PennState

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

Protocol Title: A Randomized Controlled Pilot Study of the Use of Cannabidiol in the Management of Endometriosis Pain

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Table of Contents

1.0 Objectives

1.1 Study Objectives

Our central hypothesis is that Cannabidiol will result in a significant improvement of endometriosis-related pain. This proposal seeks to (1) determine if cannabidiol will result in an overall improvement of patient-reported endometriosis associated pain (2) determine if this pain reduction is dose-dependent (3) determine if cannabidiol will result in improved sexual function (4) determine if cannabidiol will result in an overall improved quality of life among women with endometriosis (5) determine if CBD affects common inflammatory markers associated with endometriosis (6) to determine the pharmacokinetics of sublingual CBD. We propose a randomized double-blind placebo-controlled pilot study to achieve the following aims:

Aim 1: Identify the overall impact of cannabidiol (CBD) on endometriosis related pain. We plan to measure endometriosis related pain using daily self-reported Visual Analogue Scale (VAS) scores over an 8 week period.

Aim 2: Identify the dose-dependent impact of cannabidiol on endometriosis related pain. We will be dividing our patients into 3 arms – high dose CBD, low dose CBD and placebo. We plan to measure and compare endometriosis related pain using daily self-reported Visual Analogue Scale (VAS) scores.

Aim 3: Identify the overall impact of cannabidiol (CBD) on sexual function. This will be assessed via the Female Sexual Function Index (FSFI), a validated survey, to be administered to participants with current sexual partners that are sexually active.

Aim 4: Identify the impact of cannabidiol on Quality of Life (QOL) among women with endometriosis. We plan to measure QOL using the Endometriosis Health Profile-30 (EHP30), Patient Global Assessments (PGAs), and Patient Global Impression of Change (PGIC) surveys. These are validated health surveys.

Aim 5: To measure inflammatory cytokines that have been linked to the pathogenesis of endometriosis and to determine if CBD will alter these inflammatory markers.

Aim 6: On a small subset of patients (4), we will study the pharmacokinetics of sublingual CBD.

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

(1) To determine the difference in QOL measurements between study groups. The EHP30 is a validated survey used to measure quality of life outcomes in women with endometriosis. PGIC and PGAs are routinely used in endometriosis clinical trials to assess outcome measures such as dysmenorrhea, non-menstrual pelvic pain and dyspareunia.
(2) To identify the overall impact of CBD on sexual function among participants that are currently partnered and sexually active.
(3) To measure inflammatory cytokines and determine their levels before, during and at the end of the treatment cycle.
(4) To determine the pharmacokinetics of sublingual CBD

We will record pain medication usage (opioid and non-opioid). Subject reported side effects will also be monitored.

2.0 Background

2.1 Scientific Background and Gaps

Endometriosis is a clinical disease defined by the presence of endometrial glands or stroma outside of the uterine cavity. Primary symptoms include chronic pelvic pain, dysmenorrhea, dyspareunia, and infertility. It is estimated to effect up to 10% of the general female population and accounts for a disproportionately large number of women with chronic pelvic pain.[1-2] Endometriosis can have a profound impact on not only a woman's physical health, but also on their social and mental well-being.

Multiple theories exist as to the pathogenesis of endometriosis. The most commonly described is that of Sampson's Theory. According to this theory, the endometrial lining within the uterus sheds during menstruation and refluxes backwards through the fallopian tubes into the abdominal cavity. This efflux primarily settles and implants itself into the dependent portions of this space, which explains the disease's most common locations, i.e. the ovary, rectovaginal space, bladder surface and pelvic sidewalls. We also suspect that there are genetic and environmental factors that predispose specific women to become affected. On the other hand, endometriosis in extra-pelvic and extra-abdominal locations lends strength to alternative theories such as coelomic metaplasia and stem cell dysfunction.[1]

There are many challenges in the diagnosis and treatment of endometriosis. Endometriosis is poorly visualized on current imaging modalities and is unable to be diagnosed via any known laboratory values. Current standards require surgical intervention with biopsies confirming suspected histopathology. Given the invasive nature of this route and the variability of the disease's course, it is common for women to have a lengthy delay in their diagnosis, ranging on average from 7 to 11 years. [1-2]

Currently, there is no cure for endometriosis. Even after complete surgical sterilization, endometriosis and endometriosis related symptoms can persist.[3] Standard of care involves a combination of lifestyle modification, hormonal and nonhormonal medications and surgical intervention with thought given to the patient's fertility desires. Traditional physician directed medical therapies include a combination of anti-inflammatories and hormones. [4] Unfortunately, many women also will eventually incorporate opioid pain medication into their treatment plan. Women with endometriosis have a higher probability of prolonged use and/or concomitant use with benzodiazepines than the general population.[5] Due to the well-recognized opioid epidemic, there is a need to explore alternative treatments for pain, particularly if patient's are already seeking out these drugs for personal use in uncontrolled settings.

Cannabis is a well-known plant that contains more than 500 identified phytochemicals, of which over 100 are cannabinoids. The most widely studied is Δ^9-tetrahydrocannabinol (Δ^9-THC), which is the major psychoactive component of *Cannabis,* but Cannabidiol (CBD) has been increasingly favored for its reduced side effect profile and potential health benefits. CBD was first isolated from *Cannabis* in the 1940s. Both CBD and Δ^9-THC have been shown to have profound effects on human physiology through primarily what is known as the endocannabinoid system (ECS).[6]

The ECS is a group of endogenous receptors, ligands, enzymes and proteins, which are located predominantly in both the central and peripheral nervous system. The ECS has been shown to have direct effects on motor function, eating habits and of more specific interest to us, it has been shown to affect mood, immunocompetency, cell proliferation and inflammation.[7-8] Endocannabinoids are lipid derived ligands that bind to cannabinoid, vanilloid and peroxisome proliferator-activated receptors (PPAR).[6]

The mechanism of pain in endometriosis is complex and not entirely understood. It can be loosely divided into 3 types of pain (1) Nociceptive Pain (2) Inflammatory Pain (3) Neuropathic Pain. Nociceptive pain occurs in the peripheral nervous system (PNS) as a transfer of noxious stimuli via superficial or visceral receptors. Endometriosis lesions can cause mechanical pain via compression and infiltration.[11]

Endometriosis is also regarded as a chronic inflammatory state; peritoneal fluid in these patients is notable for an upregulation of nerve growth factor secondary to increased levels of inflammatory cytokines, TNF-alpha, interleukin-1beta and highly oxidated byproducts.[8] Finally, neuropathic pain results from damage to neurons and processes such as central sensitization of pain. Changes in gray matter have been shown in patients with endometriosis and chronic pelvic pain versus healthy controls.[9]

Δ^9-THC exerts its effects via the ECS by mimicking endogenous cannabinoids and binding primarily to the aptly named cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors.[8] Both are G-protein coupled receptors of which the former is found primarily in the brain and several peripheral tissues, such as the uterus, while the latter is seen affecting immunologic and gut cell function. [8]

While CBD does demonstrate a low affinity for CB2 receptors, it acts primarily through alternative mechanisms both within and outside of the ECS system depending on its dose[10]. At low concentrations, it can (1) enhance the activity of the serotonin 5-HT_{1a} receptor (2) enhance activity at glycine receptor subtypes (3) effect the transient receptor potential of ankyrin type 1 (TRPA1) channel (4) inhibit orphan G-protein coupled receptor GPR55.[6,9] Activity at the serotonin receptor may have positive effects on mood, while glycine receptors have been associated in analgesia and pain modulation. Activity at the TRPA1 channel may explain its effect in reduction in neuro-excitability and seizure threshold. Finally, although not well understood, GPR55 has been identified in the ECS pathway. Together, these may have positive effects on primarily nociceptive and neuropathic pain.

At higher levels, CBD has also been shown to activate the (PPAR- γ) and vanilloid receptors. [6]
Many of the studies on the ECS and endometriosis related pain have focused on *N-palmitoylethanolamine* (PEA), which is a minor constituent of the endocannabinoid ligand, *N*-arachidonollethanolamine (AEA). PEA activates the PPAR receptor pathway and enhances the ECS. Studies have demonstrated that the addition of PEA significantly improves pelvic pain, reduces dyspareunia and improves sexual function.[8] On the other hand, CBD has been shown to activate vanilloid receptors; these receptors have been found to be upregulated in the peritoneal fluid of endometriosis patients as well in patients with deeply infiltrative endometriosis. [11-12]

Finally, aside from alteration of pain and pain's perception in endometriosis patients, the cannabinoid system has been shown to be involved in numerous other pathways that may serve to alter the course of the disease. Cannabinoids have been implicated in the modification of cellular apoptosis, cellular migration (e.g. in cases of deeply infiltrative endometriosis), inflammation, and angiogenesis; therefore, there may be benefits of the drug to potentially modify the course of endometriosis.[13]

In summary, endometriosis is a chronic, debilitating disease that affects up to 10% of reproductive age women. Its pathophysiology is not entirely understood, but there is good evidence that inflammation and abnormal cell proliferation play a role. Current strategies for management of endometriosis pain and related symptoms often leave women unsatisfied or seeking additional treatment in the form of opioids and alternative therapies. Recent legislation (Agricultural Act of 2018) has made CBD products widely available to the average consumer. This bill descheduled hemp (any *Cannabis* variety containing less than 0.3% THC content) from the definition of marijuana in the Controlled Substances Act. Moreover, it loosened regulations on its sale and distribution. Given increasing patient interest and access to a variety of poorly monitored CBD products, it is important to study its potential therapeutic benefit in a controlled manner.

2.2 Previous Data

We do not have any preliminary data specific to the use of cannabidiol in the treatment of endometriosis related pain symptoms. The results of this study would potentially serve as preliminary data for future large multi-center studies.

There is sufficient preliminary data (for alternative disease states) in the existing literature regarding the safety and potential efficacy of Cannabidiol to support the further study of this drug.

Data has been published on the safety and efficacy of CBD in the treatment of epilepsy. Recently, a multicenter interventional trial was conducted by Devinsky, et al. to examine whether the addition of CBD would decrease seizure rates among patients with severe, refractory childhood-onset epilepsy. Their findings suggested a significant reduction in monthly motor seizures with an acceptable safety profile. [14] In June 2018, the U.S. Food and Drug Administration (FDA) approved the orphan drug, Epidiolex (Cannabidiol), which is an oral solution, to be used for two rare forms of severe epilepsy, Lennox-Gastaut syndrome and Dravet syndrome.

To date, several *Cannabis* related drugs have been approved for varying indications. Nabilone, a CB1/2 receptor agonist was approved for chemotherapy related nausea in 1981. Marinol (Δ^9-THC) was approved in 1985 as an anti-emetic and for excessive weight loss in patients with acquired immune deficiency syndrome (AIDS). In 2005, Sativex, a *Cannabis* derivative, was also approved for the treatment of cancer-related pain and neuropathic pain associated with multiple sclerosis.[13]

2.3 Study Rationale

Endometriosis is a chronic pelvic pain condition that affects up to 10% of female reproductive age women. Endometriosis has no cure and is associated with a decreased quality of life. At some point in their disease course, not only will many women will turn to opioids for pain management, they are more likely to seek off-label poorly studied therapies. Therefore, there is a need for more data on non-opioid management options for these patients obtained in a safe and controlled manner.

CBD is a phytocannabinoid derived from the Cannabis plant. Since the Farm Bill of 2018, it has been become widely popularized and distributed to the general population. CBD is known for less psychotropic effects than its counterpart, Δ^9-THC, but with potentially similar effects on pain perception, inflammation, cell-growth and regulation. Although the pathophysiology of endometriosis is not entirely understood, there is good evidence that inflammation and abnormal cell proliferation play a large role. We believe that CBD will result in a reduction in endometriosis associated pain.

We also carefully considered the following (1) CBD manufacturer (2) appropriate dosing for our intended indication and (3) ease and route of patient administration.

(1) In regards to the first issue, there are currently no federal or state regulated CBD dispensaries. Therefore, in order to obtain a quality study drug, we initially chose 3 reputable online companies and performed independent validity testing of the potential sublingual CBD sources at Penn State Health. We have worked closely in conjunction with Dr. Kent Vrana, the Chair of Pharmacology, and his laboratory in order to test the intended study drugs and to develop the protocol. From our initial round of testing, we chose the product with the most accurate CBD content (Nuleaf Naturals). During the FDA IND application process, we performed a second round of testing on the intended study drug to ensure safety up to FDA guidelines, which included microbial and mycotoxin testing.

(2) In the literature, there is a wide variety of CBD dosages cited ranging as high as 800mg oral daily. From what is known about the pharmacokinetics of CBD, it undergoes extensive first pass metabolism and absorption via oral route is only roughly 6%. Therefore, we chose a sublingual route to increase bioavailability.[10] Furthermore, high oral dosages have been reported in a variety of studies, but they have primarily been examining neurologic conditions such as epilepsy,

schizophrenia, and Parkinson's disease. Although few published trials have used a sublingual mode of delivery for CBD, it is actively being studied in multiple ongoing clinical trials.

A search conducted on 7/2/20 on clinicaltrials.gov yielded 81 registered trials looking specifically on CBD and pain. We identified studies involving a sublingual mode of delivery of which the results are summarized below. As demonstrated in the table, most dosing for sublingual CBD ranges from 5-20mg per dose.

TRIAL NUMBER	*DOSE*	*INDICATION*
NCT 03948565	*20mg BID sublingual oil*	*Chronic Pain*
NCT 04271917	*8.5 mg as needed* *18.5mg as needed sublingual oil*	*Dental Pain*
NCT 04298554	*20mg qD sublingual*	*TMJ Pain*
NCT 04195269	*10mg CBD/10mg THC BID sublingual tablet*	*Osteoarthritis Pain*
NCT 04088929	*20 mg TID sublingual tablet*	*Diabetic Neuropathy*
NCT 04193631	*5mg as needed sublingual tablet*	*Musculoskeletal pain*
15 Different Trials	*Sativex* *2.5mg THC/2.5mg CBD per spray* *Up to 8 sprays/3 hours (20 mg) or 48 sprays/24 hours (120mg) Buccal Spray*	*Various Pain*

Per the recommendations form our Co-Investigators from Pharmacology, it was also decided that given the long half-life of CBD, multiple doses per day for chronic users would not likely substantially affect the concentration of CBD. Therefore, we believe that sublingual administration of 10 to 20mg daily will be adequate to achieve an effect for our intended indication.

(3) In regards to patient administration of the study drug, we conducted a small focus group in order to determine the best way to administer the sublingual doses of the study drug. We considered the administration of 8 total drops of CBD at once, held under the tongue for one minute then swallowed, versus 4 drops held under the tongue for one minute then swallowed followed by an additional 4 drops. We concluded that 8 drops were a difficult volume to tolerate for the average study participant. If we were to increase the dose, we believe it would start to affect tolerability.

3.0 Inclusion & Exclusion Criteria

3.1 Inclusion Criteria

1. Females ages 18-45 years at the time of enrollment
2. A surgical diagnosis with direct visualization and/or histopathologic confirmation of endometriosis with associated moderate to severe endometriosis related pain (> 3 on a VAS)
3. Is not expected to undergo gynecological surgery or other surgical procedure for treatment of endometriosis during the study period
4. Agrees to use approved contraception method during the entire study
5. Patients using oral contraceptives, vaginal ring, injectable progesterone and/or GnRH agonists/antagonist for contraception and/or management of endometriosis, can be included if both they and their primary provider agree to stopping their medication and transitioning to Norethindrone acetate (NETA) as the primary treatment of endometriosis throughout the study period.

6. Patients using a progesterone containing IUD or a copper IUD for contraception and/or management of endometriosis can be included if both they and their primary provider agree to initiate Norethindrone (NETA) as the primary treatment of endometriosis throughout the study period

3.2 Exclusion Criteria

1. Women that are pregnant, breastfeeding or trying to conceive
2. Women with chronic daily opioid use and any chronic pain or frequently reoccurring pain condition, other than endometriosis, that is treated with opioids for $\geq$ 10 days per month.
3. Women who have had a bilateral oophorectomy
4. Women that are currently using *Cannabis* based products and are unwilling to stop for 30 days prior to study enrollment and for the study duration
5. Non-English speaking or inability to read and understand English
6. Women with a BMI > 35 kg/m^2
7. Women with known liver disease, such as hepatitis, or with screening LFTS (AST/ALT) > 3 times above the upper limits of normal (ULN) in the past year
8. Women with chronic alcohol use (defined as $\geq$ 3 drinks per day, averaged over one week)
9. Women with chronic use of drugs (defined as $\geq$ 10 days/month) that cause somnolence/sedation such as benzodiazepines or Central Nervous System (CNS) depressants that are unwilling or unable to discontinue the medications for the washout period and the duration of the study
10. Women who are currently taking Clobazam or Valproate and are unwilling/unable to discontinue the medication for the washout period and the duration of the study
11. Women with suicidal ideation or uncontrolled depression within the past year
12. Known history of or suspected breast cancer on screening physical exam
13. History of or active deep venous thrombosis or pulmonary embolism
14. History of or active arterial thromboembolic event (e.g. stroke, myocardial infarction)
15. Multiple (> 3) risk factors for arterial vascular disease (e.g. uncontrolled hypertension, diabetes mellitus, hypercholesterolemia, obesity and smoking)
16. Current use of a progestin-containing contraceptive implant

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 immediately with any new negative symptoms.

Known severe adverse events of the study drugs will result in the immediate cessation of the study drugs and removal from the study.

1. Severe adverse events of NETA include:
    a. (1) Stroke (2) Deep Vein Thrombosis (3) Pulmonary Embolism (4) Myocardial Infarction (5) Retinal Vein Thrombosis.
    b. Worsening or persistent migraines will result in cessation of the study drug and therefore, removal from the study.
2. Serious adverse events associated with CBD include:
    a. (1) Suicidal ideation (2) Liver Dysfunction resulting in hepatic failure, hepatic pain that limits self-care activities of daily living, or acute liver damage as measured by LFTS (elevations in ALT or AST > 3 times the ULN and for ALP or TBL > 2 times the ULN)

In the case of an inadvertent pregnancy, the study participant will be immediately withdrawn from the study.

Other adverse events will be monitored and may result in cessation of the study drug and subject withdrawal from the study as determined by the clinical investigator. When possible, we will use the definitions described by the NIH's Common Terminology Criteria for Adverse Events (CTCAE), Version 5, subjects meeting criteria for a Grade 3 CTCAE will be withdrawn from the study if they can be attributed to the study drug. If causality cannot be determined, it will be attributed to the study drug.

Examples:	Anemia	Grade 3	Hb < 8.0
	Diarrhea	Grade 3	Increase of ≥ 7 stools per day over baseline

Withdrawal of consent at any time during the study period will also constitute the withdrawal of a study subject.

3.3.2 Follow-up for withdrawn subjects

Subjects will be asked to return the study drug to the site if withdrawn from the study.

If the subject was removed for elevated LFTS, these will be followed until resolution and the patient advised to seek medical care if appropriate. If the subject is removed from the study for any of the other reasons as described in 3.3.1, she will receive the appropriate treatment and follow up based on the decision of her providing physician team.

In the case of an inadvertent pregnancy, the study participant will be immediately withdrawn from the study. The participant will be followed through during pregnancy for adverse maternal, fetal and neonatal outcomes that could be appropriately linked back to the study drug.

No further data will be collected on these patients and the subject will not be replaced.

4.0 Recruitment Methods

4.1 Identification of subjects

Potential subjects will be identified within our Minimally Invasive Gynecologic Division Outpatient clinic location or new patients referred by other physicians from other OBGYN clinics. No additional recruitment materials will be used; we have in place a system of referrals to our division for endometriosis patients from which we will pre-screen patients. We will utilize Study Finder. We will also register this study at ClinicalTrials.gov.

4.2 Recruitment process

Subjects will be recruited by various means as listed above, but primarily from the Minimally Invasive Gynecologic Division Outpatient Clinic. We will approach the potential subjects in person and/or via telephone contact and she will be given an introduction to the study. Participation will be entirely voluntary and will in no way affect her clinical care. We will ask permission to collect and share contact information with the study coordinator to assist with contacting patients for screening, recruitment, follow up visits and completing surveys.

4.2.1 How potential subjects will be recruited.

After identifying potential subjects, the study coordinator will contact the potential subject and further explain the study to them to assess eligibility and provide more information (i.e. consent document) if further eligible. Potential subject may also be a self-referral.

We do not anticipate having any difficulty recruiting these women into the study as we are currently one of the highest volume Minimally Invasive Gynecologic Surgery (MIGS) groups in the region. In 2016, we had 2700 patient encounters for endometriosis/female pelvic pain. As of August 2019, we have added two additional providers to our MIGS group.

The PI will monitor recruitment and retention rates for the study monthly to ensure that the goals are being met. In addition, we have collaborated 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. An approved online ad will be posted on public endometriosis groups.

Visitors can browse by topic or search for a keyword to discover available studies at Penn State Hershey Medical CenterWe will also register this study at ClinicalTrials.gov. If recruitment and retention are inadequate, we will use IRB approved recruitment materials to begin to advertise in the broader central Pennsylvania area and with offices known to refer endometriosis patients to our practice.

4.2.2 Where potential subjects will be recruited.

Subjects will be recruited from the Hope Drive clinic location at the Pennsylvania State University Hershey Campus, other OBGYN clinics or as a self-referral.

4.2.3 When potential subjects will be recruited.

Potential subjects will be approached during their routine clinic visit or self-referral. Once identified as a possible participant, we will offer more information and ask permission to provide their contact information to the study coordinator. From there, the study coordinator will reach out.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent.

When the study coordinator receives the name of a potential subject, a call is made to assess eligibility using the IRB approved phone script. If excluded, the phone interview is stopped at that time. If eligible the subject is scheduled for a visit. A HIPAA waiver is being requested for the purposes of pre-screening procedures (i.e. medical record review, if applicable) and verbal consent to keep contact information for future research purposes. Written informed consent will be obtained prior to enrollment into the study.

5.0 Consent Process and Documentation

5.1 Consent Process:

Check all applicable boxes below:

- [X] **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***
- [X] **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***
- [ ] **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

- [ ] **Informed consent will not be obtained – request to completely waive the informed consent requirement. *[Complete Section 5.5]***

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

In according 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 Clinical Research Center (CRC) during Visit 1 – Screening Visit. The consent document will be provided for review and discussion. Consent will be obtained prior to any study procedures being done.

5.2.2 Coercion or Undue Influence during Consent

The subject will be informed that their participation in the study is entirely voluntary. The subject will receive a copy of the consent form to read at home prior to making an enrollment 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. A copy of the signed consent form is provided to the subject.

5.3 Waiver of Written Documentation of Consent

5.3.1 Indicate which of the following conditions applies to this research:

☒ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

Describe the alternative mechanism for documenting that informed consent was obtained:

Informed consent will be obtained at Visit 1. Please see 5.3.2.

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, implied consent form, or summary explanation of the research)

A waiver of the consent process is requested for recruitment purposes in pre-screening the medical record to identify eligible subjects for the study from our clinic population. We would like to ensure that the subject is 18 -45 years old, not currently pregnant, and has a diagnosis of endometriosis. Once we have determined these baseline characteristics, we will be using the CBD Phone Screening Transcript unloaded in the recruitment materials to further screen patients prior to an in-person Screening Encounter (Visit 1). We will obtain verbal authorization

at the time of the pre-screening phone encounter or in patient clinic visit, but written Informed consent will be obtained at the Screening Encounter.

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). N/A

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement. N/A

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects
Not applicable. Subjects who do not speak English will not be enrolled as the consents and surveys will be conducted in English and would require the ability to read and speak English.

5.6.2 Cognitively Impaired Adults

5.6.2.1 Capability of Providing Consent N/A

5.6.2.2 Adults Unable to Consent N/A

5.6.2.3 Assent of Adults Unable to Consent N/A

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

5.6.3.1 Parental Permission N/A

5.6.3.2 Assent of subjects who are not yet adults N/A

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

The 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.

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 pilot study to evaluate the effectiveness of cannabidiol on the management of endometriosis-related pain.

Potential subjects will be pre-screened in the Penn State Minimally Invasive GYN Surgery Clinic for moderate to severe endometriosis associated pain (VAS > 3). Subjects will be pre-screened from new and existing patients receiving care from the MIGs division of OBGYN for the diagnosis of endometriosis. Those meeting all inclusion and exclusion criteria who are willing to participate will receive a detailed history and physical exam, appropriate bloodwork and undergo informed consented at the Screening Visit. Baseline survey data will be collected and entered into the RedCap secured database. At this time,

subjects will be set up to receive automated links via email to complete daily diary entries (including VAS scores) directly into RedCap.

After the screening visit, the subjects will be scheduled to have a 1-2 week follow-up for the enrollment visit. During that week, the patient's will be asked to complete their daily electronic diaries and screened for daily reporting adherence. Subjects having completed 5 or fewer daily diary entries during this baseline collection period will be informed of the exclusion from enrollment without at least 80% adherence to the daily diary entries and offered one additional 7-day period to improve adherence. If at the conclusion of the second 7 day run in period of gathering baseline daily diary entries, they continue to have < 80% adherence, they will be considered a screen failure and withdrawn from the study.

Randomized subjects will receive either (1) placebo (2) low dose CBD (3) high dose CBD. This study will include an 8-week intervention period during which subjects will be asked to record daily electronic VAS scores, pain medication use and a number of other parameters. They will return at week 12 for a 4 - week post-treatment visit, where they can also choose to enroll in an optional pharmacokinetic study. Participants will complete the Endometriosis Health Profile-30 (EHP-30), Patient Global Assessments (PGAs), and, if partnered and sexually active, the Female Sexual Function Index (FSFI) surveys at 0, 4 and 8, 12 weeks as well as the Patient Global Impression of Change (PGIC) surveys at 4, 8, and 12 weeks. Patients will also have bloodwork done at weeks 0, 4, 8, 12 to assess for circulating markers of inflammation. At week 8, this bloodwork will include circulating CBD levels to assess for steady state concentrations. We will perform bloodwork to assess for possible side effects e.g. liver dysfunction throughout the study duration. Please refer to Section 7.2 Study Procedures for timing and test.

Subjects will be screened for side effects and asked to record pain medication use throughout the duration of the study. At each visit, subjects will be dispensed a 4 week supply of medication **(NETA and CBD)** from the Investigational Pharmacy. They will be required to bring medication bottles to each visit to verify drug accountability. Oxycodone (if prescribed) and NETA pills will be counted and recorded. Additional refills will be provided as needed. The study drug bottle will be inspected and returned to the clinician. The patient will be provided with a new supply of study drug at Visit 3. All NETA and study drug will be returned at the completion of the study.

At the completion of the study, all subjects will be offered the opportunity to do pharmacokinetic testing with sublingual CBD until a maximum number of 4 patients are enrolled. We plan for a total of 3-4 patients. This will be entirely voluntary and they will be compensated appropriately for their time. The testing will include 24 hours of monitoring with sequential blood draws to determine the pharmacokinetic parameters of sublingual CBD after administration and one salivary pH. They will be discharged at 24 hours and asked to return to the clinic at 48 hours for one final lab draw. We will stop recruitment once we have achieved the desired number of participants.

7.2 Study Procedures

Procedure	Prescreen	Visit 1 - Screening Encounter	Visit 2 - Enrollment Visit, 0 weeks	Visit 3 – 4 weeks (+/- 3 days)	Visit 4 – 8 weeks (+/- 3 days)	Visit 5 -Week 12 (4 weeks post treatment, +/- 3 days)
Screening Criteria	X					
Informed Consent		X				
Detailed History & Physical Examination		X				
Physical Assessment (Review of systems,			X	X	X	X

adverse events, Medication Review)						
Urine Toxicology		X				X
Urine Pregnancy Test		X				X
LFTs		X		X	X	X
CBC, BMP		X			X	
Inflammatory Markers			X	X	X	X
PK (Steady State)					X	
Survey: C-SSRS		X		X	X	X
Survey: WERF		X				
Survey: EHP-30, PGA, FSFI			X	X	X	X
Survey: PGIC				X	X	X
Study Drug Dispensed			X	X		
Drug Reconciliation				X	X	
Daily Pain Scores		X	X	X	X	

Some of these visits may be done remotely via tele-health, HIPAA compliant conferencing or phone for various reasons, some of which may include the subject unexpectedly cannot make it to the research center, she lives and/or moves a significant distance away from the research center and wants to continue participation and/or there are extenuating circumstances outside of our control (e.g. pandemic). The determination to conduct the visit remotely will be made on a case-by-case basis to ensure patient safety and will not affect the integrity of the study data and outcomes.

7.2.1 Prescreen

Patients will be screened and recruited as outlined in Section 4, Recruitment Methods. If they meet outlined criteria they will be contacted by the study coordinator for Study visit 1 – Screening Visit.

During prescreening, the subject will confirm whether she is currently taking hormonal medication for contraception and/or endometriosis related issues. Depending on her current medication, she may need to delay enrollment into the study. If they are not already on NETA, they will need to consult with their primary physician in order to initiate the medication. Patients will also be advised to consult with their primary physician in order to determine whether they can initiate NETA and stop their current medication regiment. Once the patient is enrolled in the study, NETA will be provided by the IDS.

If the patient is not currently on NETA, they will need to be transitioned as follows:

1. None - No delay
2. Combined oral contraceptive – No delay
3. Etonogestrel/ethinyl estradiol vaginal ring – No delay
4. GnRH antagonist (e.g. Orlissa) – No delay
5. Long acting reversible contraception (Progesterone IUD, Copper IUD) – No delay
6. GnRH agonist (e.g. Lupron Depot): 3.75 mg must wait 1 month from administration of prior injection and 11.25 mg- must wait 3 months from administration of prior injection.
7. Injectable Progesterone (Depo Provera) – Must wait 3 months from administration of prior injection
8. Progestin-containing contraceptive implant – Excluded from the studied

For women using methods listed #1-4, they will stop/remove this form of contraception and be transitioned immediately to NETA.

For women using LARCS listed #5, they can continue this form of contraception and be transitioned immediately to NETA.

For women using methods #6-7, they must wait the listed time prior to initiation of NETA.

All subjects will be required to be on NETA for 30 days prior to the enrollment visit.

The NETA is intended for the purposes of endometriosis related standard of care and is not considered an appropriate contraceptive method for patients. Acceptable methods of contraception are listed in Section 7.2.3.

We will confirm they are not currently taking any of the exclusionary medications/drugs in their described manners. If they have recently stopped the below products, their required washout period is listed below:

1. *Cannabis* based products (this will be further confirmed on toxicology testing at the screening visit) (required washout period: 30 days)
2. Chronic daily use of drugs ($\geq$ 10 days/month) that cause somnolence/sedation such as benzodiazepines or Central Nervous System (CNS) depressants (required washout: 30 days)
3. Clobazam (required washout period: 14 days)
4. Valproate (required washout period: 14 days)

7.2.2 Study Visit 1: Screening Visit

Pre-screening will take place in the Penn State Hershey MIGS clinic or over the phone with women identified as potential candidates for study participation via prior clinic visits. If the subject meets all pre-screening criteria, she will return for a screening encounter and undergo informed consent prior to any study procedure. The subject will be given ample time to ask questions or voice concerns about the study.

A detailed history and physical exam will be performed, particularly to assess for concomitant use of anti-epileptic drugs and or underlying risk of liver dysfunction. We will need approximately 8-10 cc of blood (approximately 2 teaspoons).

1. Liver function tests (LFTs) will be drawn.
2. Baseline CBC and BMP will be drawn.
3. Screening urine toxicology will also be performed to confirm no recent THC use.
4. Urine pregnancy test will be collected.
5. Pain medication and narcotic usage from the prior month will be assessed.
6. Suicidal ideation will be assessed via the Columbia-Suicide Severity Rating Scale (C-SSRS).

If the subject is found to be pregnant, have evidence of underlying hematologic/ urologic/ hepatobiliary dysfunction or a positive urine toxicology for recent THC use, the subject will be excluded.

Current medication usage will be reviewed thoroughly with special attention paid to Cytochrome P450 (CYP) inducers and inhibitors as well as Substrates of uridine 5'-diphospho-glucuronosyltransferase (UGT). If the subject is screened into the study, their condition and corresponding medication will be recorded throughout the study. Please refer to Section 10 Risks, Drug Interactions, for additional guidelines.

Baseline survey data will be collected and entered into the RedCap secured database. This information will include the WERF EPHect Questionnaire.

At this time subjects will be set up for emails to complete VAS scores directly into RedCap. If not done already, the subject will be transitioned to norethindrone acetate to start taking immediately and given instruction on how to complete the VAS scores and study questions. It will be explained to the patient that she must complete 5 out of 7 days of surveys to be enrolled into the study. If the subject is unable to complete the 5 out of 7 days, the subject will be given one additional week to determine if compliance is attainable. If the subject is unable to do so, they will screen fail.

7.2.3 Study Visit 2 – Enrollment Visit

The subject will be scheduled for a randomization/enrollment 1-2 weeks after the screening visit. The randomization will be double blind and 1:1:1. The patient will have been expected to be on norethindrone acetate (NETA) for 30 days prior to the enrollment visit. Dosing for norethindrone acetate will start at 5mg oral daily, but may be adjusted from 2.5 mg to 15 mg depending on the subject's needs to achieve amenorrhea as this standard treatment for endometriosis or to increase compliance by reducing side effects. The study team will be responsible for adjusting dosages at subsequent study visits 3 and 4. At this visit, the subject will be randomized into Group A, Group B, Group C by IDS as long as the subject has met all the criteria for enrollment. The groups are listed below:

Group	Treatment
A	Norethindrone acetate + Placebo (Hemp Seed Oil)
B	Norethindrone acetate + low dose CBD (10mg sublingual daily)
C	Norethindrone acetate + high dose CBD (20mg sublingual daily)

The subject will be given a 4 week supply of (1) placebo (2) low dose CBD or (3) high dose CBD product and instructed on its application. The subject will also receive a 4 week supply of norethindrone. Refer to the following:

a. In the morning, take the norethindrone acetate orally with a sip of water at approximately the same time each day. This can be taken on an empty or full stomach.
b. Prior to bed, you will administer the study drug.
    1. Please refrain from eating (drinking is permissible) 60 minutes prior to administration.
    2. Place 4 drops of the study drug under your tongue.
    3. Hold the study drug under the tongue for 60 seconds. After that time, swallow any remaining drug.
    4. Repeat steps 2 and 3 for a total of 8 drops.

    Please avoid eating, drinking or smoking for 2 hours after administration.

A focus group was conducted to determine the optimal route of administration of the study drug. 1 application of 8 drops of the study drug versus 2 applications of 4 drops were compared and it was determined that the latter method was preferred.

Subjects will be instructed to take ibuprofen as first line 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, such as oxycodone. If needed, the subject will be advised to take first the ibuprofen 600mg every 6 hours as needed for pain with food, then acetaminophen 500-1000mg every 8 hours as needed for pain. For breakthrough pain, patients will need to contact the study team and they will be given a prescription for oxycodone 5mg oral every 6 hours as needed. As the pain associated with endometriosis tends to be cyclical, even if

the patient reports the pain as mild at the enrollment visit, they may suffer from an endometriosis flare requiring short term opioid use. Refill prescriptions for opioid pain medications will be provided 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.

At the enrollment visit, baseline study surveys and VAS scores will be collected and entered into the RedCap secured database. The will have inflammatory markers drawn at this visit (1 teaspoon, <5cc of blood)

Daily Diaries:
The subjects will be instructed as to how to complete their daily diaries directly into REDCap. They will enter daily VAS scores. They will be assessed as to their adherence of the study drug. We will document the daily use of any rescue analgesic medications and menstrual pattern.

Physical Assessment
A physical assessment will be performed at visits #2-5, following the detailed history and physical examination performed at the screening visit. This assessment will include, but is not limited to:

1. Vitals signs (blood pressure, pulse, O2; orthostatic assessment to be done only as indicated)
2. Detailed, but directed review of systems that will include symptoms concerning for liver disease, stroke, new/worsening migraine, deep venous thrombosis (DVT), pulmonary embolism (PE). This review of systems will include an assessment of (new onset) visual abnormalities.
3. Directed physical exam as indicated from the ROS, including an examination of the oral cavity to assess for lesions/sores
4. Adverse event assessment. Please refer to Section 3.3.1
5. Review of concomitant medications

Patient Education:
Patient will be educated on possible adverse events and concerning symptoms. If they have any of the following, they will be advised to stop the medications and contact the study investigator and/or the clinician on call to determine if they require a formal assessment: (1) Shortness of breath or difficulty breathing (2) chest pain (3) visual changes (4) persistent headache (5) severe abdominal pain (6) extensive mouth sores (7) persistent dizziness or lightheadedness (8) unilateral calf pain

Patients will be educated about the symptoms and signs of a DVT/PE and ways to reduce this risk.

Patients will also be educated about the risks of unintended pregnancy as described in the informed Consent. At the time of informed consent, the following will be reviewed with the subject:

Although norethindrone at certain dosages is approved for the indication of contraception. At the dosages this study will use, it is not indicated for this use. Therefore, you will be required to use an acceptable form of contraception during this study unless:
1. You have had both of your tubes tied
2. Have sex with a man who had a vasectomy at least 6 months ago
3. If you do not have sex with men
4. You have had a hysterectomy (removal of your uterus)

Acceptable methods include:

1. Male Condom: Use prior to intercourse. If using lubricant, choose a water soluble or silicone based as an oil-based lubricant can break down latex condoms.
2. Female Condom: Can be inserted up to 6 hours prior to intercourse; it is acceptable to use with lubricants and latex allergies.
3. Diaphragm with spermicide: Insert into the vagina so that it covers the cervix. Place spermicide on the diaphragm and around the edges prior to insertion. (Fitted by a healthcare provider)
4. Cervical cap with spermicide: Similar to the diaphragm, but smaller. Avoid this method if you have delivered a baby, as it is much less effective.
5. Vaginal sponge that contains a spermicide: Insert into the vagina before intercourse. Avoid leaving in the vagina for a prolonged period of time > 24 hours. Avoid this method if you have delivered a baby, as it is much less effective.
6. Copper IUD, Progesterone IUD
   No methods above are 100% effective at preventing unintended pregnancy even with perfect use.

7.2.4 Study Visit 3 – 4 week treatment

The subject will return in 4 weeks for a follow up visit. The study visit window will be 3 days before or 3 days after this time to account for weekends. At this time the subject will be given time to ask any questions or voice any concerns they may have had over the past 4 weeks, reviewing and recording any adverse events. The subject's compliance with daily surveys and study drug will be reviewed.

A physical assessment will be performed as detailed in Section 7.2.3. Subjects who experience severe adverse events will be instructed to stop the study drug and withdraw from the study. Please refer to Section 3.3.1.

The subject will be given another 1 month supply of the study drug and NETA as needed. As stated above, NETA dosage will be adjusted as necessary.

The subject will also complete the following surveys: (1) EHP-30 (2) PGA (3) PGIC (4) C-SSRS (5) FSFI (if partnered and sexually active) on-site prior to being discharged from the visit. The following bloodwork will be obtained: (1) Inflammatory markers (2) Monitoring LFTS. Approximately 1-2 teaspoons of blood will be drawn at this visit.

They will be required to bring all medication bottles to the visit. Oxycodone, if prescribed, and NETA pills will be counted and recorded. Additional refills will be provided as needed. The study drug bottle and NETA will be inspected and returned to the clinician. The patient will be provided with a new supply of study drug and NETA at this time.

7.2.5 Study Visit 4 – 8 week treatment

The subject will return in 4 weeks. Again, the study visit window will be 3 days before or 3 days after this time to account for weekends. At this time the subject will be given time to ask any questions or voice any concerns they may have had over the past 4 weeks, reviewing and recording any adverse events. The subject's compliance with daily surveys and the medication will be reviewed as described above in Section 7.2.3. Physical assessment will be formed as outlined in 7.2.3.

No additional medication will be provided at this visit. The patient's will be asked to complete additional surveys: (1) EHP-30 (2) PGA (3) PGIC (4) C-SSRS (5) FSFI (if partnered and sexually active). We will collect bloodwork: (1) Inflammatory markers (2) Monitoring LFTS (3) steady

state plasma concentration of CBD (4) CBC, BMP. This will be approximately 10-15cc of blood or 2-3 teaspoons. The time of their previous dose will be recorded for reference. Please see 7.2.6 for additional details on the pharmacokinetics and determination of CBD levels.

They will be required to bring all medication bottles to the visit. Oxycodone, if prescribed, and NETA pills will be counted and recorded. All unused rescue oxycodone, NETA, and unused study drug will be required to be returned at this visit for accountability purposes. Unused oxycodone will be returned to the subject. Unused NETA and unused study drug will be to Investigational Drug Services and dispensed of appropriately.

The subject will be advised to stop the study drug. If the patient would like to continue NETA for management of endometriosis pain, they will be referred to their primary OB/GYN for management of this medication.

7.2.6 Study Visit 5 – 12 week (4 weeks post treatment)

The subject will return in 4 week. The study visit will be 3 days before or 3 days after this time to account for weekends. At this final study visit, we will collect final routine bloodwork (1) LFTs (2) inflammatory markers in addition to another urine toxicology and urine pregnancy test. This is be approximately 5-10cc of blood or 1-2 teaspoons. We will complete final surveys 1) EHP-30 (2) PGA (3) PGIC (4) C-SSRS (5) FSFI (if partnered and sexually active). Physical assessment will be performed as outlined in 7.2.3.

If the subject has any abnormal test results or adverse events, these will be followed until their resolution at time intervals deemed appropriate by the clinical team. If there is an unforeseen pregnancy, the pregnancy will be followed throughout for adverse maternal, fetal and neonatal outcomes.

7.2.7 (Optional) Study Visit 6 (Eligibility window: 12-24 weeks post-enrollment)

At the initial enrollment visit, all subjects will be offered participation in the optional pharmacokinetic testing. If interested, they will complete consent during the main consent process and we will recruit until we have enrolled four participants and they have completed this Visit. As we are recruiting from the study participants, who will have already undergone rigorous screening throughout the initial study, we will not be repeating any additional testing on these patient. During this part of the study, they will also only be receiving a one-time dose of CBD. They will remain eligible to participate in this study for up to 3 months from the date of their last visit.

After completion of the initial study, the participants will undergo a 4 week washout period of the study drug, which will correspond with Visit 5 (4 week post-treatment visit).

At this time, screening measures have been set forth by the institution to test for SARS-CoV2 (the virus that causes COVID-19) if a study participant is planning to stay overnight at the Clinical Research Center.

The subjects will be screened via telephone prior to testing.

- If negative, they will proceed to testing.
- If positive, they can be rescreened in 1 or more weeks. If negative, they can proceed to testing. This can continue until the participant is no longer eligible for this portion of the study.

COVID-19 testing is currently required 5 days prior to study participation to allow appropriate time for the test to result. Testing will be done via PCR using a nasopharyngeal swab that will be

sent out to Quest Diagnostics. Once they have obtained COVID-19 testing, they will be asked to self-quarantine until their second visit at the CRC.

- If negative, they will be directed as per the COVID-19 Script for study participants when they arrive on site.
- If positive, their visit will be postponed and we will follow the COVID-19 Duration of Special Pathogen Isolation Precautions for Patients Diagnosed or Strongly Suspected to Have COVID-19 SOP for duration of isolation precautions. If they meet criteria for discontinuing isolation precautions, they will be allowed to participate in the study. Per the current SOP guidelines, positive COVID-19 patients should not be retested as according to the most recent data, there have no documented cases of re-infection worldwide.

We will continue to reference Penn State Health Pre-Operative and Pre-procedure COVID-19 Testing Standard Operating Procedure (SOP) for updated guidelines and will adjust our policies to most reflect the current institutional standards. If institutional policies change to no longer require COVID-19 testing, they will not be required for this study.

Subjects will then report to the Clinical Research Center (CRC) where they will plan to remain for 24 hours. A licensed professional will place an IV and the subject will undergo sequential blood draws to determine CBD pharmacokinetic parameters after administration of 20mg of sublingual CBD. Prior to initial administration of the CBD, a salivary pH will be obtained and recorded. They will be monitored overnight. They will then return to the CRC at 48 hours from the initial administration for one final blood draw. CBD levels will be measured using an internal assay developed at Hershey Medical Center. Approximately 10 teaspoons (about 50 ml) of blood will be drawn for this optional study visit. See details below.

Pharmacokinetic procedures: Blood will be drawn at time 0 hours, 0.25 hours, 0.5 hours, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours and 48 hours following administration of 20 mg of sublingual cannabidiol. These time points are chosen to allow determination of the Cmax, and terminal half-life of CBD.[19] Sublingual dosing affords higher bioavailability than oral dosing of cannabinoids. All blood samples for PK analysis will be separated by centrifugation immediately following the draw and plasma will be stored at -80° C until analysis. Samples will be analyzed using a literature method based on LC/MS technology.[20] The method will be translated and validated in the lab of Dr. Jeffrey Neighbors, Director of the Penn State Cancer Institute emerging ADME/PK & Correlative Science Shared Resource using a Waters Acquity UPLC system with MS/MS multiple reaction monitoring of the CBD fragmentation m/z 313.10 to m/z 245.2 in negative ion mode. Quantification will be based on use of d3-CBD (Sigma Aldrich) as an internal standard.

7.3 Duration of Participation

Study participation is expected to be 13-14 weeks. For those who participate in the optional PK study, participation may extend to 12-24 weeks post-enrollment.

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

7.4.1 Description

Cannabis is a well-known plant that contains more than 500 identified phytochemicals of which over 100 are cannabinoids. The most widely studied is Δ^9-tetrahydrocannabinol (Δ^9-THC), which is the major psychoactive component of *Cannabis,* but Cannabidiol (CBD) has been increasingly favored for its reduced side effect profile and potential health benefits. CBD was first isolated

from *Cannabis* in the 1940s. CBD, unlike Δ^9-THC, does not bind to CB1 and CB2 receptors, which accounts for its lack of typical psychotropic effects, but is still appears to work via alternative mechanisms via the endocannabinoid system. The ECS has been linked mood, immunocompetency, cell proliferation and inflammation.

The CBD used for the study will be purchased from an online retailer, Nuleaf Naturals. We will purchase their full spectrum hemp CBD oil (60mg/mL). Please refer to 7.4.6.1 in regards to internal and external validity testing for this product.

7.4.2 Treatment Regimen

Group	Treatment
A	Norethindrone acetate (5mg daily) + Placebo
B	Norethindrone acetate (5mg daily) + Low dose CBD (10mg sublingual daily)
C	Norethindrone acetate (5mg daily) + High dose CBD (20mg sublingual daily)

Arm A (Placebo): In Arm A, the participant will be placed on the daily placebo and standard endometriosis treatment (norethindrone acetate 5mg daily, initial dose) medication. Placebo will be taken sublingually and the norethindrone will be taken orally. Norethindrone will be taken for up to 12 weeks during the study period and the study drug for up to 8 weeks during the study period.

Arm B (Low Dose CBD): In Arm B, the participant will be placed on the daily low dose CBD (10mg sublingual daily) and standard endometriosis treatment (norethindrone acetate 5mg daily, initial dose) medication. CBD will be taken sublingually and the norethindrone will be taken orally. Norethindrone will be taken for up to 12 weeks during the study period and the study drug for up to 8 weeks during the study period.

Arm C (High Dose CBD): In Arm C, the participant will be placed on the daily high dose CBD (20mg sublingual daily) and standard endometriosis treatment (norethindrone acetate 5mg daily, initial dose) medication. CBD will be taken sublingually and the norethindrone will be taken orally. Norethindrone will be taken for up to 12 weeks during the study period and the study drug for up to 8 weeks during the study period.

The subject randomized in a double-blinded fashion to a 4 week supply of either the (1) placebo (2) low dose CBD or (3) high dose CBD product and instructed on its application. The subject will also receive a 4 week supply of norethindrone, which will be unblinded. Refer to the following:

c. In the morning, take the norethindrone acetate orally with a sip of water at approximately the same time each day. This can be taken on an empty or full stomach.
d. Prior to bed, you will administer the study drug.
    1. Please refrain from eating (drinking is permissible) 60 minutes prior to administration.
    2. Place 4 drops of the study drug under your tongue.
    3. Hold the study drug under the tongue for 60 seconds. After that time, swallow any remaining drug.
    4. Repeat steps 2 and 3 for a total of 8 drops.

    Please avoid eating, drinking or smoking for 2 hours after administration.

Patient instructions will be identical. The placebo dose will be 8 drops of oil (8 drops of hemp seed oil - 0mg of CBD), the low dose CBD group will receive 8 drops of oil (8 drops of a solution of 60mg/mL CBD oil + hemp seed oil in a 1:1 ratio for a dose of 10mg of CBD), while the high

dose CBD group will receive 8 drops of oil (8 drops of 60mg/ml CBD oil for a dose of 20mg of CBD).

The dosage and route of administration of CBD is highly varied. In regards to dosage, human studies have been performed using CBD dosages that range from 1.5mg – 800mg per day.[18] These studies have consistently shown that high doses of oral CBD fail to produce the typical adverse effects (impaired psychomotor & cognitive function) seen with Δ^9-THC and that CBD is generally well tolerated with a reasonable safety profile.[10]

In regards to the route of administration, multiple methods have been reported that include oral, sublingual, intranasal, intravenous and inhalation via smoking. CBD is known to undergo extensive first pass effect (bioavailability of 6%) making oral administration ineffective in delivery. On the other hand, sublingual administration, which will bypass this effect, resulted in consistent mean CBD concentrations compared to oromucosal spray or oropharygyneal administration. Moreover, this route is preferable to inhalation given its ease of use.[18]

Of note the mean half-life of CBD is reported as 1.09 and 1.97 hours (10mg vs 20mg) after single oral administration, but after chronic oral administration the mean half-life was noted to be 2-5days.[18]

With current data, we believe 10mg vs. 20mg of CBD given sublingually over 8 weeks to be an appropriate dose to see effect in our primary outcome without any overt or serious risk to our participants. We do not foresee dose adjustments to these medications.

7.4.3 Method for Assigning Subject to Treatment Groups

The statistician involved in this study will develop the programs necessary for the random number generator to create the randomization. Investigational Drug Services (IDS) will be performing randomization via REDCap to ensure proper blinding of the study team. They will also be responsible for distributing the study medications according to assigned group as per their standard operating procedure.

7.4.4 Subject Compliance Monitoring

For norethindrone, low and high dose CBD, the study team will be dispensing study medications. Adherence will be assessed daily via diary entries. Compliance monitoring will be done for all arms. These email are automatically generated via the Redcap system. It will be further verified at monthly visits using pill counts and/or visual inspection of liquid containing bottles as indicated.

7.4.5 Blinding of the Test Article

The norethindrone provided will be in individual identical packets. All study participants will be receiving norethindrone as standard of care treatment for endometriosis and this drug will not be blinded. The placebo, low and high dose CBD will be provided in identical vials. CBD Concentration will be adjusted so that subjects are each receiving equal volume of drug. In addition, CBD oil is usually blended with a carrier oil, such as coconut oil or hemp seed oil. The placebo drug consists of the same carrier oil.

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. Investigational Drug Services will be responsible for blinding the test drug to the investigators and to the participants.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The study drug (CBD) will be obtained from an online source (Nuleaf Naturals). Testing to ensure quality up to the FDA standards of an oromucosally (sublingual)-administered drug product intended for use as a drug in a patient population have been performed. This testing was done by Keystone laboratories located in Harrisburg, PA.

The placebo (hemp seed oil) will also be obtained from an online source (Organic Infusions) and has been subjected to the same testing as described above.

The norethindrone will be purchased through a pharmacy wholesaler from a manufacturer. The manufacturer, lot information, and expiration for the product used in the study will be documented by the IDS pharmacy.

The norethindrone, hemp seed oil (placebo), cannabidiol products (study drug) will be monitored, held, packaged, and dispensed by our Investigational Drug Services (IDS) Pharmacy. IDS will be responsible for randomization.

Oxycodone will be provided as a rescue pain medication if requested by the participant AND determined to be medically necessary. An oxycodone prescription will be provided to the participant's pharmacy of choice. Oxycodone use will be monitored by self-report in the daily electronic diaries.

7.4.6.2 Storage

The drug will be stored with the Investigational Drug Services Pharmacy at Penn State Health. They will monitor the drug's stability and will assume appropriate storage conditions per institutional policy.

7.4.6.3 Preparation and Dispensing

Investigational Drug Services Pharmacy at Penn State Health will be responsible for packaging and dispensing the study drug per protocol and institutional policy.
IDS will prepare and dispense the 20mg sublingual CBD used for the pharmacokinetic portion of the study.

7.4.6.4 Return or Destruction of the Test Article

We will be requiring the return of all unused study drug, placebo and norethindrone medications at the conclusion of the study.
There will be no study drug to return or destroy at the end of the pharmacokinetic portion of the study.

7.4.6.5 Prior and Concomitant Therapy

See Section 7.2.1 Prescreen

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

We plan to enroll and randomized 36 participants.

We would anticipate a 50% screen failure rate. There are multiple on-going endometriosis studies that have screen failure rates less than 10%, but given the nature of this study with daily compliance requirements, we anticipate the screening failure rate to be higher. Based on these estimates, we would anticipate screening roughly 70 patients to enroll our target number.

8.2 Sample size determination

We have chosen to enroll 36 participants. We have chosen this number based on the 2005 paper on pharmaceutic statistics by Julious et al., which states that 12 participants in a pilot study maximizes the balance between feasibility and precision.[15]

Given that this is a pilot study, we will not be using a power calculation to determine sample size. Information from this study will be used to determine the appropriate sample size to power further investigation.

8.3 Statistical methods

The statistical methods will primarily be descriptive given the sample size and intent of the study.

The primary study endpoint of daily pain (as measured using VAS) will be compared between groups using the area under the curve over the course of the 8-week 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. It is well described that endometriosis pain has a cyclic and not a linear pattern. This makes the use of averages and means less useful for monitoring progression of pain. The area under the curve of plots of daily pain should capture endometriosis "flairs" and cyclic pain allowing more accurate comparison between study groups.

We will account for the use of rescue analgesics in the efficacy analysis of CBD and ERP. We will adjust the pain score for analgesic use during the intervention. We will take into account that ERP is often cyclical.

We will compare changes from baseline in secondary study endpoints such as quality of life (QOL) and sexual function as assessed via validated surveys and inflammatory cytokines. We will compare these findings across treatment arms.

9.0 Data and Safety Monitoring Plan

9.1 Periodic evaluation of data

Adverse event reporting will be reviewed monthly at departmental meetings while this study continues. Annual reports will be made to the Penn State IRB as per the current protocol.

9.2 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. The intensity of the event will be evaluated and recorded as one of the following:

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

The study team will be required to assess for adverse events throughout study. 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. 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.

Please refer to Section 3.3.1. Criteria for Removal from Study

9.3 Method of collection of safety information

Study data will be managed using RedCap, a secure web application designed to support data capture for research studies. Well-designed data collection forms will be developed to minimize data collection and recording errors; forms will be designed to collect longitudinal and cumulative information regarding adverse events and concomitant medication usage.

Adverse events will be categorized and patients experiencing adverse events during the treatment will be recorded in RedCap. Patient's will be potentially removed from the study if deemed medically necessary. The principle investigator and IRB will be notified immediately of serious adverse effects.

9.4 Frequency of data collection

Data collection will begin immediately upon enrollment.

9.5 Individuals reviewing the data

The Principal Investigator will receive immediate notification of all serious 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.

9.6 Frequency of review of cumulative data

Data will be reviewed every 6 months.

9.7 Statistical tests

N/A

9.8 Suspension of research

The study participant will be withdrawn and/or the study will be stopped at any time if there are any serious, life threatening adverse events that occur as a result of administration of the test drug. The principal investigator or another licensed professional will be available 24/7 hours to determine the severity and causality of the reported adverse event.

10.0 Risks

Cannabidiol is generally well tolerated with a good safety profile. In clinical trials, a wide range of oral dosages have been used ranging from 1.5-800mg/day.[10]

Common risks of Cannabidiol include decreased appetite, somnolence, fatigue, sleep disorder (insomnia), diarrhea, hypersensitivity reactions (rash), infection and liver dysfunction. Because trials are conducted under widely varying conditions, the adverse events observed in one trial cannot be directly compared to the rates in our trial or in observed practice.

Cannabidiol has been associated with dose related elevation of liver transaminases; these effects typically took place within the first 2 months of treatment. Resolution occurred in one third of patients with continuation of medication and without dose reduction; approximately two third resolved with cessation or reduction of the drug. The majority of these cases took place with concomitant use of valproate and to a lesser degree, clobazam. In patients taking an oral solution at a dose of 10mg/kg/day, there was a 1% risk of elevated transaminase levels (elevated three times the upper normal limit), compared with 17% taking a dose of 20mg/kg/day.[16] These dosages are significantly higher than our planned dosages.

Other serious side effects include suicidal ideation and this would result in removal from the study. Less common effects include weight loss, decreases in hemoglobin and hematocrit, and a reversible increase in creatinine in healthy adults.[16]

Risk of Norethindrone: Serious adverse reactions with the use of norethindrone are: (1) stroke (2) deep vein thrombosis (3) pulmonary embolism (4) myocardial infarction (5) retinal vein thrombosis. Adverse reactions commonly reported by norethindrone users are: irregular uterine bleeding, nausea, breast tenderness, and headache. Worsening or persistent migraines will result in cessation of study drug.

Pregnancy Risks: Subjects will be required to be non-pregnant at the start of this study. They will also be required to use contraception throughout their participation time. There is currently no adequate data on the developmental risk associated with use of CBD in pregnant women. Administration of CBD to pregnant animals demonstrated an increased risk of fetal toxicity (increased mortality, decreased fetal weight/growth, delayed sexual maturation, long-term neurobehavioral changes). These effects were observed at levels 7-16Xs the recommended maximum level in humans at 20mg/kg/day.[17] At high doses, there was also noted to be an increased risk of structural malformation, adverse effects on male reproductive organs, and fertility. In the case of an inadvertent pregnancy, the study participant will be immediately withdrawn from the study.

Risk of Drug Interactions:
Data from the Epidiolex trials demonstrate significant drug interactions. Co-administration of CBD with certain home medications may result in lower efficacy or high potency of either the CBD or a subject's current medication. These primarily involve Cytochrome P450 Inducers and Inhibitors as well as Substrates of uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes.

1. Co-administration of CBD with a moderate to strong inhibitor of CYP3A4 or CYP2C19 may increase plasma concentration levels. This may result in higher than anticipated levels of CBD.

    a. Weak inhibitors of CYP3A4 include: amiodarone
    a. Moderate inhibitors of CYP3A4 include: moclobemide, erythromycin, fluconazole, , diltiazem, verapamil, delavirdine, amprenavir, fosamprenavir, conivaptan.
    b. Strong inhibitors of CYP3A4 include: Clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir.
    c. CYP3A4 and CYP2C19 inhibitors of unknown potency include: miconazole and chloramphenicol
    d. Strong inhibitors of CYP2C19 include: fluconazole, fluoxetine, fluvoxamine, ticlopidine, , moclobemide
2. Co-administration of CBD with a strong inducer of CYP3A4 or CYP2C19 may result in lower than expected plasma concentration levels of CBD.
    a. Strong inducers of CYP3A4: enzalutamide, apalutamidz, phenytoin, carbamazepine, and St. John's wort.
    b. Moderate inducers of CYP34A or CYP2C19 include: rifampin, rifapentine, efavirenz, phenobarbitol
    c. Glucocorticoids, , , topiramate, carbamazepine, modafinil, , , oxcarbazepine, nevirapine have an unspecified potency
3. There do exist a number of CYP2C19 inducers of weak or unspecified potency that include modafinil, , prednisone, aspirin, norethindrone, but currently none are considered strong inducers of CYP2C19

4. In vivo data demonstrates co-administration of CBD increases concentration of CYP2C19 substrates
    a. CYP2C19 substrates include amitriptyline, citalopram, clomipramine, diazepam, imipramine, phenytoin, omeprazole, R-warfarin, lansoprazole.
5. In vitro data suggest a potential reduction in substrates of CYP2C8 and CYP2C9 (e.g. phenytoin) as clinically appropriate. There is potential for both inhibition and induction by CYP1A2 and CYP2B6 substrates/
6. In vitro data suggest a reduction in substrates of UGT1A9 and UGT2B7 as clinically appropriate.
    a. UGT1A9 substrates examples include diflunisal, Propofol, fenofibrate, etodolac, indomethacin, sorafenib
    b. UGT2B7 substrates examples include gemfibrozil, lamotrigine, morphine, lorazepam, diclofenac, ibuprofen, naproxen

Given the unknown effects of the intended CBD dosages and its interactions with the above medications, we will not plan to make dose adjustments as there would be scant information guiding those adjustments. Patients will be monitored per protocol for adverse events at their visits and with routine bloodwork. They will be be removed from the study if they meet criteria outlined in 3.3.1.

Each study participant will be watched carefully for side effects, particularly if there are medication known to commonly affect liver function, however, doctors do not know all the discomfort and risks that may occur. With all drugs there is the possibility of complications and side effects that are not known at the time. These may be mild or serious, and in some cases may be very serious and permanent. 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, subject will be advised to stop taking the study drug (s) and seek immediate medical help.

The study participants will be advised to contact the study doctor or staff with any questions or concerning symptoms.

Risk of Standard of Care medications: Patients will receive standard medications to help prevent and control their endometriosis related pain such as tylenol, ibuprofen and oxycodone. The study doctor can discuss the risks associated with these medications.

Risk of Randomization**:** The patient will be assigned to a treatment program by chance. The treatment received may prove to be less effective or to have more side effects than the other research treatment(s) or other available treatments.

Risks of standard venipuncture**:** The discomfort associated with removing blood by venipuncture (by needle from a vein) is a slight pinch or pin prick when the sterile needle enters the skin. The risks include mild discomfort and/or a black and blue mark at the site of puncture. Less common risks include a small blood clot, infection or bleeding at the puncture site, and on rare occasions fainting during the procedure

Risk of Loss of Confidentiality: There is a slight risk of confidentiality associated with participation in this 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 will be restricted to study personnel.

Risk to Others: Given the route of the drug, there will be minimal to no risk to others who are not subjects. The subjects will be advised to keep this drug in a locked and secure space, away from children and/or adults that may come in contact with this drug.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

The potential benefits to a subject may be a decrease in endometriosis related pain and narcotic use and an improved quality of life.

11.2 Potential Benefits to Others

Endometriosis is a devastating disease that affects up to 10% of reproductive aged women. The pathophysiology of endometriosis is not well understood, however, there is strong evidence that inflammation plays a large role in the symptoms associated with endometriosis. Current management strategies often result in the addition of opioid-based treatments. Given the current opioid epidemic, it is important to consider non-opioid based therapies. CBD has shown promise in other pain related disorders and may potentially decrease pain and improve the quality of life and sexual function in women with endometriosis. Endometriosis has been associated with a significantly decreased quality of life and recognized as a disease with a high economic burden.

12.0 Sharing Results with Subjects

N/A

13.0 Subject Payment and/or Travel Reimbursements

Subjects will receive $175 at the completion of the study - $50 per visit after the screening visit and $25 for the post treatment visit. Subjects that participate in the pharmacokinetic arm of this study will be compensated an additional $500. The subjects will spend 24 hours in the Clinical Research Center with an additional visit at 48 hours. They will be compensated at a rate of $20 per hour for their time.

The payment will be provided by an external company, Greenphire Clincard. Details regarding compensation for patients are outlined in the Consent Form as follows:

You will receive $50 per visit after the screening visit and $25 for the post treatment visit for your participation in this research study for a total of $175. If you do not complete the study for any reason, you will be paid for the visits you have completed. The payment will be provided by Greenphire Clincard (see below)

If you choose to complete the optional pharmacokinetic portion of this study, you will be compensated an additional $500.

This reimbursement will be issued by an external company called Greenphire, which will issue your reimbursement. You will be issued a ClinCard, which is a debit card that your funds are loaded onto and can be used at your discretion. The research team will give Greenphire some personal information about you, as described below. Greenphire will only use your personal information to process this reimbursement and will not share it with anyone for any other purpose. Details of the debit card system are explained on an additional sheet. If you lose the card, you may be responsible for the replacement fee.

When a visit is completed, funds will be approved and loaded onto your card. The funds will be available within 2-3 business days. In order to assign a ClinCard to you and load funds onto the ClinCard, Greenphire will need your Study/Subject ID, Name, Address, and Social Security Number.

You will have the option to receive updates related to payment alerts via text message and/or email message. Standard text messaging rates will apply. In order to send you messages Greenphire will need your Mobile Phone Number and/or E-mail Address.

Payment received as compensation for participation in research is considered taxable income. If payments from Greenphire exceed $600 in any one calendar year, Greenphire will file a 1099 (Miscellaneous Income) form on behalf of Penn State.

Travel reimbursement will not be provided as part of the study protocol.

14.0 Economic Burden to Subjects

14.1 Costs

All tests and procedures required for participation in the study will be paid for by the internal grants. There are no additional costs to subjects participating in the research.

14.2 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 an 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.

15.0 Resources Available

15.1 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.

The immunoassays will be run by Dr. Elizabeth Proctor. Her lab is located at 500 University Drive MC R130. The PK study will be conducted by the lab of Dr. Jeffrey Neighbors and his lab is located at 500 University Drive T4115

15.2 Feasibility of recruiting the required number of subjects

The principal investigator sees on average 10 patients each week with endometriosis; approximately 30-40 are seen total with the MIGS practice. Ideally up to 10% of those potential subjects would be interested in this project.

15.3 PI Time devoted to conducting the research

The principal investigator has dedicated research time and is available to see study patients 5 days/week.

15.4 Availability of medical or psychological resources

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

15.5 Process for informing Study Team

The PI and study team members will complete required study specific training prior to the start of the trial. Ongoing communication in-person, via email and telephone will also take place.

16.0 Other Approvals

16.1 Other Approvals from External Entities N/A

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ 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 – **Penn State Health 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" in CATS IRB.

☒ 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 – **Penn State Health 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" in CATS IRB.

☒ 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 – **Penn State Health 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 Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team 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.

17.0 Multi-Site Study

17.1 Other sites N/A

17.2 Communication Plans N/A

17.3 Data Submission and Security Plan N/A

17.4 Subject Enrollment N/A

17.5 Reporting of Adverse Events and New Information N/A

17.6 Audit and Monitoring Plans N/A

18.0 Adverse Event Reporting

18.1 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.

18.2 Recording of Adverse Events

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(s) or device(s) 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:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

18.3 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.

18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.4.1 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.

18.4.2 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.

18.5 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.

18.6 Unblinding Procedures

The Investigational Pharmacy at Penn State Hershey Medical Center will be responsible for randomization, blinding and unblinding as needed. Investigators will have the discretion of unblinding the physicians at any time if warranted for safety and/or scientific reasons.

18.7 Stopping Rules

The principle investigator will receive immediate notification of all serious adverse events. The principle investigator will meet with the research team after the receipt of any report of any major serious adverse event and determine whether the participant will need to be removed from the study or whether the study should be paused until further investigation.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Study Monitoring Plan

19.1.1 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 assume 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.

19.1.2 Safety Monitoring

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **Research Coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA and/or DSMB of all Unanticipated Problems/SAE's.

20.0 Future Undetermined Research: Data and Specimen Banking

20.1 Data and/or specimens being stored N/A

20.2 Location of storage N/A

20.3 Duration of storage N/A

20.4 Access to data and/or specimens N/A

20.5 Procedures to release data or specimens N/A

20.6 Process for returning results N/A

21.0 References

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22.0 Confidentiality, Privacy and Data Management

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