endometriosis associated pain as reported in daily VAS between study groups.

1.3 Secondary Study Endpoints

The secondary study endpoints will include the following quality of life measures:
1) Patient's Global Impression of Change (PGIC) surveys
2) Endometriosis Health Profile-30 (EHP 30) surveys
3) Patient Global Assessment (PGA)- pain, dysmenorrhea, non-menstrual pelvic pain

Additional secondary outcomes will include pain medication use (opioid and non-opioid). Subject reported daily analgesic use (NSAIDs and opioid) will be recorded and narcotic prescriptions will be verified using the state run Prescription Drug Monitoring Program monthly. Subject reported side effects to medications will also be monitored.

2.0 Background

2.1 Scientific Background and Gaps

Endometriosis is a significant public health problem. It is estimated to occur in 6-10% of the general female population.[1,2,13] It is defined as the presence of endometrial glands and stroma located outside of the intra-uterine cavity.[2,14] The primary symptoms of endometriosis are debilitating, cyclic pelvic pain and infertility.[3,4] The prevalence of endometriosis among women with pelvic pain or infertility increases to 40% when compared to their healthy peers. Some experts suggest that endometriosis is present in over 70% of women with chronic pelvic pain.

The exact cause of endometriosis remains unknown; however, the major mechanism is thought to be retrograde menstruation, otherwise known as Sampson's Theory.[1,2] During menses the uterine lining, known as the endometrium, breaks down and begins to separate from the muscular portion of the uterine cavity. This process results in bleeding. The muscular portion of the uterus then contracts and expels the endometrial tissue and blood through the cervix into the vagina and out of the body. For many women, a small amount of endometrial tissue and blood is expelled in a retrograde fashion through the fallopian tubes and into the abdominal cavity.[1,2] The blood and endometrial tissue then settle into the dependent parts of the pelvis. This theory is consistent with the clinical presentation of endometriosis, as the most common locations of endometriosis are the ovary, the recto-vaginal space, the pelvic sidewall along the course of the ureter and the bladder surface.[1,2]

Endometriosis implants, although small, can have a major impact on the quality of life for many women. Endometriosis is associated with pain that is disproportionate to cellular injury and seems to be hyper responsive to inflammatory processes.[1,2,14] In addition, they are responsive to the changes in hormone levels, particularly estrogen and progesterone, which fluctuate during the menstrual cycle.[1,2,4] These hormonal changes along with the significant inflammation that occurs immediately before and during menses play a large role in the symptoms of debilitating pain experienced by women. Some women experience similar symptoms during other clinical situations leading to inflammation in their pelvis. For example, constipation, diarrhea, or bladder infections are some of the many other causes of significant pain in endometriosis patients.

There are many challenges in the diagnosis and management of endometriosis. Current standards require surgery with either pathologic confirmation of biopsied lesions or direct visualization of "classic" appearing lesions for diagnosis. Endometriosis is not visualized via any current imaging techniques. Blood, urine and other body fluid evaluation cannot provide a diagnosis either. The invasive nature of diagnostic testing often leads to a delay in diagnosis of 6-11 years among women, including those with symptoms highly suggestive of endometriosis. Unfortunately, this leads to delays in treatment.

Given the frequent delays in diagnosis, many women also have narcotic pain medications incorporated into their treatment plan secondary to the severity and recurrent nature of endometriosis-associated pain.[1,3,9,15] This often occurs with or without a formal diagnosis of endometriosis. Currently, I work at a regional referral center for the management of endometriosis. Many patients present to our clinic already have been exposed to narcotic pain medications prior to their initial consultation.

Current literature reports that in 2014 alone US retail pharmacies dispensed 245 million prescriptions for opioid based narcotic pain relievers.[15] Three to four percent (9.6-11.5 million) of the adults in the US population are prescribed long-term opioid therapy.[15] Currently, there are no published data evaluating the utilization of long-term opioids in the endometriosis population. Secondary to this knowledge gap we evaluated data from a national, longitudinal, claims-based database to evaluate opioid use in endometriosis patients. We identified 706, 863 women meeting inclusion criteria that had the diagnosis of endometriosis and also had at least 1 year of continuous data prior to and 2 years of continuous data following the diagnosis of endometriosis. We found several strong correlations between endometriosis and opioid use. Among women with endometriosis not only was there a significant increase in the percentage of subjects getting a prescription for opioids (56.3% vs 34.5%) in endometriosis patients vs. controls, but women with endometriosis who received opioids were more likely to receive multiple prescriptions and had a higher median cumulative dose of opioids that their matched controls (manuscript in preparation). Due to the growing opioid epidemic and the limited effective treatments for endometriosis related pain, there is a dire need to understand

the extent of opioid utilization in this patient population. We must continue to work to develop effective non-opioid based treatments that alleviate endometriosis-associated pain symptoms and decrease the use of narcotic pain medications for endometriosis.

Naltrexone is an opioid antagonist that is FDA approved for the treatment of opioid and alcohol dependence. Naltrexone is thought to act through competitive antagonism at the level of opioid receptors in the central nervous system.[6,5] Naltrexone is absorbed orally and metabolized into its active metabolite 6-beta-naltrexone during its first pass through the liver.[5] It is widely distributed throughout the body giving it great bioavailability. Naltrexone is primarily excreted in urine.[5] There is emerging evidence that when used at a significantly reduced dose (approximately 1/10 the dose traditionally prescribed), naltrexone has different pharmacologic effects.[6,5] Low dose naltrexone (LDN) has been used and studied in other chronic conditions. Most of the data are related to multiple sclerosis, Crohn's disease, and fibromyalgia.[6,5] Current literature reports that LDN is well tolerated with minimal side effects. The most common side effect reported was vivid dreams.[5] There is still a significant lack of randomized controlled trials for LDN use in any condition; however, both animal and human studies have demonstrated promising results.

LDN is thought to function through multiple different mechanisms that would be expected to benefit women suffering with the chronic symptoms of endometriosis-associated pain. Three of these mechanisms will be discussed here. First, LDN causes upregulation of opioid receptors and increased endogenous opioid production.[6,5,12] Second, it blocks toll-like receptor 4 (TLR4) in glial cells found in the central and peripheral nervous system. Finally, LDN has been demonstrated to impact the production of peripheral inflammatory cytokines.

Dr. Ian Zagon and team have done significant amounts of work in this area using rodent models. Their hypothesis of the mechanism of action of LDN is that is causes transient and incomplete blockade of opioid receptors. This phenomenon has been demonstrated with both naltrexone and naloxone in multiple studies. The consequence of exposure to LDN has been referred to as an opioid rebound effect. This leads to improved endogenous analgesia through increased opioid production and sensitivity.[6,5,12,16,17] The concept of inducing a paradoxical effect with variable doses of medication acting at opioid receptors is not novel to naltrexone; in fact it has been demonstrated previously with low-dose morphine. Multiple previous studies have also demonstrated hyperalgesia in rats when exposed to morphine as low doses.[5] The effect was routinely described at doses around 1/10 the standard dose given to treat pain. The paradoxical effects of naltrexone also seem to present as doses around 1/10 the standard treatment doses.[5]

It is well know that inflammation is a key component in endometriosis-associated pain.[1,2] Non-steroidal anti-inflammatory medications are considered first line treatment for endometriosis, but often fall well short of providing adequate pain control.[3,4] Evidence suggests that women with endometriosis can be thought of as having a pelvic inflammatory condition.[2] Additionally, endometriosis lesions are associated with increased peritoneal vascularity and innervation.[2] This is thought to play a significant role in pain. It is hypothesized that the combination of increased nerve density along with recurrent inflammatory processes in the female pelvis (e.g. menses) cause devastating symptoms often presenting similar to neuropathic pain.[1,2,14] The evidence that LDN has antagonistic effects on TLR4 in the glial cells suggests that it could be an ideal medication choice for endometriosis-associated pain.[6,5] Activation of the microglia in the central nervous system has been shown to increase inflammatory and excitatory factors leading to pain sensitivity as well as other symptoms. To the contrary, opioids have been shown in previous studies to stimulate TLR4 activity leading to opioid induced inflammation.[6,5] This may be one explanation as to why opioid therapy has not demonstrated improved outcomes with chronic use in endometriosis or other chronic inflammatory conditions such as fibromyalgia.

These data are further supported by other studies performed using dextro-naltrexone. This stereoisomer of naltrexone is active at the glial cell and not at the opioid receptor. Dextro-naltrexone demonstrated both analgesic and neuroprotective properties.[5]

Most research demonstrating the general anti-inflammatory effects of LDN have been completed in animal models, but there are some pilot studies demonstrating this effect in humans as well. Multiple pilot studies have demonstrated decreased levels of inflammatory markers in women with fibromyalgia following administration of LDN.[5,7,18] Fibromyalgia (similar to endometriosis) is considered an inflammatory disorder. One study demonstrated that women with fibromyalgia and an elevated erythrocyte sedimentation rate (ESR), which is a serum marker for inflammation, had improved response rates to LDN as compared to women with fibromyalgia and a normal ESR.[7] A separate 10-week crossover trial using LDN in women with fibromyalgia demonstrated significantly decreased plasma concentrations of multiple key pro-inflammatory cytokines as well as a 15% reported decrease in fibromyalgia associated pain.[18]

In summary, endometriosis is a devastating disease that impacts nearly 1:10 women in the reproductive years or their life. The pathophysiology of endometriosis is not completely understood, however, there is strong evidence that inflammation plays a major role in the symptoms associate with endometriosis. Current strategies for the management of endometriosis-associated pain often leave women seeking additional relief in the form of opioid-based treatments. In light of the current opioid epidemic it is important that we continue seek non-opioid based therapies that can provide symptomatic relief while we continue to try and better understand this debilitating disease. LDN has gained some popularity as an off-label treatment for inflammatory conditions such as multiple sclerosis, Crohn's disease and fibromyalgia, but the literature has nothing to offer in the way of significant randomized controlled trials to adequately test the mounting evidence that LDN is beneficial in chronic inflammatory conditions to include endometriosis.

2.2 Previous Data

Our preliminary data includes a retrospective analysis of national claims data; we compared narcotic use in 706,863 women with endometriosis with age- and region-matched controls without endometriosis. In the two years following the diagnosis of endometriosis, 56.3% of women with endometriosis had filled a prescription for narcotic pain medication as compared to 34.5% of the controls over a similar two-year time frame (manuscript in preparation). It is critical that we find non-narcotic alternatives to symptom management for this group of women suffering during what should be the peak of their productive years of life. We do not have preliminary data specific to the use of LDN. The results of this study would potentially serve as preliminary data for future large-scale multi-center studies. There is sufficient preliminary data (for alternative disease states) in the existing literature regarding the safety and potential efficacy of LDN to support the further study of LDN. These studies are also discussed in more detail in the background section of the protocol.

2.3 Study Rationale

Naltrexone hydrochloride is a well-known, competitive opioid antagonist traditionally used to treat opioid overdose or addiction. At much lower doses, naltrexone has significantly different pharmacologic properties. Low-dose naltrexone (LDN) acts on non-opioid receptors in the central nervous system to decrease activation of microglial cells and decrease plasma levels of multiple inflammatory cytokines. LDN has also been shown to transiently block all three subtypes of opioid receptors (μ,κ,δ) resulting in an upregulation of not only opioid receptors, but also increasing endogenous opioid production. Early studies of LND in other inflammatory disorders, such as inflammatory bowel disease and fibromyalgia, have demonstrated promising results. Since the pelvic pain associated with endometriosis is due in part

to increased peritoneal inflammation, LND has the potential to provide non-narcotic analgesic relief by decreasing endometriosis-associated inflammation.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

Inclusion

- Premenopausal female ages 18 to 45 years old on the day of signing informed consent.
- Must agree to use only study-specific analgesic medications during the study and is not known to be intolerant to them.
- Diagnosed with endometriosis and has had, within the last 10 years prior to signing the informed consent, surgical diagnosis with direct visualization and/or histopathologic confirmation of endometriosis.
- Is not expected to undergo gynecological surgery or other surgical procedures for treatment of endometriosis during the study period.
- Agrees to use contraception if not surgically sterile during the entire study.
- Patients using oral contraceptives, LARCs and/or GnRH agonists/antagonists for contraception and/or management of endometriosis, with a stable regimen, will be able to continue in the study, however, women using oral contraceptives and GnRH agonist/antagonists will be switched to Norethindrone acetate during the 1-2 week run-in period as prescribed by principle investigator.

3.2 Exclusion Criteria

Exclusion

- Women that are pregnant, breastfeeding or trying to conceive.
- Patients with chronic daily opioid use and any chronic pain or frequently reoccurring pain condition, other than endometriosis, that is treated with opioids or requires analgesics for more than 7 days per month.
- Patients with abnormal liver function tests (greater than 3x normal limit) in the past year or history of liver disease. Routine screening of liver function is not required.
- Non-English speaking or inability to read and understand English secondary, in part, to the need to read and report daily results in English.
- Undiagnosed vaginal bleeding
- Patients with history of opioid, illicit drug or alcohol abuse
- Patients currently taking thioridazine
- Patients with a history of suicidality
- Patients with current or history of unstable depression or other psychiatric disorder who, by PI judgement, are unstable or not well controlled
- Known, suspected or history of cancer of the breast
- Active deep vein thrombosis, pulmonary embolism or history of these conditions
- Active or recent arterial thromboembolic disease (e.g., stroke, myocardial infarction)

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Subjects will be removed from the study for safety reasons. Subjects will be evaluated for potential negative reactions to study medications at each visit. Additionally, subjects will be advised to contact the study team with any new negative symptoms to arrange evaluation.

Additionally, unintended pregnancy during the study period will meet criteria for withdrawal from the study.

Withdraw of consent at any time during the study period will also constitute the withdrawal of study subjects.

3.3.2 Follow-up for withdrawn subjects

The statistical methods allow for withdraw/screen fails. Subjects will be asked to return the study drug to the site if withdrawn or removed from the study. No other safety follow-up planned.

If the subject is removed from the study for any of the above reasons, she will receive the appropriate treatment based on the decisions of her providing physician team. No further data will be collected on these patients.

4.0 Recruitment Methods

4.1 Identification of subjects

Potential subjects will be identified within our Minimally Invasive Gynecological (MIGS) Division Outpatient clinic location and others identified as having endometriosis within PennState Women's Health department. We have created an endometriosis database, which we use to screen potential subjects that may qualify for this study. We will also utilize an approved flyer, patient recruitment letter, StudyFinder and EIM report request to identify potentially eligible subjects. In addition, we have developed a MIGS Research Patient Form to give clinic patients at their intake to gauge potential interest in any current studies within the Minimally Invasive Gynecologic Surgery Division.

4.2 Recruitment process

Subjects will be recruited from various MIGS and Women's Health clinic locations within Penn State Health. Participation will be purely voluntary. Subjects will be compensated for their time and effort. Written informed consent will be obtained prior to the study. We will use a study coordinator to assist us with contacting patients for their follow up visits and completing their surveys.

We do not anticipate having any difficulty recruiting these women into the study given our extensive experience with this to date. We are currently one of the highest volume Minimally Invasive GYN Surgery groups in the region. In 2016 we had 2700 patient encounters for endometriosis/female pelvic pain. Additionally, 80% of these encounters involved patients located within 10 counties that included Dauphin County and those counties adjacent to Dauphin County within the Penn State Health region. The close proximity of the patients will help increase the likelihood of patient participation. In the past 12 months has seen 275 new patient consults, with nearly 900 total clinic visits and over 950 surgical procedures performed specifically for endometriosis or pelvic pain.

We will meet on a regular basis to discuss how well we are doing with recruitment and retention. We have designed an easy to follow study, thus we do not anticipate difficulty with retaining these subjects. Based on our previous clinical trials involving women with endometriosis, we assume an 80% retention rate and we will recruit an average of 64 subjects per year.

4.3 Recruitment materials

The PI will monitor recruitment and retention rates for the study monthly to ensure that the goals are being met. In addition, we will collaborate with the Penn State Clinical Trials Office and Office of Marketing and Communications to promote the study and increase recruitment efforts. IRB approved flyers will be hung in our Minimally Invasive GYN Surgery and around campus at approved locations. The MIGS Research Patient Form will be given to patients at their clinic visits, collected by clinic staff, and then forwarded to study coordinators to contact patients with applicable study information. Patient recruitment letters will be sent to previous study participants with endometriosis who wished to be contacted for future research opportunities to start. The letter will also be used to provide study information to all identified endometriosis patients within PennState Women's Health (via EIM request).

We will also utilize StudyFinder, which is an online database that connects interested volunteers with a variety of studies, which University researchers are conducting. Visitors can browse by topic or search for a keyword to discover available studies at Penn State Hershey Medical Center. StudyFinder is also promoted to the community through Web advertising, Google search and billboards. We will also register this study at ClinicalTrials.gov. If recruitment and retention are inadequate, we will begin to advertise in the broader central Pennsylvania area and with offices known to refer endometriosis patients to our practice.

4.4 Eligibility/screening of subjects

When the study team receives information about a potential subject, follow-up is made to verify eligibility. If excluded, no further questions are asked and they are thanked for their time. If eligible the subject is scheduled for a visit.

Follow-up includes a phone screen of the potential subject by asking questions such as, ensuring the subject is premenopausal and in between the ages of 18 and 45 years old, agree to only use study-specific analgesic medications during the study and if intolerance to oxycodone and ibuprofen are known, agrees to use Norethindrone acetate and either their LARC or other barrier contraception while in the study, if the subject plans on becoming pregnant or trying to conceive at any point during the study, if the subject has any chronic daily narcotic use and any chronic pain other than endometriosis, and verify the subject is able to speak and read English to answer the surveys. We will also confirm that the subject is willing and able to be reliably contacted by email for study specific purposes.

If the participant passes the phone screen, the participant will be scheduled for a screening visit. After consent and receiving Norethindrone acetate, an email will be sent for the subject to complete the daily surveys for next 6-7 days. Upon completion of the surveys, the participant will pass or fail the screening process.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

In accordance to HRP-090 SOP for the Informed Consent Process, the potential subject will be given a copy of the most current approved consent document for review in advance. The consent process will take place in a private room setting in the clinic or the Clinical Research Center (CRC). The consent document will be

provided for review and discussion will take place. Consent will be obtained prior to any study procedures being done.

5.1.1.2 Coercion or Undue Influence during Consent

The subject will be informed that their participation in the study is voluntary. The subject will receive a copy of the consent form to read at home prior to making a screening appointment. At the time of consent, all sections of the informed consent will be thoroughly reviewed with the subject and all of the subject's questions will be answered prior to signing. Once all questions have been answered and the subject verbalizes understanding of the study and its requirements and agrees to participate, the subject and coordinator sign the consent form. A copy of the signed consent form is provided to the subject.

5.1.2 Waiver or alteration of the informed consent requirement

A waiver of the consent process is requested for recruitment purposes in pre-screening the medical record to identify eligible subjects for the study. The pre-screening is a phone screen of the potential subject to ask questions such as, ensuring the subject is premenopausal and in between the ages of 18 and 45 years old, agree to only use study-specific analgesic medications during the study and if intolerance to oxycodone and ibuprofen are known, agrees to use oral contraceptive Norethindrone acetate and other barrier contraception while in the study, if the subject plans on becoming pregnant or trying to conceive at any point during the study, if the subject has any chronic daily narcotic use and any chronic pain other than endometriosis, and verify the subject is able to speak and read English to answer the surveys. This ensures that we are giving the right subject a scheduled screening visit.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

In accordance to HRP-091 SOP for Written Documentation of Consent, The consent form will be the most currently approved watermarked version and in a language understandable to the subject. All appropriate signatures will be obtained; one copy will be given to the subject and another will be place in the medical record.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Not applicable.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Not applicable. Subjects who do not speak English will not be enrolled due to the need to consent and surveys are all in English, which would require the subjects to read and speak English.

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

Not applicable

5.3.2.2 Adults Unable To Consent

Not applicable

5.3.2.3 Assent of Adults Unable to Consent

Not applicable

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

Not applicable

5.3.3.2 Assent of subjects who are not yet adults

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Subjects who are identified through review of PHI will be contacted and offered information about the study. If they are not interested, we will not keep any of their PHI on any paper or electronic screening logs, they will only be identified by initials and date they were contacted. Those who do agree to participate will have their PHI retained as described for this study.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

This protocol has strict and specific inclusion/exclusion criteria for subjects to qualify. Access to PHI in the medical record of a potential subject is necessary to assess eligibility prior to giving study information and the consent process. Discussion about the research will take place only if the patient appears to be eligible based on pre-screening efforts.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

The waiver is requested during pre-screening efforts and pre-enrollment to assess and identify only those women potentially eligible as well as the ability of the patient to be compliant to daily surveys.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

We propose to conduct a randomized double-blind placebo-controlled trial to evaluate the effectiveness of low-dose naltrexone (4.5 mg daily) in combination with a standard treatment (norethindrone acetate daily) on management of endometriosis-associated pain. Potential subjects will be screened in the Penn State Minimally Invasive GYN Surgery clinic for endometriosis-associated pain for greater than 6 months. Subjects will be screened from new and existing patients in the Minimally Invasive GYN Surgery clinic as well as from referral sites including surrounding general OBGYN and Primary Care practices. Those meeting all inclusion and exclusion criteria that are willing to participate will receive a detailed history and physical exam. Baseline survey data will be collected and entered into the RedCap secured database. At this time subjects will be set up for daily emails to complete VAS scores directly into RedCap. The first visit will be scheduled 1 week following the screening visit.

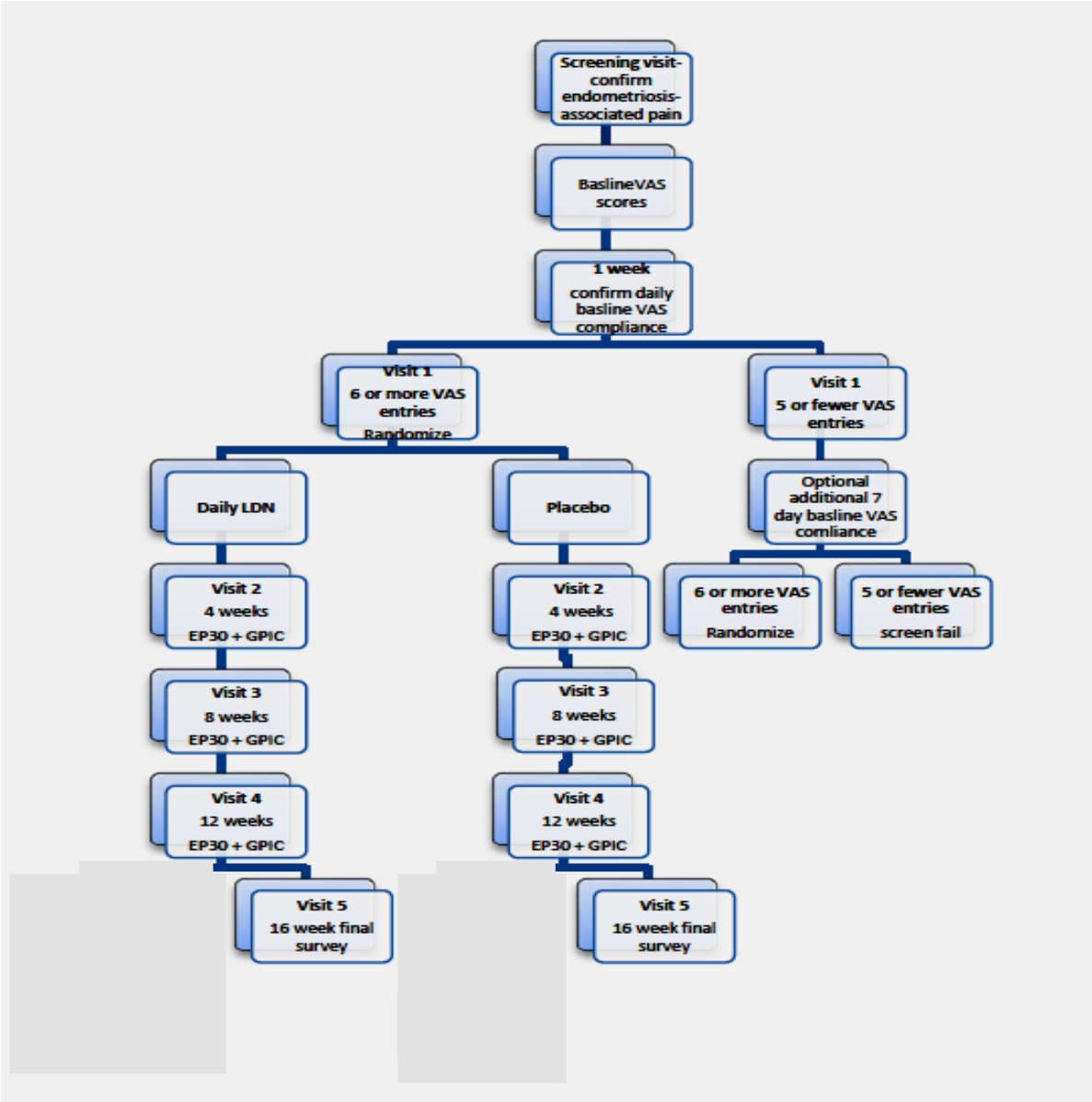
During the first visit subjects will be screened for daily reporting compliance. Subjects having completed 5 or fewer daily VAS scores and surveys during the baseline collection will be offered one additional 7-day period to improve compliance. If at the conclusion of the second 7-day run-in period of gathering daily baseline VAS scores and survey responses they continue to have 5 or fewer entries per week they will be considered a screen failure and withdrawn from the study. Those subjects meeting the 6 entry or more threshold of daily reporting at either visit 1 or following the second 7 day run in period will be randomized in the study.

Randomized subjects will receive norethindrone acetate 5 mg (up to 15 mg depending on subject's needs) daily plus LDN 4.5 mg daily or norethindrone acetate 5 mg (up to 15 mg) daily plus placebo. If the subject is taking norethindrone acetate prior to the study, she will remain on her current dose to start the study. Dose adjustments will be made, if needed, to achieve amenorrhea or minimize uterine bleeding. Menstrual status will be assessed and documented in a progress note if this should occur either in person at a study visit or via telephone in the interim. Norethindrone acetate is provided in 5mg tablets; if dosing adjustment is needed, the study staff will arrange to ship additional study drug via FedEx.

The study will include a 12-week intervention period during which subjects will be asked to record daily electronic VAS scores, report daily analgesic use (NSAIDs and opioids) and complete surveys every 4 weeks. VAS scores will be reported daily. Patient Global Impression of Change (PGIC), Patient Global Assessments (for pain, dysmenorrhea, nonmenstrual pelvic pain and function) (PGAs) and Endometriosis Health Profile-30 (EHP 30) surveys will be completed at 4-week intervals during the intervention (0, 4, 8, and 12 weeks). Subjects will be asked to complete a brief telephone interview visit at 16 weeks to complete final quality of life surveys (EHP 30, PGAs and PGIC).

Subjects will be screened for side effects and asked to record pain medication use throughout the duration of the study. Subjects will be dispensed a 4-week supply of medications from the Investigational Pharmacy. They will be required to bring medication bottles to each visit for counting and drug accountability. Any remaining capsules will be returned to the pharmacy. All study subjects and investigators will remain blinded to the study group until the completion of the study. In the event subjects cannot attend study visits in-person due to extenuating circumstances (e.g. related to COVID-19 pandemic), remote visits can be completed via telephone for which questionnaires will be sent via REDcap and IDS will ship of study drug. Drug accountability and monitoring for side effects can also be done via telephone.

7.2 Study Procedures



Visit Table Summary of Study Procedures

Procedure	Pre-screen	Screening Visit (beginning of Run-in week)	Visit 1 Enrollment – Randomization (Day 1)	Visit 2* 4-weeks (Day 28-30)	Visit 3* 8-weeks (Day 56-58)	Visit 4* 12-weeks (Day 84-86)	Visit 5 16-weeks Phone f/u (Day 114-121
Screening Criteria	X						
Informed Consent		X					
WERF Questionnaire		X					
Physical		X					
Past Medical History		X					
EHP-30		X	X	X	X	X	X
PGIC				X	X	X	X
PGAs		X	X	X	X	X	X
Study Drug Dispensed & Compliance		X (Only Norethindrone Acetate given, if needed)	X	X	X	X	
Daily Pain, Analgesic and Study Medication Assessment		X (6-7 days)	X (Daily)	X (Daily)	X (Daily)	X (Daily)	X (Daily)
Screening/Assessment of Adverse Events		X	X	X	X	X	X

(*) – these asterisked visits can be done remotely via telephone, if warranted due to extenuating circumstances.

7.2.1 Screening visit:

Screening Visit 1:
Pre-screening will take place over the phone with women identified as potential candidates for study participation via clinic visits or other previously discussed methods of subject recruitment. Initial contact will be made via the telephone to assess women's interest in participation. As per standard of care, narcotic usage is assessed during routine clinic visits.

If the subject meets all pre-screening criteria, the subject will be scheduled for a screening visit. At the screening visit, the informed consent will be reviewed and the subject will be given ample time to ask any questions or concerns about the study. Once informed consent is signed, the subject information will be placed in redcap and a test email will be sent to the subject. Those meeting all inclusion and exclusion criteria that are willing to participate will receive a detailed past medical history and physical exam. Baseline surveys and any adverse events will be collected and entered into the RedCap secured database.

The subject will complete the WERF survey, VAS score, EHP-30 and PGAs during the visit to ensure understanding and allow the coordinator to help with any questions. The subject will be given a 2 week supply of Norethindrone acetate to start during the run-in period and given instruction on how to complete the daily VAS scores and study questions. It will be explained to the subject that they must complete at least 6 out of the 7 days of surveys to be enrolled into the study. If the subject is unable to complete the 6 out of 7 days of surveys, the subject will be given one additional week to determine if compliance is attainable. (This will ensure provide ample opportunity for

enrollment for potential subjects with unpredictable barriers to completion in the first 7 days.) If the subject is unable to do so, they will be a screen fail. Those completing greater than or equal to 6 entries in either of the 7-day periods will be eligible for enrollment in the study. In the event of needing an additional 7-day run-in period, data points during the screening period will **not** be assessed in aggregate for eligibility.

7.2.2 Study Visit 1: Randomization/ Enrollment

The subject will be scheduled for a randomization/ enrollment visit one week after the screening visit. At this visit, the subject will be randomized into group A or B by IDS as long as the subject has met all the criteria for enrollment. This study will compare low dose naltrexone with a placebo, or sugar pill. Both study groups will receive norethindrone acetate for treatment of their endometriosis during the study period. Dosing for norethindrone acetate will be 5 mg to 15 mg depending on the subject's needs and will be adjusted as needed to achieve amenorrhea or minimize uterine bleeding as this standard treatment for endometriosis. The 2 groups are listed below:

Group	Treatment
A	Norethindrone acetate (daily) + Placebo (4.5 mg daily)
B	Norethindrone acetate (daily) + Naltrexone (4.5 mg daily)

The subject will be given 1-month supply of Norethindrone acetate and 1-month (30 day) supply of study medication and instructed to take it once a day. The subject will take the first dose of study drug in clinic with study personnel present.

Study subjects will receive education on analgesics approved for use in the study which are also within the standard of care for the management of pelvic pain associated with endometriosis. As standard of care for these patients, study subjects will be instructed to take ibuprofen as first time treatment and acetaminophen if additional pain relief is needed, both of which are available over the counter. Only if requested will a stronger medication be prescribed like oxycodone. If needed, to relieve pain, the subject will be advised to take first the ibuprofen 600 mg every 6 hours as needed for pain with food, then acetaminophen 1000mg every 6 hours as needed for pain. Subjects needing additional pain relief will need to discuss this with the study team in which oxycodone 5 mg every 6 hours as needed for pain will be prescribed. Refill prescriptions for opioid pain medication will be provided using the same dose and quantity beyond the screening visit on an as needed basis and will not be routinely provided at any subsequent study visits unless there is a documented need. The subject will complete an EPH-30 and PGAs surveys at the visit. The subject will be instructed to complete their daily surveys which include the VAS and medication compliance. We will also review and record any adverse events. At this time, we will also review compliance of daily reporting since the previous visit. Surveys will be sent via email through a secure link with RedCap and completed on-site during the visit.

7.2.3 Study visit 2: 4-week treatment

The subject will return in 4 weeks for a follow up visit. At this visit the subject will be given time to ask any questions or concerns they may have had over the past 4 weeks. The subject's compliance with daily surveys and medication compliance will be reviewed. The subject's medications will be counted and returned if needed.

The subject will be given another 1-month supply of Norethindrone acetate and 1-month supply of study medication. They will be instructed to take each once a day. To relieve pain, the subject will be advised to take Ibuprofen and acetaminophen as needed and oxycodone (if applicable). The

subject will complete the EPH-30, PGAs and PGIC survey prior to being discharged from the visit. We will also review and record any adverse events. The subject will be instructed to complete their daily surveys which include the VAS and medication compliance. Surveys will be sent via email through a secure link with RedCap and completed on-site during the visit.

7.2.4 Study visit 3: 8-week treatment

The subject will return in 4 weeks for a second follow up visit. At this visit, the subject will be given time to ask any questions or concerns they may have had over the past 4 weeks. The subject's compliance with daily surveys and medication compliance will be reviewed. The subject's medications will be counted and returned if needed.

The subject will be given another 1-month supply of Norethindrone acetate and 1-month supply of study medication and instructed to take it once a day. To relieve pain, the subject will be advised to take Ibuprofen and acetaminophen as needed and oxycodone (if applicable).. The subject will complete the EPH-30, PGAs and PGIC survey prior to being discharged from the visit. We will also review and record any adverse events. The subject will be instructed to complete their daily surveys which include the VAS and medication compliance. Surveys will be sent via email through a secure link with RedCap and completed on-site during the visit.

7.2.5 Study visit 4: 12-week treatment

The subject will return in 4 weeks for a final follow up visit. At this visit the subject will be given time to ask any questions or concerns they may have had over the past 4 weeks. The subject's compliance with daily surveys and medication compliance will be reviewed. The subject's medications will be counted and collected as the treatment period is completed. The subject will complete the EPH-30, PGAs and PGIC survey prior to being discharged from the visit. We will also review and record any adverse events. The subject will be instructed to complete their daily survey which is the VAS and pain medication consumption. Surveys will be sent via email through a secure link with RedCap and completed on-site during the visit.

Subjects will be offered continuation of norethindrone acetate daily and a prescription for this medication will be provided if needed as continued management of endometriosis at the conclusion of the study. No additional study medication will be provided at this visit. Subjects will be asked to continue to complete daily reports throughout the next 4-week period to assess symptoms following discontinued use of the study drug.

7.2.6 Follow up phone visit: 4-weeks after completion of study medication.

The subject will receive a follow-up phone call from the study coordinator 4 weeks after the completion of the study medication. At this visit the subject will be given time to ask any questions or concerns they may have had over the past 4 weeks. The subject's compliance with daily surveys will be reviewed. The subject will be emailed the EPH-30, PGAs and PGIC surveys via email through a secure link with RedCap. We will also review and record any adverse events. The subject will be thanked for participating in the study.

7.3 Duration of Participation

16 weeks

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Naltrexone is an opioid antagonist that is FDA approved for the treatment of opioid and alcohol dependence. Naltrexone is thought to act through competitive antagonism at the level of opioid receptors in the central nervous system.[6,5] Naltrexone is absorbed orally and metabolized into its active metabolite 6-beta-naltrexone during its first pass through the liver.[5] It is widely distributed throughout the body giving it great bioavailability. Naltrexone is primarily excreted in urine.[5] There is emerging evidence that when used at a significantly reduced dose (approximately 1/10 the dose traditionally prescribed), naltrexone has different pharmacologic effects.[6,5] Low dose naltrexone (LDN) has been used and studied in other chronic conditions. Most of the data are related to multiple sclerosis, Crohn's disease, and fibromyalgia.[6,5] Current literature reports that LDN is well tolerated with minimal side effects. The most common side effect reported was vivid dreams.[5]

7.4.2 Treatment Regimen

Arm A: *Placebo:* In Arm A, the participant will be placed on the daily placebo and standard endometriosis treatment (norethindrone acetate 5 to 15mg daily dose) medication. All medications will be taken orally. Pill counts (or case packet counts) will be monitored at each in patient study visit. Norethindrone will be taken for up to 14 weeks during the study period and the study drug will be taken for up to 12 weeks during the study period.

Arm B: *Low dose naltrexone:* In Arm B, the participant will be placed on daily low dose naltrexone (4.5 mg daily) and standard endometriosis treatment (norethindrone acetate 5 to 15mg daily dose). All medications will be taken orally. Pill counts (or case packet counts) will be monitored at each in patient study visit. Norethindrone will be taken for up to 14 weeks during the study period and the study drug will be taken for up to 12 weeks during the study period.

7.4.3 Method for Assigning Subject to Treatment Groups

Randomization is a critical feature of a clinical trial because it prevents treatment-selection biases. The statistician involved in this study will develop the programs necessary for the random number generator to create the randomization; however, the final random seeds used to generate the randomization scheme will be prepared by a statistician in PSU's Department of Public Health Sciences independent of the study in order to keep this study's statisticians blinded as well. The randomization scheme for this study will use variable-size, random permuted blocks to ensure that ensure the number of participants in each treatment arm. IDS will be performing randomization to ensure proper blinding of the study team. They will also be responsible for distributing the study medications according to assigned group as per there standard operating procedure.

7.4.4 Subject Compliance Monitoring

For daily low dose naltrexone or placebo and norethindrone acetate, study team will be dispensing study medication on visits. Study team will count study medication on visits. Participants are to bring study medication with them to each visit for compliance calculation.

7.4.5 Blinding of the Test Article

The naltrexone, norethindrone acetate, and placebo will be provided in individual packets that will be identical. The drug will be kept and dispensed in the Investigational Pharmacy at Penn State Hershey Medical Center and they will hold the randomization and unblinding key as needed. The investigators and biostatisticians will remain blinded to the allocation sequence and patient assignment.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The naltrexone, norethindrone acetate, and placebo will be monitored and dispensed by our Investigational Drug Services (IDS) Pharmacy. IDS will hold the randomization and unblinding key as needed. Participants will be given study drug to take one daily as prescribed.

7.4.6.2 Storage

Stability will be monitored and appropriate storage conditions will be assured by IDS Pharmacy. The drug will be kept and dispensed in the Investigational Pharmacy at Pennsylvania State Hershey Medical Center.

7.4.6.3 Preparation and Dispensing

The Investigational Pharmacy at Penn State Hershey Medical Center will dispense the study drug and placebo per institutional policy.

7.4.6.4 Return or Destruction of the Test Article

The Investigational Pharmacy at Penn State Hershey Medical Center will destroy returned study drug packets as per institutional policy.

7.4.6.5 Prior and Concomitant Therapy

All concomitant medications will be documented. There are no prohibited medications or therapies throughout the study.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

We plan to enroll 160 subjects over approximately 3 years of the 5-year study. Based on our previous clinical trials involving women with endometriosis, we assume an 80% retention rate and will recruit an average of 64 subjects per year (5-6 per month). We will have access to patients from a referral network that in the past 12 months has seen 275 new patient consults, with nearly 900 total clinic visits and over 950 surgical procedures performed specifically for endometriosis or pelvic pain. To maximize the success of the proposed study, we will monitor recruitment and retention rates for the study monthly to ensure that the goals are being met. In addition, we will collaborate with the Penn State Clinical Trials Office and Office of Marketing and Communications to promote the study and increase recruitment efforts.

We would anticipate a 50% screen failure rate secondary to the requirement of 85% compliance with daily electronic reporting during the one week run in period prior to randomization in the study. We have multiple on-going endometriosis studies that have scree-failure rates of less than 10% without the

stringent requirement of compliance, however, secondary to the nature of this study design, maximal compliance with daily reporting in necessary. Based on these estimates we would anticipate screening 320-350 patients to enroll our target of 160 subjects.

8.2 Sample size determination

The primary outcome will be the average area under the curve (AUC) as determined by the daily VAS scores collected per participant over the course of the trial. Previous studies have demonstrated that a 10 mm change in VAS scores and demonstrated a standard deviation of 20 mm. Using these previously published data as a guide for our sample size estimation, we believe a standardized effect size (i.e., the difference in the AUC VAS score means between the two intervention groups divided by the standard deviation) of 0.5 will be clinically relevant to detect. Furthermore, based on our prior research with endometriosis patients, we anticipate a withdrawal rate of 20%. Therefore, we propose a target sample size of 160 (80 per intervention) randomized participants for this trial. Such a sample size yields 80% statistical power with a two-sided, 0.05 significance level test to detect a standardized effect size of 0.5, while accounting for the 20% withdrawal rate. The true statistical power actually may exceed 80% because our statistical methodology will include partial data for those participants who withdraw (up to the point in time at which they withdraw).

8.3 Statistical methods

The VAS scores will be collected daily from 1-week pre-intervention to 12 weeks post-intervention. Prior to analysis, the AUC VAS scores will be calculated per participant separately for the 1-week pre-intervention period and the randomization to 12 weeks post-intervention period. Subsequently, the AUC VAS score data will be normalized per participant to an average AUC VAS score per week (i.e., 7 days) to account for participants that withdraw early from the study. The primary outcome of interest is the AUC VAS scores from randomization to 12 weeks post-intervention period. For this primary outcome, a linear mixed-model will be used to compare the average AUC VAS scores from randomization to 12 weeks post-intervention between the two intervention groups, adjusting for the covariate of opioid intake during the 12-week trial as measured in morphine equivalent units (MEUs)) and using the subject as a random effect in the model.

A secondary analysis with AUC VAS scores as the outcome will use a linear mixed-effects model having intervention group, the repeated factor of time period (1-week pre-intervention and randomization to 12 weeks post-intervention), the interaction of intervention group and time period, and the covariate of opioid intake during the trial as fixed effects and the participant as a random effect. Contrasts will be constructed from this mixed model to compare within and between the intervention groups with respect to AUC VAS scores. Similarly, linear mixed-effects models will be used to compare the two interventions over time with respect to the outcomes of PGIC and EHP30 which are collected at 4-week intervals over the course of the trial. Another secondary analysis will fit a linear random coefficients model to the weekly VAS scores (i.e., not AUC) to generate linear trajectories for each intervention group, adjusting for the covariate of opioid intake. From these trajectories, estimates for the rate of change (i.e., slope) over time in VAS scores will be compared between the two intervention groups. In the event linear trajectories do not fit the data well, higher order polynomials (e.g., quadratic) will be considered to estimate the curve trajectory per intervention.

9.0 Confidentiality, Privacy and Data Management

9.1 Confidentiality

9.1.1 Identifiers associated with data and/or specimens

See HRP-598 Research Data Plan Review Form

9.1.1.1 Use of Codes, Master List

See HRP-598 Research Data Plan Review Form

9.1.2 Storage of Data and/or Specimens

See HRP-598 Research Data Plan Review Form

9.1.3 Access to Data and/or Specimens

See HRP-598 Research Data Plan Review Form

9.1.4 Transferring Data and/or Specimens

See HRP-598 Research Data Plan Review Form

9.2 Subject Privacy

See HRP-598 Research Data Plan Review Form

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

Adverse event reporting will be reviewed at regular research meetings led by principle investigator. Annual reports will be made to the Penn State IRB as per the current protocol.

10.2 Data that are reviewed

Adverse events are defined as unfavorable medical changes that occur during or after the study initiation, that may or may not be related to or caused by study participation. Adverse events are not procedures or surgeries (the medical condition that caused the need for the procedure or surgery is the adverse event or pre-existing conditions or illnesses that do not worsen during the study period. The intensity of the event will be evaluated and recorded as one of the following:

Mild intensity – events may or may not be volunteered by the patient. The patient is aware of the event but it is easily tolerated.
Moderate intensity – signifies discomfort sufficient to interfere with normal activities. A change in therapy may or may not be indicated.
Severe intensity – side effects are almost always brought up by the patient, definitely interfere with functioning, and require a medical intervention.

The investigator will be obligated to pursue and provide information as requested by the FDA, when applicable. In general, this will require a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, including concomitant medications and illnesses, must be provided. The investigator's assessment of causality must also be provided. If causality is unknown, it should be attributed to study participation. The certainty of the relationship of the event to

study participation will be recorded as “Possible Related” or Not Possibly Related.” The situation surrounding the event should be assessed to determine whether it is related to the study.

10.3 Method of collection of safety information

Study data will be managed using REDCap (Research Electronic Data Capture), a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g., for data types and range checks), audit trails, a randomization module, and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

Well-designed data collection forms (i.e. CRFs) will be developed to minimize data collection and recording errors. Separate data collection forms will be designed based on who is collecting the data and when and where the data are collected. Forms will be designed to collect cumulative information such as adverse events and the use of concomitant medications.

10.4 Frequency of data collection

All data collection will begin immediately upon enrollment.

10.5 Individuals reviewing the data

The PI will receive immediate notification of all serious adverse events, and a regular report summarizing recruitment and all other adverse events. The required offices will be notified immediately of SAEs as per our safety plan and a summary of the reported adverse events will be presented per policy.

10.6 Frequency of review of cumulative data

Refer to section 10.5

10.7 Statistical tests

Refer to section 10.2

10.8 Suspension of research

Not applicable

11.0 Risks

Risks of Norethindrone: Serious adverse reactions with the use of norethindrone are serious cardiovascular events and stroke, vascular events, and liver disease. Adverse reactions commonly reported by norethindrone users are: Irregular uterine bleeding, nausea, breast tenderness, and headache

Risks of Low Dose naltrexone: Adverse reactions to low dose naltrexone can include hepatotoxicity, depression and suicidality, allergic reactions, eosinophilic pneumonia, muscle cramps, dizziness or syncope, somnolence or sedation, decreased appetite, and insomnia.
Everyone taking part in the study will be watched carefully for side effects; however, doctors do not know all the discomforts and risks that may happen. With all drugs there is the possibility of

complications and side effects that are not known at this time. These may be mild or serious, and in some cases may be very serious, long-lasting, or may never go away. There is also a risk of death.

If you experience any side effect (or other health issues) during this study, let your study doctor know immediately. If you are not honest about your side effects, you may harm yourself by staying in this study. If you do not understand what any of these side effects mean, please ask the study doctor or study staff to explain the words to you.

Common side effects of naltrexone at higher doses include:

- Nausea, vomiting, diarrhea or constipation
- Stomach pain or cramping
- Loss of appetite
- Headache
- Dizziness
- Nervousness, irritability, or anxiety
- Tearfulness
- Increased or decreased energy

This study plans on using low dose naltrexone at a much lower dose than typically available. Multiple studies have used similar doses of naltrexone (3 – 4.5 mg) in both adult and children with no significant adverse reactions. There is no evidence reported of interactions of low dose naltrexone with other medications. The most commonly reported side effects in studies using low dose naltrexone include:

- Difficulty falling and/or staying asleep (insomnia)
- Vivid dreams
- Headaches.

Though it is an uncommon event, there is a risk of unexpected allergic reaction to the study drug which may include hives, rash, swelling or difficulty breathing. If one of the mentioned symptoms appears, stop taking your study drug(s) and seek immediate medical help.

Risk of Loss of Confidentiality: There is a slight risk of loss of confidentiality associated with participation in the study. To mitigate this risk, all subjects will be assigned a unique study ID that will be used throughout the study to identify each subject. The list linking identifiable information from the study ID will be maintained in the REDCap database designed for this study. REDCap uses secure passwords and access to the database would be restricted to study personnel.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

The potential benefits to subject may be a decrease in pain and narcotic use.

12.2 Potential Benefits to Others

Endometriosis is a devastating disease that impacts nearly 1:10 women in the reproductive years or their life. The pathophysiology of endometriosis is not completely understood, however, there is strong evidence that inflammation plays a major role in the symptoms associate with endometriosis. Current strategies for the management of endometriosis-associated pain often leave women seeking additional relief in the form of opioid-based treatments. In light of the current opioid epidemic it is important that we continue seek non-opioid based therapies that can provide symptomatic relief while we continue to try and better understand this debilitating disease. LDN has gained some popularity as an off-label

treatment for inflammatory conditions such as multiple sclerosis, Crohn's disease and fibromyalgia, which can potentially be utilized in endometriosis as well.

13.0 Sharing Results with Subjects

There is no information for the patient to receive as no diagnostics will be done.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Subject will receive $25 at the completion of the screening visit and $100 additional at the completion of the study for a total of $125. We will not be providing travel reimbursement as part of this study protocol.

15.0 Economic Burden to Subjects

15.1 Costs

All tests and procedures required for participation in the study will be paid for by the sponsor. There are no additional costs to subjects participating in the research. Analgesics taken during the study will be paid for by the subject and/or her insurance.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

Locations for study visits may include the Penn State Women's Health Clinic at Hope Drive and the Clinical Research Center at the Penn State Hershey Medical Center.

16.2 Feasibility of recruiting the required number of subjects

The PI sees approximately 10 patients each week with endometriosis; approximately 30-40 are seen total within the Minimally Invasive GYN Surgery practice.

16.3 PI Time devoted to conducting the research

The PI has dedicated research time and is available to see study patients 2-3 days/week and the co-Investigator on the study asback up.

16.4 Availability of medical or psychological resources

Resources will be made available at the Penn State Hershey Medical Center, if warranted.

16.5 Process for informing Study Team

The PI, study coordinator(s) and other study team delegates will complete required study specific sponsor training throughout the conduct of the trial. OBGYN Research study team meeting occur on a

weekly basis to inform all members of the study status, responsibilities and trainings can take place. On-going communication via email and telephone will also take place.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not applicable

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☒ Clinical Research Center (CRC) Advisory Committee– All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☒ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

18.1 Communication Plans

Not applicable

18.2 Data Submission and Security Plan

Not applicable

18.3 Subject Enrollment

Not applicable

18.4 Reporting of Adverse Events and New Information

Not applicable

18.5 Audit and Monitoring Plans

Not applicable

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might

	have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

19.2 Recording of Adverse Events

Research subjects will be routinely questioned about adverse events at study visits or survey completion days. All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator. An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- Test finding is accompanied by clinical symptoms
- Test finding necessitates additional diagnostic evaluation or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy.

19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.6 Unblinding Procedures

The Investigational Pharmacy at Penn State Hershey Medical Center and they will hold the randomization and unblinding key as needed. The investigators and biostatisticians will remain blinded to the allocation sequence and patient assignment. Investigator will have the discretion of unblinding the physicians at any time if it is warranted for safety and/or scientific reasons.

19.7 Stopping Rules

The principle investigator will receive immediate notification of all serious adverse events, and a regular report, at six month intervals, summarizing recruitment and all adverse events, by treatment in a blinded fashion. The principle investigator will meet with research team after the receipt of the scheduled reports or after any major serious adverse event.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

The study will be monitored by the Clinical Trial Monitoring Team from the Department of Public Health Sciences at Penn State Hershey College of Medicine. The monitors will provide an independent review of the regulatory and subject records and the data collected to assure compliance with the protocol, GCP, and applicable federal regulations. The monitoring will occur

at regular intervals after the enrollment of the first subject and the times will be predetermined by the monitoring plan developed by the Clinical Trial Monitoring Team.

20.1.2 Safety Monitoring

See Section 10.0 for data and safety monitoring plan.

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored

Not applicable

21.2 Location of storage

Not applicable

21.3 Duration of storage

Not applicable

21.4 Access to data and/or specimens

Not applicable

21.5 Procedures to release data or specimens

Not applicable

21.6 Process for returning results

Not applicable

22.0 References

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