IRB-HSR PROTOCOL

Investigator Agreement

BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of UVA prior to publication that you will contact the Dean's office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB-HSR On-line training and the IRB-HSR has been notified.
6. That all personnel working on this protocol will follow all IRB-HSR Policies and Procedures as stated on the IRB-HSR Website http://www.virginia.edu/vprgs/irb/ and on the School of Medicine Clinical Trials Office Website: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training or experience to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment
10. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office , UVa Police as applicable.
17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
19. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time.
20. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study. These are considered institutional records and may not be transferred to another institution. A copy of the documents may be taken with the Principal investigator when transferring to another institution.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

Signatures

Principal Investigator

_____	_____	_____
Principal Investigator Signature	Principal Investigator Name Printed	Date

Department Chair

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound

_____	_____	_____
Department Chair or Designee Signature	Department Chair or Designee Name Printed	Date

The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol.
The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator

Background and Brief Summary

Background

1. Has another IRB ever not given approval to this protocol?No.

2**. Provide additional background information.**

Adolescent hyperandrogenemia (excess androgen production) occurring before or during early puberty appears to be a precursor to adult polycystic ovary syndrome (PCOS). PCOS affects about 6% of women of childbearing age in the United States. Those who suffer from this disorder often experience irregular menstrual periods, excess facial and body hair, and weight gain. PCOS is also a leading cause of infertility. Women with PCOS often report irregular menstrual cycles as adolescents. A study of adolescents with menstrual irregularities showed that some subjects normalize endocrine function as they mature, while a majority maintained hyperandrogenism in conjunction with high levels of luteinizing hormone (LH) and polycystic ovaries (Venturoli et al. 1987). In addition, girls with high levels of serum androgens often have lower fertility rates in adulthood (Apter and Vihko 1990).

We propose that adult PCOS, and perhaps adolescent hyperandrogenemia, are due in part to dysregulation of pituitary and ovarian hormones. Synthesis and secretion of LH and follicle stimulating hormone (FSH) are primarily regulated by gonadotropin releasing hormone (GnRH). Both LH and FSH are secreted by the same gonadotrope cell, and the frequency of stimulation of this cell by GnRH in part determines which hormone is released. In primates, rapid GnRH frequencies (approx. 1 pulse/ hour) favor LH secretion whereas slower GnRH stimuli (1 pulse/ 3 hours or less) favor FSH release (Wildt et al. 1981). In normal women, the cyclical rise and fall in hormone levels control follicular maturation and ovulation. Early studies showed an initial predominance of FSH in the follicular phase, with a subsequent rise in estradiol (E_2)(Speroff et al. 1971). In the late follicular phase, LH increases as a consequence of increased GnRH secretion. Following ovulation, rising levels of E_2 and P then reduce GnRH pulse frequency, allowing a rise in FSH for the next cycle of follicular maturation.

One feature of adult PCOS is increased mean serum levels of LH and increased LH pulse frequency, presumably due to increased stimulation of the pituitary by excess hypothalamic secretion of GnRH. Since women with PCOS maintain high levels of LH and low levels of FSH, follicle maturation and ovulation do not occur normally. Girls with hyperandrogenemia in adolescence also have an increased frequency of LH pulses when compared to age matched controls (Apter et al. 1994).

If hyperandrogenemic adolescents could be treated effectively before or during pubertal maturation, development of clinical PCOS as an adult could potentially be avoided. One proposed cause of both hyperandrogenemia and PCOS is a defect in GnRH pulse modulation, which normally happens as puberty progresses. GnRH is secreted by a part of the brain called the hypothalamus. In normal pubertal maturation the increase in GnRH pulse secretion during sleep stimulates LH and ovarian E_2 and P secretion. Feedback of these hormones reduces GnRH pulses during daytime hours, initiating cycles of ovarian-hypothalamic feedback regulation which mature into the patterns seen in normal ovulatory cycles. Recent studies have shown that E_2 and P can slow LH pulses in adult women with PCOS, but higher concentrations of P are needed to inhibit LH pulse frequency (Daniels and Berga 1997, Pastor et al. 1998). If hypothalamic (GnRH pulse generator) sensitivity to inhibition by P is reduced during pubertal maturation, the low levels of P present during the initial development of ovarian cyclicity may not be adequate to suppress GnRH/LH pulse secretion. This could lead to LH excess and relative FSH deficiency. Administering oral doses of P in early adolescence may compensate and restore normal ovarian-hypothalamic feedback. In turn, increasing amounts of naturally secreted P in

subsequent cycles could eventually normalize the system.

The long term goal of this line of investigation is to determine if E_2 and P treatment of adolescents with hyperandrogenemia can slow the GnRH pulse generator to promote FSH production and the advent of normal menstrual cycles. As an initial step we propose to determine if the GnRH pulse generator is relatively insensitive to E_2 and P inhibition in hyperandrogenemic adolescent girls.

Brief Summary

Please see abstract below.

Will this study collect data and or specimens in a retrospective manner, prospective manner or both?
Prospective

Investigators Experience\

The PI and co-investigators have extensive experience in studies of the early manifestations and abnormalities of pubertal maturation during research over the past 25 years. Much of this research has involved joint collaboration with colleagues in the Department of Pediatrics, and this continues in the present application with co-investigators in the Dept. of Pediatrics. These individuals are specialists in pediatric endocrinology and are well versed and have expertise in dealing with children of the age ranges included. The group currently has 13 ongoing, IRB-approved studies in the adolescent population, including 12 that involve overnight admissions with frequent blood sampling. Over 100 girls to date have enrolled in overnight studies.

Sponsor Information

This study is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NIH-NICHD).

Support Source

Is there a support source for this study? No

Sharing of Data/Specimens

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have "permission" to share data/ specimens outside of UVa other than for a grant application and or publication. This "permission" may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

Do you confirm that no data will be shared outside of UVa, beyond using these data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed? Yes.

Do you confirm that no specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed? Yes.

International Research

1. Will this study be done outside the U.S. under the oversight of a UVA PI? No.

Hypothesis to be Tested

Adult women with polycystic ovarian syndrome (PCOS) are relatively resistant to suppression of GnRH/LH pulse frequency by the combined slowing effects of estrogen and progesterone. We propose to test whether adolescent girls with hyperandrogenemia, which is thought to be a precursor to PCOS, are also relatively resistant to LH pulse frequency suppression by estrogen and progesterone.

Abstract

Adolescent hyperandrogenemia appears to be a precursor to adult polycystic ovary syndrome (PCOS). We have found that adult women with PCOS have a reduced sensitivity to progesterone inhibition of GnRH pulsatility. We propose to examine progesterone inhibition of GnRH pulsatility in normal and hyperandrogenemic adolescent girls to determine whether this may be an underlying cause of hyperandrogenemia, and eventually, PCOS. The results will help us understand the causes of PCOS and may lead to preventative treatment.

Human Participants

Ages 8-18 years
Sex **Female**
Race All races will be recruited and enrolled.

Subjects- see below

1. Provide target # of subjects (at all sites) needed to complete protocol to obtain statistically significant results.

52

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.

The historic dropout/withdrawal rate in JMC010/IRB#8588 procedures is 35%. We anticipate a need to enroll 79 subjects in order to get the complete data on 52 subjects needed to obtain statistically significant results.

3. How many subjects will be enrolled at all sites? 79.

4. How many subjects will sign a consent form under this UVa protocol? 79.

Clinical Data Repository

1. Will you be obtaining data from the UVa Clinical Data Repository (CDR)? No.

Participation of Children

1. Explain why this research topic is relevant to children.

This is a study of the effects of progesterone administration on gonadotropin (LH) dynamics during puberty. It will advance our knowledge of the mechanisms of normal puberty. Moreover, it will provide important foundational data pertinent to our hypotheses regarding the development of polycystic ovary syndrome during adolescence. If our hypotheses are correct, this study could provide critical data implicating a specific mechanism by which hyperandrogenemia can cause abnormal gonadotropin secretion in those who may go on to develop PCOS. This in turn may provide a sound rationale for treatment of hyperandrogenemic girls in adolescence. If hyperandrogenemic girls could be treated effectively during pubertal maturation, development of clinical PCOS as an adult could be potentially avoided.

2. Is the knowledge being sought in this study already available for children or is it currently being acquired through another ongoing study?

There is very limited data on the sensitivity of the GnRH pulse generator to suppression by estradiol and progesterone during the early pubertal period. The knowledge being sought is not currently being acquired through another ongoing study.

3. Provide data that is available in adults in order that the IRB may judge the potential risk in children. If there is no adult data available, provide reasons why not. If this information is available in a sponsor's protocol, you may reference the section # here and not duplicate the information.

Given that the data sought in this protocol is specific to the peripubertal period of development, there are no similar data in adults. However, very similar studies (frequent blood sampling for LH pulse analysis before and after 7 d of estradiol and progesterone) have been performed by our group in adults without significant adverse effects (Pastor el al. 1998). In addition the 62 adolescent girls who have completed the study thus far in IRB-HSC 8588 have had no adverse outcomes.

4. Is the potential subject population likely to include wards of the state or children who are more at risk for becoming a ward of the state?
Yes.

4a. Is the research is this protocol related to the childs' status as a ward of the state? No.

4b. Is the research to be conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards? Yes.

4c. Are you aware of the following requirement?
If the consent form contains a signature line for both parents the study team will notify the IRB immediately, if at any time during the course of the research, it becomes known that a potential subject is a ward of the state or that a child already enrolled in this protocol becomes a ward of the state. Yes.

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

- Girls ages 8 to 18
- Hyperandrogenemic (testosterone level > 0.4 ng/mL and/or hirsutisim)
- Normal screening labs (with exception of the expected hormonal abnormalities inherent in hyperandrogenemia)

2. List the criteria for exclusion

- Abnormal screening labs (with exception of the expected hormonal abnormalities inherent in hyperandrogenemia)
- Congenital adrenal hyperplasia.
- Hemoglobin <11.5 g/dL for non-African American subjects; Hemoglobin < 11.0 g/dL for African American subjects (Subjects will be offered the opportunity to take iron supplementation for 60 days if their hemoglobin is below the above stated guidelines, and will then return for retesting of their hemoglobin. If still below the guidelines, they will be excluded.
- Weight < 31 kg
- History of peanut allergy, deep venous thrombosis, breast cancer, endometrial cancer, or cervical cancer
- On hormonal medications (including oral contraceptive pills) or on medications known to affect the reproductive axis within 3 months of the study

- Pregnant or breastfeeding
- Participation in a research study within the past 30 days that involved taking a study drug.
- Participation in a research study that involved taking up to or greater than 473 ml's of blood within the past 60 days.
- Cigarette smoking
- History of surgery that required bedrest within the past 30 days
- Family history of hypercoagulability or unexplained thromboembolic disease (not in setting of bedrest, surgery, or malignancy)

3. List any restrictions on use of other drugs or treatments.
Subjects must discontinue all hormonally-active medications at least 3 months prior to the frequent sampling study (and 2 months prior to screening visit) and must not take any other medications known to affect the reproductive axis during the study. There are no dietary requirements for this study.

Study Design: Biomedical

1. Will controls be used?

Yes. Controls (normal healthy volunteers) will be used included in all analyses. Thus far, 28 controls have completed the study. Since this is adequate for our purposes, no additional controls will be enrolled. For the remainder of the study, only girls with hyperandrogenemia will be studies.

►IF YES, explain the kind of controls to be used.

Normal-weight, healthy adolescent girls.

2. What is the study design?

Biomedical

3. Is randomization involved?

No.

4. Does the study involve a placebo?

No.

Recruitment

1. Do you confirm that you are aware of the following?

Yes.

- *Finders fees paid to an individual are not allowed by UVa Policy*
- *All recruitment materials must be approved by the IRB-HSR prior to use. Informational letters to colleagues which potential subjects will not see do not need IRB approval. The advertisements should be submitted to the IRB after the protocol has been approved.*
- Only those individuals listed as personnel on this protocol may recruit and or conduct the consenting process with potential subjects.

2. How do you plan to <u>identify</u> potential subjects

_X___Potential subject is approached by the treating physician/ health care provider and given information about the study and provides the potential subject the information necessary to contact the study team if they are interested.

_X__Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc. *If this is checked #3 below should be checked INDIRECT CONTACT.*

3. How will potential subjects be <u>recruited?</u>

__X__ Indirect contact (flyer, brochure, TV, broadcast emails, etc.)

4. If you plan to enroll students, patients, staff, employees of any person listed on this protocol, do you agree to the following to avoid the appearance of coercion?

Yes.

- For potential subjects who will be recruited by local advertisements and/or flyers, these subjects will initiate contact with the study team. . The PI or study staff cannot initially contact someone requesting them to enroll.
- Subjects who are also study team members, laboratory staff or their coworkers will be told their participation is strictly voluntary.
- Subjects will be advised that grades, employability, relationship with physician at UVa etc. will not be affected by their decision to participate or not.
- Subjects who are initially approached regarding participation in this trial will be informed of all other potential treatment options (if applicable), and will be assured that whether or not they decide to participate in the study, their care will not be affected.

5. **Do you plan to ask the subjects to do anything for the study prior to signing a consent?** Yes.
►IF YES, explain in detail what you will ask them to do.

We will request that subjects come to the screening visit while fasting for at least 8 hours. We will tell potential subjects that only subjects who have taken no hormonally-active medications for 2 months prior to screening are eligible for screening study, although we will not advise anyone to stop prescription medications without first consulting their personal physician.

NOTE:

- *Only those members of the study team with a DEA# (license to prescribe drugs) are allowed to determine if a potential subject may be asked/informed to stop taking a drug which is an exclusion criteria.*
- *It is recommended that the potential subject notify their health care provider if they plan to stop a prescription drug.*

6. Will the study procedures be started the same day the subject is recruited for the study?
No.

7. How will the consenting process take place?

An outpatient screening visit is scheduled for volunteers who preliminarily qualify for the study. Copies of the approved consent and assent forms are sent to potential subjects beforehand, and we request that the volunteer and her parents review and discuss the forms prior to the screening visit. The screening visit is held in an outpatient screening room in the CRU or alternate UVA clinical unit. This allows for a private conversation between the study physician, the potential participant, and at least one of her parents (other individuals such as family members are allowed in the room if desired by the potential participant). The screening visit usually occurs in the morning, although rarely it will occur in

the afternoon. The aims, procedures, and potential risks of the study are first explained by the study physician. Importantly, the potential participant and her parents (if under 18) are given an opportunity to ask any questions, and concerns are addressed. In cases where the potential participant wants to begin the study and her parents concur, the participant, parents, and physician sign the consent form. In cases where only one parent is able to come to the screening visit, we allow the second parent to sign the form in advance of the visit. This is done in conjunction with a conversation during which we offer that parent an opportunity to ask any questions and confirm that they understand the study and are willing for their daughter to participate. We routinely inform potential participants verbally that signing the consent form does not compel them to continue participation in the study. The remainder of the outpatient screening visit (i.e., history, physical, screening blood tests) occurs immediately thereafter. Participants generally begin the main part of the study within 1-2 months of the screening visit.

8. Do you need to perform a "dry run" of any procedure outlined in this protocol? No.

Biomedical Research

NOTICE: Investigators who are Members of the Clinical Staff at the University of Virginia Medical Center must have been granted clinical privileges to perform specific clinical privileges whether those procedures are experimental or standard. The IRB cannot grant clinical privileges. Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise. Contact the Clinical Staff Office- 924-5871 for further information.

1. What will be done in this protocol?

All procedures performed in this protocol are being done solely to answer a research question and generate generalizable knowledge.

Outpatient Screening

After a potential subject is identified, we will arrange for her to come to the CRU or alternate UVA clinical unit for an outpatient screening exam. The goals and procedures of the study will be explained to the potential subject and her parents (if applicable), and they will be given the opportunity to ask any questions. The potential subject and her parents (if applicable) will be asked to sign the assent and consent forms.

- A physician will record a family and personal medical history and perform a physical exam.
- Subjects will need to fast for a minimum of 8 hours prior to screening blood draw.
- Blood will be drawn for screening tests (CBC, Chem 17 including LFTs, prolactin, LH, FSH, E_1, E_2, P, total T, androstenedione, 17-OHP, DHEA-S, fasting insulin, glucose, TSH, hCG, cholesterol, LDL and HDL).
- Patients with elevated 17-OHP on screening will be referred to their pediatricians for further testing to rule out congenital adrenal hyperplasia. They will only be able to continue with the study if they have documented normal 17-OHP levels following a cosyntropin stimulation test
- Potential subjects must fall within the normal range on all blood tests to be admitted to the study, except for hyperandrogenemic girls who will be expected to have some abnormal hormone levels.
- In addition, if the subject's hemoglobin is less than 11.0 for African American subjects or < 11.5 for non-African American subjects at the time of screening, we will offer the option of taking

oral iron supplementation at a dose of 1-2 mg/kg for 60 days. Subjects weighing ≤ 36 kg will be given 300-325 mg oral ferrous gluconate daily (containing 36 mg of elemental iron); subjects weighing >36 kg will be given 300-325 mg oral ferrous gluconate twice daily. Following the course of iron supplementation, the subject will then return to the CRU or clinical unit for a repeat hematocrit and hemoglobin, and will only be able to proceed with the study if her hemoglobin is greater than or equal to 11.5 g/dL for non-African American subjects or greater than or equal to 11.0 g/dL for African American subjects.

- If the screening tests show that the subject is eligible for the study, she will be given oral iron supplementation at a dose of 1-2 mg/kg for 30 days to help prevent anemia during and after the study. Subjects weighing ≤ 36 kg will be given 300-325 mg oral ferrous gluconate daily (containing 36 mg of elemental iron); subjects weighing >36 kg will be given 300-325 mg oral ferrous gluconate twice daily. The admission can take place any time during or after the iron supplementation.

Day 0: First inpatient admission

The subject will be admitted to the CRU, alternate UVA hospital unit, or off-site hotel at 1700 hr, when a hemoglobin test will be done. In order to continue with the admission, girls must have a hemoglobin of at least 11.0 g/dL for African American subjects or at least 11.5 g/dL for non-African American subjects. In general, parents are welcome to stay with their child at the off-site hotel if they wish. If the overnight portion of the study is to be done at an off-site hotel, the subject may stay without a parent or legal guardian, as long as two CRU staff are present. Whether or not a parent needs to remain during the overnight admission will be discussed when the visit is scheduled. . If the overnight portion of the study is to be done at a hotel, the hemoglobin check will be done at the CRU 1-5 days prior to the overnight admission. Alternatively, subjects may come to the CRU early on the day of their admission before their scheduled admission time. The study team will be responsible for scheduling this with the subject. A urine pregnancy test will be done. The pregnancy test must be negative for continued participation. A small amount of topical lidocaine/prilocaine cream (EMLA cream) may be applied to facilitate IV line placement. An IV line will be placed in a forearm vein and blood draws will begin at 1900 hr. Samples will be taken every 10 minutes. Most samples will be 0.75 mL, used to analyze levels of FSH and LH. 2.5 mL samples will be taken every 2 hours to analyze levels of estradiol, progesterone, testosterone, cortisol and DHEA An additional 3.0 mL sample will be analyzed for fasting insulin, Insulin-like Growth Factor 1 (IGF-1), fasting glucose, estrone, sex hormone binding globulin, DHEA-S, androstenedione and a number of cytokines and adipokines, including adiponectin, leptin, resistin, PAI-1, IL-1b, IL-6, IL-8, TNFa, MCP-1, HGF and NGF. (Due to new technologies adipokines and cytokines can be measured in a total of 25 ul of serum, thereby allowing us to measure these without substantially increasing the necessary blood volume).
A formal "lights out" will occur at 2300 hr so that we may observe any nocturnal changes in LH release patterns. Q10 minute blood sampling will end at 0600 hr. There will be one final blood draw at 0700 hr. During blood sampling, activity (e.g., awake, sleeping) will be recorded by the nurse every 10 minutes. Additionally, periods of sleep will be estimated using wrist actigraphy (Motionlogger Basic-L; Ambulatory Monitoring, Inc.). The Motionlogger Basic-L is a watch-like device (that includes an accelerometer) that will be worn on the wrist by the research participant during the overnight admission. The subject will be offered meals at standard CRU meal times.

Day 1: Study medications

Starting the day of discharge from the first inpatient admission, subjects will be given oral

estrogen (estrace, 0.5-1 mg once a day) and oral progesterone suspension (20 mg/ml, 25-100 mg) three times a day at 0700, 1500, and 2300 hr to achieve mean plasma concentrations over the range of 2-8 ng/ml for seven days. Each subject will be instructed to eat a small snack with the medication. It has been observed that the absorption of progesterone is influenced by the presence or absence of food. Subjects will continue their iron supplementation.

Days 3, 5: Outpatient blood draws

On study days 3 and 5, subjects will have blood drawn at 1700 hr (two hours after the 1500 hr progesterone dose) to check serum estrogen and peak progesterone levels.

Day 7: Second inpatient admission

The second inpatient admission will begin on day 8. The procedure will be identical to the first inpatient admission.

Subjects will discontinue estrace and progesterone after the completion of the second inpatient admission. At discharge, the subject will be given oral iron supplementation at a dose of 1-2 mg/kg for 30 days to help prevent anemia after the study. Subjects weighing ≤ 36 kg will be given 300-325 mg oral ferrous gluconate daily (containing 36 mg of elemental iron); subjects weighing >36 kg will be given 300-325 mg oral ferrous gluconate twice daily.

Follow-up (Optional)

Follow-up questionnaires and/or phone interviews will be completed by the subjects 3, 6 and 12 months after the study asking about the onset and frequency of menses and changes in hirsutism. During these interviews, we will specifically address whether pre-menarchal girls had a withdrawal bleed following the study, and if so, whether or not they subsequently continued menstruating. Whenever possible we will also see the patients on 2-3 occasions during the 12 months to obtain blood for T, DHEA-S, E_2, and P measurements (depending on cycle stage).

The PI will inform the subjects verbally of all incidental findings that are of clinical significance or are of questionable significance**.** A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic

2. Does the study involve the administration/ dispensing of a drug? Yes.

►IF YES, where will the subjects be seen for the administration/dispensing of the drug?

___X__ Inpatient Unit: *CRU, alternate UVA hospital unit, or off-site hotel.*__

3. If a potential subject does not meet the inclusion/ exclusion criteria will you repeat any of the screening procedures/ tests? Yes.

►IF YES, explain.

Patients with an elevated 17-OHP on screening will be referred to their pediatricians for further testing to rule out congenital adrenal hyperplasia. They will only be able to continue with the study if the have documented normal 17-OHP levels following a cosyntropin stimulation test. Additionally if safety labs

are abnormal during screening (e.g., abnormal liver tests, abnormal TSH), subjects will be asked to return once for repeat (confirmatory) labs to exclude lab error. Repeat testing will generally occur within one month of the original screening lab draw. If exclusionary lab values are confirmed on such repeat testing, subjects will be excluded from participation. The exact amount of blood drawn will depend on the labs being repeated, but the total amount of blood drawn will not exceed 5 ml.

4. If clinically meaningful results are obtained during the course of the study, explain how you will notify the participant.

We will contact the custodial parent(s) via phone and make general recommendations (e.g., follow-up with the subject's primary care physician). We will generate a letter to the primary care physician (with a copy to the subject and her parent[s]) detailing the clinically meaningful results and associated findings of relevance.

5. What treatments, normally used, will be omitted for the study?

Treatments for hyperandrogenemic girls include use of metformin and/or oral contraceptives to regulate hormone levels and/or spironolactone to reduce excess facial and body hair. In order to conduct our study, treatment will necessarily be delayed. However, since our study only takes one week to complete, no undue hardship will be experienced by girls who volunteer for the study.

6. Will any of the treatments/ procedures be done for research purposes only? Yes.

►IF YES, explain:

All procedures are being done for research purposes only.

7. If the study involves drawing blood, will the blood be drawn from central lines? No.

8. What details of the study are best kept secret from the participants?

None of the details of the study will be kept from the participants. Study participants and their parents will be advised of any and all aspects of the study. They will have ready access to their individual results after the data have been analyzed, and they may contact us to find out the results of the entire study once it has been completed.

9. Will subjects with a GFR<45 mL/min receive Gadolinium? No.

Drug Information

1 What is the drug name, manufacturer and IND# if available?

- Micronized progesterone powder (Spectrum Chemical Manufacturing Corporation, Irving, CA), IND# 64,126

2. If IND application has been submitted to the FDA, who is the Principal Investigator on the IND?

Dr. John Marshall

3. What is the phase or stage of this study?

Not applicable.

4. What dose will be utilized in this study?

20 mg/ml, 25-100 mg

5. What will be the frequency of dosing in this study?

Three times a day at 0700, 1500, and 2300 hr

6. What will be the duration of dosing in this study?

7 days.

7. What route of administration will be utilized?

PO

8. Will drug need to be prepared by the UVa Investigational Drug Service (IDS)?

__X___ YES

8a. Concentration

___X__ Standard

8b. Diluents

___X__ Standard

8c. Stability after prepared

___X__ Standard

8d. Special storage requirements

___X__ Standard

9. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)?

No.

10. Does the protocol provide provisions for dose titration, dose reductions, and or re-challenged (if drug is stopped), etc.? No.

11. How will missed doses be handled?

The subject should take the missed dose when she remembers it unless she is due for the next dose. If the next dose is due, it should be taken and the missed dose should be skipped.

12. Will a comparator (active or placebo) be utilized in the protocol?

No.

13. Does this study involve research on a drug, biologic, supplement or food additive?

No.

14 Are you using a drug/supplement/ food additive in a manner not approved by the FDA?

Yes.

14a. Describe pertinent animal data that is available regarding the toxicity/safety of this drug.

Not applicable, as abundant human data is available.

14b. Describe pertinent human data that is available regarding the toxicity/safety of this drug.

We are using a micronized progesterone suspension which is formulated/constituted by our investigational pharmacy. There are no specific data regarding human toxicity/safety of the UVAHS's progesterone suspension, but the progesterone used to formulate the suspension is FDA approved. We have used this progesterone suspension in other protocols, and we have thus far administered the progesterone suspension to 15 adolescent girls and at least 12 adult women; no adverse events have occurred.

14c. Have there been any human deaths associated with this drug?

To our knowledge, there have been no human deaths associated with micronized progesterone or Estrace.

14d. In how many humans has this drug been used previously?

The oral micronized progesterone suspension formulated by the University of Virginia Investigational Drug Pharmacy has been used in several other IRB-HSR approved protocols. We have administered the progesterone suspension to at least 62 adolescent girls and at least 13 adult women.

14e. If this protocol will be used in children describe any previous use of this drug with children of a similar age range.

The oral micronized progesterone suspension formulated by the University of Virginia Investigational Drug Pharmacy has been given to at least 62 adolescent girls as part of our protocols. There have been no adverse effects.

15. Do the following criteria apply?

_____ The investigation is intended to be reported to FDA as a well-controlled study in support of a new indication for use or intended to be used to support any other significant change in the labeling for the drug;

_____ If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is intended to support a significant change in the advertising for the product;

_____ The investigation does involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

If Not checked- explain why you believe the risk to subjects is not increased:

The oral micronized progesterone suspension formulated by the University of Virginia Investigational Drug Pharmacy has been given to at least 15 adolescent girls as part of our protocols. There have been no adverse effects.

__X__ The investigation will be conducted in compliance with the requirements for institutional review set part in part 21CFR56 and with the requirements for informed consent set forth in part 21CFR50 ; and *This item must be checked.*

__**X**__ The investigation will be conducted in compliance with the requirements of 21CFR312.7 (Promotion and charging for investigational drugs)
This item must be checked.

16. **Is this a post-marketing study? No.**

Drug Information

1 What is the drug name, manufacturer and IND# if available?

- Estrace (Warner-Chilcott, Rockaway, NJ) IND #64,126

2. If IND application has been submitted to the FDA, who is the Principal Investigator on the IND?

Dr. John Marshall

3. What is the phase or stage of this study?

not applicable

4. What dose will be utilized in this study?

Estrace, 0.5-1 mg once a day

You may reference the sponsors' protocol for questions 5-9

5. What will be the frequency of dosing in this study?

Daily

6. What will be the duration of dosing in this study?

7 days.

7. What route of administration will be utilized?

PO

8. Will drug need to be prepared by the UVa Investigational Drug Service (IDS)?

___X__ YES

8a. Concentration

___X__ Standard

8b. Diluents

___X__ Standard

8c. Stability after prepared

__X___ Standard

8d. Special storage requirements

__X___ Standard

9. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)?

No.

10. Does the protocol provide provisions for dose titration, dose reductions, and or re-challenged (if drug is stopped), etc.?

No.

11. How will missed doses be handled?

The subject should take a dose as soon as she remembers, unless it has been a full 24 hours, at which point the missed dose should be skipped and the regularly scheduled daily dose should be taken.

12. Will a comparator (active or placebo) be utilized in the protocol?

No.

13. Does this study involve research on a drug, biologic, supplement or food additive?

Yes

►IF YES, is this study investigator initiated?

14 Are you using a drug/supplement/ food additive in a manner not approved by the FDA?

Yes.

14a. Describe pertinent animal data that is available regarding the toxicity/safety of this drug.

Not applicable, as abundant human data is available.

14b. Describe pertinent human data that is available regarding the toxicity/safety of this drug.

Estrace has used extensively in women and has a well described safety profile. It is FDA approved for use in adults.

14c. Have there been any human deaths associated with this drug?

To our knowledge, there have been no human deaths associated with estrace.

14d. In how many humans has this drug been used previously?

Oral estrogens, in various formulations, have been used to treat millions of women, although exact numbers are unknown.

14e. If this protocol will be used in children describe any previous use of this drug with children of a similar age range.

Although Estrace is not often prescribed to adolescent girls, there is significant experience with estrogens in this population, generally in the form of oral contraceptive pills. Oral contraceptive pills have been shown safe and effective in adolescent girls, and are commonly used for a number of medical conditions, including hyperandrogenism, as well as for contraception. There is no data for the use of estrace in pre-pubertal girls.

15. Do the following criteria apply? *Check all that apply*

_____ The investigation is intended to be reported to FDA as a well-controlled study in support of a new indication for use or intended to be used to support any other significant change in the labeling for the drug;

_____ If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is intended to support a significant change in the advertising for the product;

_____ The investigation does involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.

If Not checked- explain why you believe the risk to subjects is not increased:

Although Estrace is not often prescribed to adolescent girls, there is significant experience with estrogens in this population, generally in the form of oral contraceptive pills. Oral contraceptive pills have been shown safe and effective in adolescent girls, and are commonly used for a number of medical conditions, including hyperandrogenism, as well as for contraception.

___X_ The investigation will be conducted in compliance with the requirements for institutional review set part in part 21CFR56 and with the requirements for informed consent set forth in part 21CFR50 ; and
This item must be checked.

__**X**__ The investigation will be conducted in compliance with the requirements of 21CFR312.7 (Promotion and charging for investigational drugs)
This item must be checked.

17. **Is this a post-marketing study? No.**

Specimens

Specimen Information

1. Describe the type of specimen to be used:
Blood and urine

2. Will the specimen be obtained BEFORE a subject has signed a consent form?
No.

3. Will you be using viable embryos?
No.

4. Will you be using embryonic stem cells?
No.

5. Will you be using discarded specimens?
No.

Specimen Labeling

1. What information/ HIPAA identifiers will be on the specimen label when it is given to the study team (from clinical labs or other source outside the study team) and/or what information will you put on the specimen.?
Name, medical record #, GCRC protocol #, time (date and clock hour) drawn.

2. If the specimen is given to the study team with information on the label will you delete any of the information on the specimen label?
No.

3. Will any additional data be linked to the specimen by way of a code?
No.

4. Will the analysis on the specimen be done soon (within 24 hours) after it is collected?
Yes and No (see the explanation below)
Samples from the screening exam that are analyzed by UVA clinical labs will be run within 24 hrs.

►IF NO, where will the specimen be stored until analysis is done?
Some samples from the screening exam (FSH, LH, P, prolactin, T4, E_2 and T) will be analyzed and stored by the Research Assay and Analysis core lab
All samples from the inpatient admissions will be analyzed and stored in the Center for Research in Reproduction Ligand Core lab.

Specimen Shipping

1. Do you plan to ship any specimens outside of UVA?No.

Payment

1. Are subjects compensated for being in this study?
Yes.

1a. What is the maximum TOTAL compensation to be given over the duration of the protocol?
$200 in gift cards.

1b. Explain compensation to be given.
All participants will receive a $75 Charlottesville Fashion Square Mall gift card per inpatient admission. In addition, participants will receive a $50 bonus for study completion, also in the form of a gift card. Therefore, a participant who completes the entire study will receive a total of $200 in gift cards. If a subject only completes one inpatient admission, she will be given a $75 gift card.

1c. Is payment pro-rated

Yes.

2. Are subjects being reimbursed for travel expenses (*receipts /mileage required***)?**

Yes

►**IF YES, explain rate/ amount/ upper limits of reimbursements.**

When round trip travel exceeds 100 miles, we will make available travel reimbursement at the proposed Virginia state allowance, not to exceed $100 per trip. Subjects will be paid by check. Receipts and documentation for mileage will be required to be submitted to the study team.

3. Is money paid from UVa or State funds (including grant funds)?

Yes.

3a. How will the researcher compensate the subjects?

__X___ Gift card

3b. Which category/ categories best describes the process of compensation?

__X___ Compensation will include an alternative method (petty cash, gift card, other) and tax information will be collected.

►If an alternate method will be used justify why you are unable to issue checks through the UVa Oracle or state system.

This study involves preadolescent and adolescent girls. In past and on-going studies involving the same patient population, we have found that the girls prefer being given gift cards directly at the end of the study to receiving a check in the mail 4-6 weeks later, and this preference is reflected in our ability to recruit subjects. Therefore, we prefer to compensate these subjects with gift cards. We obtain social security numbers for IRS purposes.

Retention Plan

1. **Will the outside sponsor provide incentives (in addition to any payment/ reimbursement) for the subjects to remain in the study?** No.

Family History/Pedigree

1. **What kind of information is being sought?** Family history.
   (No questionnaire is being used).
2. **What identifiers will be recorded with the info (e.g. names, initials, relationship such as mother, father, brother, sister, random number)?**
   Relationship only.
3. **Does any of the information sought potentially expose the subject or a family member to additional risk?** No

Bio-statistical Analysis-GCRC

1. **What are your plans for the statistical analysis?**

   Analysis of data will be done by the research assistant using computer statistics programs. Microsoft Excel will be used to for routine data analysis, including comparisons between groups of BMI, baseline hormone levels, etc. Cluster analysis of LH pulsatility will be done using the Cluster7 program. We will consult with a statistician for regression analysis.

The primary outcome variable in this study is the reduction in LH pulse frequency after one week of estradiol and progesterone.

In the original power analysis we estimated that we should aim to study 15 normals and 15 hyperandrogenemic girls. Given a power of 0.8 and a type I error rate of 0.05, this would allow us to detect a difference in LH pulse frequency over 12 hours of 1.9 pulses.

After 29 subjects were enrolled, a second power calculation was performed with the aid of Jim Patrie of the Department of Health Evaluation Sciences taking into account the preliminary data. This calculation showed that in order to detect a difference in reduction of LH pulse frequency of 1 pulse/11 H between hyperandrogenemic subjects and normal controls with a power of 0.8 and type I error rate of 0.05, we will need to enroll 30 hyperandrogenemic subjects and 30 normal controls.

2. What is the primary outcome variable upon which a sample size estimate is based?

Reduction in LH pulse frequency

3. Do you have an adequate sample size, or is my sample size larger than necessary?

The sample size of 79 should allow us to detect a difference in reduction of LH pulse frequency of 1 pulse/11 H between hyperandrogenic subjects and normal controls with a power of 0.8 and a type 1 error rate of 0.05 These calculations take into account the 35% historical dropout/withdrawal rate.

Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?

Although individual subjects are not likely to benefit from participating in this study, it will advance our knowledge of hyperandrogenemia in adolescent girls and the mechanisms of development of polycystic ovary syndrome. If our hypothesis is correct and hyperandrogenemic girls are less sensitive to progesterone inhibition of GnRH secretion, subsequent studies could explore treating hyperandrogenemia by administration of progesterone. If hyperandrogenemic girls could be treated effectively before or during pubertal maturation, development of clinical PCOS as an adult could be potentially avoided.

2. Analyze the risk-benefit ratio.

This study involves negligible risks, but may provide valuable information about the development of polycystic ovary syndrome (PCOS). Although there are not any direct benefits to the individual study participants, there are significant potential benefits to society as a whole and women with PCOS in particular. The currently available treatments for PCOS in adults are not very effective, and PCOS occurs in 6% of women of childbearing age in this country. We hope that a better understanding of PCOS and its precursors will eventually lead to early recognition and prevention or the disorder as well as more effective treatments. Therefore, potential benefits are great while risks are very small.

3. Do you plan to use MRI with Gadolinium in subjects with a GFR<45, acute kidney injury, history of paraproteinemia such as multiple myeloma, hepatorenal syndrome or liver transplant?No.

Data and Safety Monitoring Plan

1. Definition:

1.1 How will you define <u>adverse events</u> (AE)) for this study?

__X___An adverse event will be considered any undesirable sign, symptom or medical or psychological condition **even if the event is not considered to be related** to the investigational drug/device/intervention. Medical condition/diseases present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment/intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research. Adverse events also include any problems associated with the use of an investigational device that adversely affects the rights, safety or welfare of subjects.

1.2 How will you define <u>serious adverse events</u>?

__X___A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

1.3 What is the definition of an <u>unanticipated problem?</u>

Do not change this answer

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

1.4 What is the definition of a <u>protocol violation</u>?

Do not change this answer

A protocol violation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the IRB-HSR prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices

(GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or UVa staff. These protocol violations may be major or minor violations.

Additional Information: see the IRB-HSR website at http://www.virginia.edu/vpr/irb/HSR_docs/Forms/Protocol_Violations_%20Enrollment_Exceptions_Instructions.doc

1.5 If pregnancy occurs how will this information be managed?

__X___ Adverse Event- will follow adverse event recording and reporting procedures outlined in section 3.

1.6 What is the definition of a Protocol Enrollment Exception?

__X___NA- No outside sponsor

1.7 What is the definition of a data breach?

Do not change this answer

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

2. Identified risks and plans to minimize risk

2.1 What risks are expected due to the intervention in this protocol?

Expected Risks related to study participation.	**Frequency**
Expected Risks related to study participation- volume of blood drawn	
• Significant anemia related to frequent blood sampling (hematocrit < 30%)	____Occurs frequently ____Occurs infrequently ____Occurs rarely __X_Frequency unknown, but likely to be very rare
• Mild anemia (hematocrit < 36%) related to frequent blood sampling	____Occurs frequently ____Occurs infrequently __X_Occurs rarely ____Frequency unknown
Expected Risks related to study participation- micronized progesterone	
GI upset (nausea, abdominal bloating, diarrhea)	____Occurs frequently ____Occurs infrequently __X_Occurs rarely

	____Frequency unknown
CNS effects (sleepiness, headache, dizziness, fatigue, emotional lability, irritability)	____Occurs frequently ____Occurs infrequently __X_Occurs rarely ____Frequency unknown
Risk associated with estradiol:	
GI upset (nausea, abdominal bloating, diarrhea)	____Occurs frequently __X_Occurs infrequently __ _Occurs rarely ____Frequency unknown
Breast Tenderness	____Occurs frequently __X Occurs infrequently __ _Occurs rarely ____Frequency unknown
Deep vein thrombosis	____Occurs frequently ____Occurs infrequently __ _Occurs rarely __X_Frequency unknown, however occurs very rarely with long-term estrogen use (as with oral contraceptive pills), so would expect to be exceedingly rare with the short term administration in this protocol
Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol

Risk associated with IV needle placement:

Expected Risks related to study participation- IV placement	**Frequency**
• Infection at needle site	☐ Occurs frequently, ☐ Occurs infrequently ☐ Occurs rarely ☒ Frequency unknown, but likely to be very rare
• Bleeding at needle site	☐ Occurs frequently, ☐ Occurs infrequently ☒ Occurs rarely ☐ Frequency unknown
• Blood clot at needle site	☐ Occurs frequently, ☐ Occurs infrequently ☒ Occurs rarely ☐ Frequency unknown
• Pain at needle site	☒ Occurs frequently, ☐ Occurs infrequently ☐ Occurs rarely ☐ Frequency unknown
• Bruise at needle site	☒ Occurs frequently, ☐ Occurs infrequently ☐ Occurs rarely

	☐ Frequency unknown

Risk associated with iron supplementation

Expected Risks related to study participation- iron supplementation	**Frequency** *Please pick one frequency from each box below*
• nausea	☐ Occurs frequently, ☒ Occurs infrequently ☐ Occurs rarely ☐ Frequency unknown
• constipation	☐ Occurs frequently, ☒ Occurs infrequently ☐ Occurs rarely ☐ Frequency unknown
• dark or black stools	☒ Occurs frequently, ☐ Occurs infrequently ☐ Occurs rarely ☐ Frequency unknown

Risk associated with EMLA cream (topical lidocaine and prilocaine, used to alleviate pain): The risks of lidocaine and prilocaine in general may include (frequency not defined) hypotension, angioedema, shock, hyperpigmentation, erythema, itching, rash, burning, urticaria, burning, stinging, edema bronchospasm, and hypersensitivity reactions. However, in the case of topical lidocaine/prilocaine use, the non-dermatologic adverse events mentioned above would be extremely unlikely unless large amounts of topical lidocaine/prilocaine were used (allowing significant systemic absorption).

Risk regarding wrist actigraphy: There are no known risks associated with the use of wrist actigraphy.

Risk of not being able to take hormonal medications: The risk of not taking hormonal medications is pregnancy.

2.2 List by bullet format a summary of safety tests/procedures/observations to be performed.

- Sterile technique will be used.
- Before participation in the study, all participants will be required to have a normal hemoglobin (≥11.0 g/dl for African American subjects and ≥ 11.5 g/dL for non-African American subjects). Hemoglobin levels will be measured prior to every admission, and the admission will only continue if the hemoglobin level is ≥ 11.0 g/dL for African American subjects or ≥ 11.5 g/dL for non-African American subjects.
- Blood loss will be carefully recorded and limited to a maximum of 7cc/kg (10% of estimated total blood volume) in 8 weeks. A total of 216.5 ml of blood will be drawn during the study (including estimated waste from frequent blood draws). Therefore, girls weighing less than 31 kg will not be able to participate. Iron supplementation (325 mg once or twice a day dependent on weight) will be prescribed to all participants.
- Topical lidocaine and prilocaine (EMLA) cream may be used to lessen pain associated with IV needle insertion.
- We will warn participants against becoming pregnant during the study. We will ask that the patient use a barrier method of birth control as needed during the study. Prior to each admission, β-hCG levels will be measured; if the β-hCG is positive, the study will be discontinued.

2.3 Under what criteria would an INDIVIDUAL SUBJECT'S study treatment or study participation be stopped or modified

___X__At subject, PI or sponsor's request

___X__Treatment would be stopped if the subject had a serious adverse event deemed related to study

___X__ The study would be stopped in the patient has a positive pregnancy test or a hematocrit <36 and hemoglobin <12 prior to any of the 2 admissions.

2.4 Under what criteria would THE ENTIRE STUDY need to be stopped.

__X___Per IRB, PI, DSMB, or sponsor discretion

___X__ Other: If there are an excessive number of unexpected adverse events that significantly alter the risk/benefit ratio for the study, the study will be terminated. All adverse events will be evaluated both individually and cumulatively by the study team and principal investigator as they arise, allowing for timely decisions regarding study continuation/termination.

2.5 What are the criteria for breaking the blind/mask?

__X___NA – Not blinded/masked

2.6 **How will subject withdrawals/dropouts be reported to the IRB prior to study completion?**

__X___IRB-HSR continuation status form

3. Adverse Event / Unanticipated Problem Recording and Reporting

3.1 Will all adverse events, as defined in section 1.1, be collected/recorded?Yes

3.2 How will adverse event data be collected/recorded?

__X__Spreadsheet *(electronic*)

3.3. How will AEs be classified/graded?

___X__Mild/Moderate/Severe

__X__Serious/Not serious *Required for all protocols*

3.4 What scale will the PI use when evaluating the relatedness of adverse events to the study participation? C*heck all that apply.*

__X___The PI will determine the relationship of adverse events to the study using the following scale:

Related:	AE is clearly related to the intervention
Possibly related:	AE may be related to the intervention
Unrelated:	AE is clearly not related to intervention

3.5 When will recording/reporting of adverse events/unanticipated problems begin?

__X___After subject signs consent

3.6 When will the recording/reporting of adverse events/unanticipated problems end?

__X___30 days post study drug/device/intervention

3.7 How will Adverse Events, Unanticipated Problems, Protocol Violations Violations and Data Breaches be reported?

Type of Event	**To whom will it be reported:**	**Time Frame for Reporting**	**How reported?**
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation (Note: An internal event is one that occurs in a subject enrolled in a UVa protocol.)	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. .	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations	IRB-HSR GCRC	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Protocol Violations (Note the IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.) Or Enrollment Exceptions	IRB-HSR GCRC	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*

Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- UVa Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Phone- (434) 924-7166

OUTSIDE SPONSOR			
All Serious adverse events	Sponsor GCRC	*Within 24 hours.*	We will send an email, fax, or letter to the GCRC.

UVa PI Held IND/IDE			
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibly related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA	Annually	IND annual report

4. How will the endpoint data be collected/recorded.

__X__Database: The endpoint data will be collected and maintained in a database kept on the CRU server.

5. Data and Safety Oversight Responsibility

5.1. Who is responsible for overseeing safety data for this study ?

__X__No additional oversight body other than PI at UVa (*skip question 5.2*)

5.2. What is the composition of the reviewing body and how is it affiliated with the sponsor? *N/A*

5.3. What items will be included in the aggregate review conducted by the PI?

__X__All adverse events

__X___Unanticipated Problems

__X___Protocol violations

__X___Audit results

__X___Application of study designed stopping/decision rules

__X___Early withdrawals

__X___Whether the study accrual pattern warrants continuation/action

__X___Endpoint data

5.4 **How often will aggregate review occur?**
For additional information on aggregate review see:
www.virginia.edu/vpr/irb/hsr/continuations.html#aggreview

__X___Annually

5.5. How often will a report, regarding the outcome of the review by the DSMB/DSMC, be sent to the UVa PI?

A copy of these reports must be sent to the IRB and GCRC if applicable as soon as they are received by the PI. Do not wait until the next continuation to submit them to the IRB.

__X___ NA- there is no DSMB/ DSMC overseeing this study

5.6. How will a report of the information discussed in question 5.4 OR 5.5 be submitted to the IRB?

__X___Part of IRB-HSR continuation status form

Waiver of Documentation of Consent for Minimal Risk Screening Procedures

1. Does this study involve high risk genetic testing in which samples are not de-identified? No.

2. Does this study involve the use or disclosure of psychotherapy notes for research purposes? No.

3.Does this study meet the following criteria? No.

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;

4. Does this study meet the following criteria?

Yes.

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

5. Provide a short paragraph describing the study which will be given to the potential subject either verbally or in writing.

Subjects will be asked to fast (nothing to eat or drink except water after midnight) prior to the screening visit. Subject will be advised that only individuals who have taken no hormonally-active medications for 3 months prior to the study will be eligible for participation. Subject will be advised to consult her personal physician prior to stopping any medications.

Privacy Plan for Studies With Consent

1. Describe your plan to protect the identifiable data from improper use and disclosure.

_X___ Option # 2

Health information/specimens may be stored with HIPAA identifiers.

Specimens will be stored with or without HIPAA identifiers depending on security measures in place (see below).

1a. Will any of the data be stored electronically at UVa? Yes.

►IF YES, where will it be stored?

__X___ a Health Systems Computing Services (HS/CS) managed server that is configured to store data regulated by HIPAA, using the CRU u drive.

1b. Will any of the data be stored in hard copy format at UVa *e.g.- on paper***?** Yes.

►IF YES, where will it be stored?

__X___ case report forms will be stored in a secure area with limited access.

1c. The following procedures will also be followed

- Only investigators for this study and clinicians caring for the patient will have access to the data. They will each use a unique log-in ID and password that will keep confidential.
- If specimens stored: The following security precautions will be implemented for specimens stored at UVa: ***:***

  ___X__Access to the freezer/room will be limited to study personnel
- Each investigator will sign the University's Electronic Access Agreement available at http://www.itc.virginia.edu/policy/form/eaa.pdf and forward the signed agreement to the appropriate department as instructed on the form.

  If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again.
- UVa Institutional Data Protection Standards will be followed http://itc.virginia.edu/security/dataprotection
- If identifiable data (*data with health information and HIPAA identifiers*) is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the ITC Policy "Electronic Storage of Highly Sensitive Data".http://itc.virginia.edu/security/highlysensitivedata/
- If the HIPAA identifiers and health information are combined on an additional computer off UVa premises, the researcher will follow the UVa "Guideline for Safeguards When

Removing PHI Off- Premises for Work"
https://www.healthsystem.virginia.edu/intranet/privacyoffice/Policies/PHI_Off_Premises.doc

- The data will be securely removed from the server, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy.
https://etg07.itc.virginia.edu/policy/policydisplay?id=IRB-004
- The data may not be analyzed for any other study without additional IRB approval

2. Describe your/central registry's plan to destroy the HIPAA identifiers at the earliest opportunity consistent with the conduct of the research.

___X__ The HIPAA identifiers (except full dates and or address information if needed) will be destroyed as soon as all publications are complete.
This wording would allow the researcher to keep HIPAA identifiers until all queries/ request for additional information from publisher are addressed

3. **Do you confirm that you will not reuse the identifiable data (HIPAA identifiers or health information) or disclose any of this information to any other person or entity except as outlined in this protocol, except as required by law, for authorized oversight of the research study, or use it for other research unless approved by the IRB-HSR?** Yes.

This means that after the study is closed at UVa:

- ***You cannot contact the subject by any method (you cannot call them, send a letter, talk to them in person about the study, etc) without additional IRB approval***
- ***You cannot use the data for any research that is not already described in your IRB protocol without additional IRB approval (if you change your hypothesis you must modify your protocol)***
- ***You cannot share your research data with another researcher outside of your study team without additional IRB approval***
- ***Any health information with HIPAA identifiers will be shredded or discarded by using recycling bins for confidential material found in clinic settings. For large item disposal of confidential material contact Environmental Services at 2-4976 or University Recycling at 2-5050.***

TABLE A: HIPAA Identifiers

1. Name
2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of the zip code if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same 3 initial digits contains more than 20,000 people and (2) The initial 3 digits of a zip code for all such geographic units containing 20,000 is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older. *[This means you may record the year but not record the month or day of any date related to the subject if the subject is under the age of 89. In addition if the subject is over the age of 89 you may not record their age and you may not record the month, day or year of any date related to the subject]*
4. Telephone numbers
5. Fax numbers
6. Electronic mail addresses
7. Social Security number
8. Medical Record number

9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother's maiden name, first 3 letters of last name.)

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Principal Investigator (Print)	**Principal Investigator (Signature)**	**Date**