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 including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
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 , experience or credentialing 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. If the current PI is leaving UVa permanently, a new PI will be assigned PRIOR to the departure of the current PI.
20. All study team members will have access to the current protocol and other applicable documents such as the IRB-HSR Application, consent forms and Investigator Brochures.

21. 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.
22. No data/specimens may be taken from UVa without a signed Material Transfer Agreement between OSP/SOM Grants and Contracts Office and the new institution. Original study files are considered institutional records and may not be transferred to another institution. I will notify my department administration regarding where the originals will be kept at UVa. The material transfer agreement will delineate what copies of data, health information and/or specimens may be taken outside of UVa. It will also approve which HIPAA identifiers may be taken outside of UVa with the health information or specimens.
23. If any member of study team leaves UVa, they are STRONGLY ENCOURAGED to use Exit Checklist found on IRB-HSR website at http://www.virginia.edu/provost/facultyexit.pdf.

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.

Investigators Experience

The PI is a board certified general pediatrician and fellowship-trained board eligible pediatric endocrinologist who has been working with children clinically for the last 10 years. The PI has performed clinical research as a medical student, as a pediatric endocrinology fellow, and as a UVA faculty member (Department of Pediatrics, Division of Endocrinology). The PI has been actively involved in the current clinical research protocols of Dr. John Marshall studying the early manifestations and abnormalities of PCOS in pubertal girls. All sub-investigators have experience via participation in the pediatric protocols of the adolescent PCOS research group within the UVA Center for Research in Reproduction led by Drs. John Marshall and Chris McCartney.

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

Brief Summary/Abstract

Women with PCOS have decreased GnRH pulse generator sensitivity to suppression by estradiol and progesterone. Adolescent hyperandrogenemia is thought to be a precursor of adult PCOS. In previous studies, while some hyperandrogenic girls have decreased hypothalamic sensitivity to progesterone similar to their adult counterparts with PCOS, others maintain normal hypothalamic progesterone sensitivity. The girls with decreased hypothalamic progesterone sensitivity have higher fasting insulin levels despite similar BMIs, suggesting that hyperinsulinemia may in part mediate the reduction in sensitivity. We hypothesize that metformin will improve hypothalamic progesterone sensitivity in hyperandrogenic adolescent girls by improving insulin sensitivity and lowering insulin levels. LH (GnRH) pulse frequency will be assessed before and after 7 days of oral estradiol and progesterone in hyperandrogenic adolescent girls both before and after 3 months treatment with Metformin 1000 mg BID. Progesterone adjusted change in 11-hour LH pulse frequency will be used as the measure of hypothalamic progesterone sensitivity.

Background

Etiology of PCOS

Polycystic ovarian syndrome (PCOS) is a common clinical disorder affecting 6-7% of reproductive aged women. PCOS is associated with hyperandrogenism, multiple ovarian cysts, and oligo- or amenorrhea (Stein and Leventhal 1935). It is also a leading cause of infertility. The etiology for PCOS has not yet been elucidated. It has been proposed that hyperinsulinemia, altered ovarian steroidogenesis, and neuroendocrine abnormalities may play key roles either alone or in combination.

Neuroendocrine Abnormalities in PCOS

Neuroendocrine abnormalities, whether primary or secondary, play an important role in PCOS. A group of neurons collectively known as the GnRH pulse generator control the pulsatile secretion of GnRH (gonadotropin releasing hormone) from the hypothalamus. GnRH, in turn, controls the synthesis and secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the pituitary gland. LH and FSH are both made by the same gonadotrope cell, and which hormone is preferentially synthesized and secreted depends in part on the GnRH pulse frequency. In primates, a GnRH pulse frequency of 1 pulse per hour favors secretion of LH, whereas slower pulses, on the order of 1 pulse every three hours, favor release of FSH (Wildt 1981). In normally cycling women, the GnRH pulse frequency in the follicular phase is relatively fast, favoring LH secretion. Following the rise in estrogen and progesterone after ovulation, there is a slowing of GnRH pulse frequency, resulting in a decrease in LH and increase in FSH synthesis, which is important for subsequent follicular development. Physiologic doses of exogenous progesterone have been shown to slow LH, and by inference GnRH, pulsatility when given during the follicular phase (Soules et al 1984). Therefore, progesterone plays an important role in regulating the GnRH pulse generator.

PCOS is characterized by persistently rapid LH (GnRH) pulse frequency without the cyclic luteal phase slowing seen in ovulatory women. Our group has shown that women with PCOS have reduced hypothalamic sensitivity to progesterone mediated suppression of LH (GnRH) pulsatility compared to ovulatory controls (Pastor et al 1998). Thus, they require higher plasma progesterone concentrations to achieve the same degree of GnRH suppression seen in controls. Especially when coupled to the fact that women with PCOS generally have low levels of progesterone secondary to infrequent ovulation, this relative insensitivity contributes to the persistently rapid GnRH pulsatility characteristic of PCOS. The resultant increase in LH leads to augmented ovarian androgen production, while the resultant decrease in FSH leads to impaired follicular development and anovulation. Androgens play an important role in mediating hypothalamic progesterone insensitivity, as progesterone sensitivity can be restored in women with PCOS with the use of the androgen blocker flutamide (Eagleson et al 2000). In adult women, short term treatment with the insulin sensitizer Metformin does not normalize hypothalamic progesterone sensitivity (Eagleson et al, 2003).

Adolescent Hyperandrogenemia as a Precursor for PCOS

Excess androgen production during adolescence is thought to be a precursor of adult PCOS. Women with PCOS often report a history of irregular menstrual cycles during adolescence. A study of girls with menstrual irregularities showed that while some subjects normalized endocrine function as they mature, the majority maintained hyperandrogenism along with the elevated LH levels and polycystic ovaries characteristic of PCOS (Venturoli et al. 1987). Adolescent hyperandrogenemia has also been shown to be associated with higher androgen levels and lower fertility rates in adulthood (Apter and Vihko 1990).

Similar to women with PCOS, girls with hyperandrogenemia have an increased frequency of LH pulses when compared to age matched controls (Apter et al. 1994). An ongoing study by our group (IRB-HSR# 8588) is investigating whether the progesterone insensitivity of the GnRH pulse generator in adult women with PCOS is also seen in adolescent girls with hyperandrogenemia. Analysis of the data to date suggests that overall the hyperandrogenic adolescent girls have decreased hypothalamic progesterone sensitivity when compared to adolescent controls. However, one subgroup of the hyperandrogenic girls have marked progesterone insensitivity similar to that seen in adult women with PCOS, while another subgroup retains relatively normal hypothalamic progesterone sensitivity despite similarly elevated androgen levels. In an effort to understand the factors that may make some girls more susceptible to the adverse neuroendocrine consequences of hyperandrogenemia, we have analyzed the differences between these two subgroups. Fasting insulin levels were higher in the progesterone-insensitive group than in the progesterone-sensitive group (31.2$\pm$3.3 vs. 20.9$\pm$3.7 uIU/ml, p=0.02) despite similar BMIs (33$\pm$4 vs. 34$\pm$2 kg/m2). This suggests that hyperinsulinemia may have neuroendocrine actions during adolescence that are not present in adults. Alternatively, these findings may indicate differential sensitivity to the adverse effects of androgens on both hypothalamic P sensitivity and insulin resistance.

A better understanding of the factors that make adolescent girls more or less susceptible to the adverse neuroendocrine effects of elevated androgens will hopefully lead to improved prevention and treatment strategies for PCOS. In this study, we propose to explore the role of hyperinsulinemia on neuroendocrine function in hyperandrogenic adolescent girls by assessing the effect of the insulin sensitizer Metformin on hypothalamic progesterone sensitivity. Other differences between the progesterone sensitive and progesterone insensitive subgroups, including racial and ethnic differences between the two populations and a trend towards

older gynecologic age in the progesterone insensitive population, are being pursued through other ongoing studies (IRB-HSR# 8588 and 12160).

Hypothesis to be Tested

We hypothesize that metformin will improve the sensitivity of the GnRH pulse generator to suppression by estradiol and progesterone in hyperandrogenic adolescent girls. LH pulse frequency will be assessed before and after 7 days of oral estradiol and progesterone both before and after treatment with metformin. The primary linear contrast will compare the progesterone adjusted change in 11-hour LH pulse frequency between the 1st and the 2nd admissions ($\Delta_{(2-1)}$) (pre-metformin) to the progesterone adjusted change in the 11-hour LH pulse frequency between the 3rd and the 4th admissions ($\Delta_{(4-3)}$) (post-metformin).

Study Design: Biomedical

1. Will controls be used? Yes.

►IF YES, explain the kind of controls to be used.
The subject will serve as her own control, as assessments will be made both before and after Metformin.

2. What is the study design? This study is not blinded.

3. **Does the study involve a placebo?** No.

Human Participants

Ages 10-17 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.30

2. Describe expected rate of screen failure/ dropouts/withdrawals from all sites.
In a similar study (JCM010), we have historically obtained complete, usable data in approximately 65% of the subjects who enrolled in the study. However, that study was shorter in duration and did not involve taking metformin. Because of the added length of this study, as well as the possibility that some participants may develop side effects with Metformin (most likely nausea or diarrhea) and choose to withdraw, we suspect that the screen failure/dropout/withdrawal rate will approach 50%. Therefore, we plan to enroll 60 subjects, with a goal of obtaining complete, usable data in 30.

3. How many subjects will be enrolled at all sites? 60

4. How many subjects will sign a consent form under this UVa protocol? 60

Inclusion/Exclusion Criteria

1. List the criteria for inclusion

- Girls ages 10 to 17
- Hyperandrogenemic (free testosterone greater than 2 standard deviations above the mean for normal control subjects of the same Tanner Stage and/or hirsutism)
- Creatinine clearance > 90 ml/min as calculated by the Cockcroft-Gault equation
- Hemoglobin ≥ 11.0 g/dL for African American subjects; Hemoglobin ≥ 11.5 for non-African American subjects
- Normal screening labs (with exception of the expected hormonal abnormalities inherent in hyperandrogenemia)
- Sexually active subjects must agree to abstain or use double barrier contraception during the study
- Subjects must agree not to take any other medications during the course of the study without approval by the study investigators.

2. List the criteria for exclusion

- Abnormal screening labs (with the exception of the expected hormonal abnormalities inherent in hyperandrogenemia)
- Creatinine clearance less than 90 ml/min as calculated by Cockcroft-Gault equation
- Hemoglobin <11.5 g/dL for non-African American subjects; Hemoglobin < 11.0 g/dL for African American subjects
- Abnormal liver function tests (including AST, ALT, Bilirubin, Albumin, and Alkaline Phosphatase)
- Weight < 34 kg
- History of renal dysfunction, liver dysfunction, congestive heart failure, deep venous thrombosis, breast cancer, endometrial cancer, or cervical cancer
- Pregnant or breast feeding
- On medications known to affect the reproductive axis within 3 months of the study (including oral contraceptive pills, metformin, and spironolactone)
- Are currently participating in another study or have been in one in the last 30 days.
- Subjects using restricted medication (see restrictions below) are excluded unless the subject's primary care provider approves stopping the medication.

3. List any restrictions on use of other drugs or treatments.

Subjects must not take medications known to affect the reproductive axis (including oral contraceptives, metformin, and spironolactone) for 90 days prior to and during the study.

Subjects must not take medications that have the potential to increase metformin blood concentration (including cationic drugs such as amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin which are eliminated by renal tubular secretion have the potential for interaction with metformin by competing for common renal tubular transport systems; cimetidine, which increases (by 60%) peak metformin blood concentrations; furosemide which can increase metformin blood concentration without altering metformin renal clearance; and nifedipine, which can increase metformin absorption). Subjects should limit their intake of alcohol.

Statistical Considerations

1. **Is stratification/randomization involved?** No.

2. What are the statistical considerations for the protocol?

Sample Size Calculation. The primary aim will be to compare the change in 11-hour LH pulse frequency between the 1st and the 2nd admissions ($\Delta_{(2-1)}$) to the change in the 11-hour LH pulse frequency between the 3rd and the 4th admissions ($\Delta_{(4-3)}$). To perform the sample size calculation, we assumed that the linear contrast $\Delta_{(4-3)} - \Delta_{(2-1)}$ will follow a normal distribution with standard deviation 1.02 units. Base on the sample size formula for the paired one-sample standard normal z-test, our calculation indicates that if 30 subjects complete the study, we will have at least an 80% chance of detecting a 1.02 unit or greater difference between $\Delta_{(4-3)}$ and $\Delta_{(2-1)}$ with the two sided type I error rate of the statistical test not exceeding 0.05.

Our prior studies indicate that the subject dropout rate in this study population should not exceed 50%, so 60 subjects will be enrolled to insure that we have 30 completers.

Statistical Analysis: The 11-hour LH pulse frequency data from study admissions 1-4, will be analyzed by way of a mixed-effects linear model. The four 11-hour LH pulse frequency measurements; one measurement from each admission, will function as the respond data. The study admission will be treated as a categorical explanatory factor in the analysis, while the mean 11-hour progesterone level from each admission will be treated as a continuous covariate. Hypothesis testing will be conducted by constructing *apriori* defined within-subject linear contrasts of the 11-hour LH pulse frequency measurements. The primary linear contrast will compare the progesterone adjusted change in 11-hour LH pulse frequency between the 1st and the 2nd admissions ($\Delta_{(2-1)}$) to the progesterone adjusted change in the 11-hour LH pulse frequency between the 3rd and the 4th admissions ($\Delta_{(4-3)}$). We will base our decision whether to reject the null hypothesis that $\Delta_{(4-3)} - \Delta_{(2-1)}=0$ on a two-sided $p\leq 0.05$ decision rule. We will used the same decision rule to determine whether $\Delta_{(2-1)}=0$ and $\Delta_{(4-3)}=0$. The SAS PROC-MIX procedure (SAS Institute Inc., Cary NC) will be used to conduct the aforementioned data analysis.

3. Do you have an adequate sample size, or is your sample size larger than necessary?
We calculated that we will need a sample size of 60 subjects in this study in order to achieve a statistical significance with a power of 80% and Type 1 error rate of 0.05. Given the historical screen failure/dropout/withdrawal rate for 8588/JCM010 of 35% and the additional demands of this study secondary to the addition of metformin, we anticipate a screen failure/dropout/withdrawal rate of around 50%. Therefore, we propose enrolling up to 60 girls with the goal of obtaining complete, analyzable data in 30. We believe this sample size is adequate and not excessive.

4. What is your plan for primary variable analysis?
The primary linear contrast will compare the progesterone adjusted change in 11-hour LH pulse frequency between the 1st and the 2nd admissions ($\Delta_{(2-1)}$) to the progesterone adjusted change in the 11-hour LH pulse frequency between the 3rd and the 4th admissions ($\Delta_{(4-3)}$).

5. What is your plan for secondary variable analysis? Not applicable.
6. Have you been working with a statistician in designing this protocol? Yes.

IF YES, what is their name? Jim Patrie

Biomedical Research

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 Consent and 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 consent and screening exam. The goals and procedures of the study will be explained to the potential subject and her parents, and they will be given the opportunity to ask any questions. The potential subject and her parents will be asked to sign the assent and consent forms. A physician will record a 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, Comprehensive metabolic panel, prolactin, LH, FSH, E_1, E_2, P, total T, androstenedione, 17-OHP, DHEA-S, fasting insulin, Insulin-like Growth Factor 1 (IGF-1), glucose, SHBG, TSH, hCG, cholesterol, LDL, HDL, 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). In the rare event a subject has an elevated 17-OHP on screening, she will be given a repeat 17-OHP. If the value remains elevated, she will be referred to her pediatrician 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 cortrosyn stimulation. 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. Subjects will be administered 1 month of iron supplementation following screening, provided their screening labs show they are eligible to participate in the study. As soon as screening lab results are available, and subjects are found to be eligible for study participation, subjects weighing ≤ 36 kg will be given 1- 325 mg tablet a day and subjects weighing >36 kg will be given 2- 325 mg tablets a day. The first overnight admission may occur anytime within this 30 day period or after the 30 day period. Subjects will be given the option to pick up this supply of iron in the Clinical Research Unit or have it mailed to them.

If admission is scheduled to occur greater than one month after the most recent hemoglobin (such as that obtained during screening), a hemoglobin will be repeated 2-5 days before the overnight admission. Documentation of hemoglobin ≥ 11.5 g/dL for non-African American subjects and documentation of hemoglobin ≥ 11.0 g/dL for African American subjects in the previous month is required for the frequent sampling protocol. If overnight admission is scheduled to occur greater than 3 months after screening, then the safety labs (complete blood count, comprehensive metabolic panel) will be repeated at this time.

Day 0: Admission #1

Note:

- Admission #1 will occur on Day 7-11 of the cycle in girls who are cycling with some regularity and on day ≥7 in those with infrequent cycles (girls with < 10 cycles per year) provided they have a progesterone level of < 1.5 ng/mL within 3 days of their scheduled first admission. If the progesterone level is >1.5 ng/mL within 3 days of the first admission, the first admission will be cancelled.

- At each overnight admission a urine HCG will be done to rule out pregnancy and must be negative for the study to continue.

Subjects will be instructed to eat a diet including at least 150 gm of carbohydrate a day for the 3 days preceding the admission. Written and oral instructions regarding this diet will be given at the time of the screening. The subject will be admitted to the CRU, alternate UVA hospital unit, or off-site hotel at 1700 hr. 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.A small amount of topical lidocaine/prilocaine cream (EMLA cream) may be applied to facilitate IV line placement.. If IV placement is found to be difficult, the IV team may be called to assist in obtaining adequate access. Frequent 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 5 mL sample at 6 AM will be analyzed for lipids, estrone, SHBG, DHEA-S, androstenedione, IGF-1, 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. A formal "lights out" will occur at 2300 hr so that we may observe any nocturnal changes in hormonal secretion patterns. During the admission, the subject will wear a wrist actigraph (Motionlogger Basic-L; Ambulatory Monitoring, Inc.) to estimate periods of sleep (Motionlogger Basic-L; Ambulatory Monitoring, Inc.). The Motionlogger Basic-L is a watch-like device that includes an accelerometer. Q10 minute blood sampling will end at 0600 hr, although one additional Q2H sample will be drawn at 0700 hr. At 07:00 hr, the subject will also undergo a 2-hour oral glucose tolerance test. 75 grams of glucose will be administered at 07:00 (Time 0), with 2.5 ml blood draws for glucose, insulin, and c-peptide at times 0, 10, 20, 30, 60, 90, and 120 minutes. The subject will be offered dinner at standard CRU meal time and will be offered breakfast following completion of the blood draws. They will not have anything to eat or drink except water from 2300 hr until the completion of the blood draws. At the time of discharge, the subjects will be given oral estrogen, progesterone, and iron supplements.

Day 1: Begin Estradiol and Progesterone

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 for seven days. The first dose will be given at 1500 on the day of discharge. If the 1500 dose is incompatible with school schedules, alternative dosing schedules can be arranged. Generally this will entail taking the afternoon dose immediately upon returning home from school without any change in the morning and evening dosing times. Dosages will be based on weight. The target mean plasma progesterone concentration is 2-8 ng/dL. Each subject will be instructed to eat a small snack with the progesterone syrup as it has been observed that the absorption of progesterone is influenced by the presence or absence of food.

Subjects will also be given oral iron supplementation at a dose of 1-2 mg/kg. Subjects will be given iron tablets (which contains 27 - 65 mg elemental iron) with proper dose instructions. Subjects weighing $\leq$ 36 kg will be given 1 tablet a day and subjects weighing >36 kg will be given 2 tablets a day to be taken for the duration of the study.

Day 3 and Day 5: Outpatient blood draws

On study days 3 subjects will have blood drawn at 1700 hr (two hours after the 1500 hr progesterone dose to check serum estrogen, peak progesterone levels, and hemoglobin. On study day 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 7. The procedure will be identical to the first inpatient admission until 07:00 hr. An OGTT will not be done during this admission; however, a fasting glucose and insulin will be drawn at this time and then the admission will end at 07:00 hr. Subjects will be required to bring any unused estrogen and progesterone (or the empty bottles) to the admission. Subjects will discontinue the estradiol and progesterone after the completion of the second inpatient admission, but will continue taking iron supplementation. At the time of discharge, subjects will be given Metformin.

Day 8: Begin Metformin

Starting the day of discharge from Admission #2, subjects will begin taking Metformin 500 mg daily.

Day 14: Increase Metformin dose

On Day 14, the dose of Metformin will be increased to 500 mg twice a day. The subjects will be contacted by phone to inquire regarding adverse events related to the metformin and to remind them to increase the dose of the medication.

Day 21: Increase Metformin dose

On Day 21, the dose of Metformin will be increased to 1000 mg in the morning and 500 mg at night. The subjects will be contacted by phone to inquire regarding adverse events related to the metformin and to remind them to increase the dose of the medication.

Day 28: Increase Metformin dose

On Day 28, the dose of Metformin will be increased to 1000 mg twice a day. The subjects will be contacted by phone to inquire regarding adverse events related to the metformin and to remind them to increase the dose of the medication.

Day 42-49: Outpatient blood draw

Girls will come in after an overnight (>8 hour) fast and have blood drawn for testosterone, SHBG, fasting insulin, fasting glucose, and comprehensive metabolic panel.

Day 84: Admission #3

Note: Admission #3 is timed to the subject's cycles, and therefore is unlikely to occur exactly on Day 84. All girls will take at least 11 weeks (77 days) of Metformin and will then come in for admission #3 at the first appropriate time in their cycle, which will be either on Day 7-11 of their cycle or day ≥7 in those with infrequent cycles (girls with < 10 periods per year) provided they have a progesterone level of < 1.5 ng/mL within 3 days of their scheduled first admission. If the progesterone level is >1.5 ng/mL within 3 days of the first admission, the admission will be cancelled.

Admission #3 will be identical to Admission #1. Subjects will be instructed to eat a diet including at least 150 gm of carbohydrate a day for the 3 days preceding the admission

Day 85: Begin Estradiol and Progesterone

Starting the day of discharge from the third 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 for seven days. Doses will be the same as on Days 1-7. Subjects should continue to take Metformin 1000 mg twice a day and iron supplementation.

Day 87 and Day 89: Outpatient blood draws

On study days 3 subjects will have blood drawn at 1700 hr (two hours after the 1500 hr progesterone dose to check serum estrogen, peak progesterone levels, and hemoglobin. On study day 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 91: Admission #4

Admission #4 will be identical to Admission #2.
Following the final blood draw for Admission #4, the patient will discontinue all study medications.

Follow-up

There is an optional 1 year follow up period. If the subject agrees to participate, she will complete follow-up questionnaires and/or phone interviews 6 and 12 months after the study. These questionnaires/interviews will ask about the frequency of menses and changes in hirsutism. Whenever possible we will also see the subjects on 1-2 occasions during the 12 months to obtain blood for T, SHBG, fasting insulin, fasting glucose, DHEA-S, E_2, and P measurements (depending on cycle stage).

2. List the procedures, in bullet form, that will be done for research as stipulated in this protocol. Do NOT list those procedures which are being ordered for clinical care.

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

3. Will any of the procedures listed in item # 2 have the potential to identify an incidental finding? Yes.

►**IF YES,** ***check one of the following two options:***

__X___The examination(s) utilize(s) the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.

- The PI takes full responsibility for the identification of incidental findings:
- 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**.**

4. Do any of the procedures listed above, under question # 2, utilize any imaging procedures (e.g. ultrasound, CT scans/ x-rays etc.)? **No.**

5. **Will you be using viable embryos? No.**
6. **Will you be using embryonic stem cells? 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

3. Does any of the information sought potentially expose the subject or a family member to additional risk?No.

Specimens: Will not be used for Genetic Research or Banking

If the specimens in this protocol will only be used for Genetic Research and or Specimen Banking, you may delete the Specimen Labeling and Specimen Shipping sections below.
If specimens will be taken for other reasons, the questions below should be answered and referenced to the samples taken for things other than Genetic Research and or Specimen Banking.

Specimen Information

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

2. Will the specimen be obtained BEFORE a subject has signed a consent form? No.
3. Will you be using discarded specimens?No.

►IF NO, and taking a blood sample, will blood be taken more than 2 times/week?
Yes.
►IF NO, and taking a blood sample, check the option(s) below which match the subject population.

_X____ non- healthy or pregnant adults and/or children
_____ Amount will NOT exceed the lesser of 50ml or 3 ml/kg in an 8 week period
___X__ Amount will exceed the lesser of 50 ml or 3 ml/kg in an 8 week period

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 #, CRU 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 (TSH, LH, FSH, P, Testosterone, E_2, c-peptide, and insulin) and 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.

Data and Safety Monitoring Plan

If you have any questions completing this section call 982-4311, 924-8660 or 243-9847 for assistance
A Sponsor is defined as entity that will receive data prior to publication.

1. Definition:

1.1 How will you define adverse events (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 serious adverse events?

__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 unanticipated problem?

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 protocol violation?

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?

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?

Risk associated with frequent blood sampling:

Expected Risks related to study participation.	**Frequency** *Please pick one frequency from each box below*
• significant anemia related to frequent blood sampling (hematocrit < 30%)	☐ Occurs frequently, ☐ Occurs infrequently ☐ Occurs rarely ☒ Frequency unknown, but very rare
• mild anemia (hematocrit < 36%) related to frequent blood sampling	☐ Occurs frequently, ☒ Occurs infrequently ☐ Occurs rarely ☐ Frequency unknown

Risk associated with IV needle placement:

Expected Risks related to study participation.	**Frequency** *Please pick one frequency from each box below*

• Infection at needle site	☐Occurs frequently, ☐Occurs infrequently ☐Occurs rarely ☒Frequency unknown, but very rare
• Fainting	☐Occurs frequently, ☐Occurs infrequently ☐Occurs rarely ☒Frequency unknown, but 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

Risks associated with iron supplementation:

Expected Risks related to study participation.	**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

Risks associated with Progesterone:

Expected Risks related to study participation.	**Frequency** *Please pick one frequency from each box below*
• Mood changes/irritability	☐Occurs frequently, ☒Occurs infrequently ☐Occurs rarely ☐Frequency unknown
• Fluid retention	☐Occurs frequently, ☒Occurs infrequently ☐Occurs rarely ☐Frequency unknown

• Withdrawal bleeding 1-5 days after stopping progesterone	☒Occurs frequently, ☐Occurs infrequently ☐Occurs rarely ☐Frequency unknown

Risks associated with Estradiol:

Expected Risks related to study participation.	**Frequency** *Please pick one frequency from each box below*
• Nausea	☐Occurs frequently, ☒Occurs infrequently ☐Occurs rarely ☐Frequency unknown
• Fluid retention	☐Occurs frequently, ☒Occurs infrequently ☐Occurs rarely ☐Frequency unknown
• Breast Tenderness	☐Occurs frequently, ☒Occurs infrequently ☐Occurs rarely ☐Frequency unknown
• Deep vein thrombosis	☐Occurs frequently, ☐Occurs infrequently ☐Occurs rarely ☒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

Risks associated with Metformin:

Expected Risks related to study participation.	**Frequency**
• Diarrhea	☒Occurs frequently, ☐Occurs infrequently ☐Occurs rarely ☐Frequency unknown
• Nausea	☐Occurs frequently, ☒Occurs infrequently ☐Occurs rarely ☐Frequency unknown
• Lactic Acidosis	☐Occurs frequently, ☐Occurs infrequently ☐Occurs rarely ☒Frequency unknown, but very rare

Other Risks:

Expected Risks related to study participation.	**Frequency**
Reproductive Risks	Minimized due to the requirements of this

Specify potential reproductive risks	protocol.
Violation of subject's privacy and confidentiality	Minimized due to the requirements of the privacy plan in this protocol

NOTE: Risk of unplanned pregnancy: If a research subject is sexually active and stops using hormonal contraception while failing to use another non-hormonal method of contraception, there is a risk of unplanned pregnancy. (However, subjects will be counseled to use non-hormonal methods of contraception if sexually active.)

NOTE regarding the 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).

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 studies, all participants will be required to have a normal hemoglobin (≥11.5 g/dL for non-African American subjects and ≥ 11.0 g/dL for African American subjects). Hemoglobin levels will be measured prior to every admission. For African American subjects, if the hemoglobin level is <11.0, the study will be discontinued. For non-African American subjects, if the hemoglobin level is <11.5 g/dl, the study will be discontinued.
- 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 467 ml of blood will be drawn during the study (including estimated waste from frequent blood draws), with no more than 243.5 being drawn during any 8 week period. Therefore, girls weighing less than 35 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.
- We will warn participants against becoming pregnant during the study. We will require that sexually active subjects use effective double barrier methods of birth control as needed during the study. β-hCG levels will be measured at screening and prior to each admission; 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___ Other: The study would be stopped if the patient has a positive pregnancy test or if hemoglobin levels were below the required levels (For African American subjects, they must have a hemoglobin of ≥ 11.0. For non-African American subjects, they must have a hemoglobin of ≥ 11.5.

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

These are called stopping rules for early termination of the entire study.

List criteria regardless of whether the study is sponsored or not.
Be sure to include any criteria for which the UVa PI would halt the study at UVa.

___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___Paper AE forms/source documents

___X__Spreadsheet *(paper or electronic*)

3.3. How will AEs be classified/graded?

___X__Mild/Moderate/Severe

__X__Serious/Not serious

3.4 What scale will the PI use when evaluating the relatedness of adverse events to the study participation?

__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 begins study drug/ device placement/intervention /study-related procedure/specimen collection

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

_____End of study drug/device/intervention/participation

_X____30 days post study drug

3.7 How will Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches be reported? Complete the table below to answer this question

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 *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. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	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 (*The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.)* Or Enrollment Exceptions	IRB-HSR	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

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: *specify*

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

_____Application of dose finding escalation/de-escalation rules *These should be outlined under 2.4.*

__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 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

Payment

1. Are subjects being reimbursed for travel expenses (*receipts /mileage required***)? No.**

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

2a. What is the maximum TOTAL compensation to be given over the duration of the protocol?
$400

2b. Explain compensation to be given.
All participants will receive a $75 Simon Mall gift card per inpatient admission. In addition, participants will receive a $100 bonus, also in the form of a gift card, for completing the medication regimen and outpatient blood draws. Therefore, a participant who completes the entire study will receive a total of $400 in gift cards. This payment will not be provided to the subject until the end of study participation at the last overnight admission. If a subject withdraws from the study before it is complete, she will receive a $75 gift card for each overnight admission she has completed.

2c. Is payment pro-rated (*e.g. some compensation is given even if subjects do not complete the entire study)?*

Yes. See explanation above.

If No, explain why payment cannot be pro-rated.

2d. Is money paid from UVa or State funds (including grant funds) or will items such as gift cards be distributed through UVa? Yes.

2d(i). How will the researcher compensate the subjects?

___X__ Gift cards

2d(ii). 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, securely stored, and submitted electronically to Procurement Services as required.

►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 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 the adolescent subjects with gift cards. We obtain social security numbers for IRS purposes.

IMPORTANT: If you check this box you will be required to submit the subjects' name, Social Security number, full address and amount of payment to Procurement at the end of each calendar year. The Office of the VP for Research will send you instructions on this procedure at a later date.

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?

The goal of this study is to advance our knowledge of the effects of adolescent hyperandrogenemia and the mechanisms of development of polycystic ovary syndrome. Hopefully, this knowledge will lead to more effective means of preventing and treating PCOS in the future.

While treatment is not the goal of this study, it is possible that individual subjects may experience improvement in symptoms during the course of the study given that Metformin is commonly used in clinical practice to treat adolescent hyperandrogenemia and PCOS.

2. Analyze the risk-benefit ratio.

This study involves minimal risks and may provide valuable information about the development of polycystic ovary syndrome (PCOS). There are no long-term risks associated with blood sampling or the short term administration of physiologic doses of estradiol and progesterone. Metformin is associated with minimal risk in subjects with normal kidney, liver, and cardiac function, and subjects with such organ dysfunction will be excluded from the study. This study offers significant potential benefits to society as a whole and girls with hyperandrogenemia in particular. We hope that a better understanding of the effects of hyperandrogenemia in adolescent girls and the role of adolescent hyperandrogenemia in the development of PCOS will lead to improved prevention of the disorder as well as more effective treatments. In addition, some subjects may experience improvement in their hyperandrogenic symptoms while being treated with Metformin, as this

medication is commonly used in clinical practice to treat adolescent hyperandrogenia and PCOS. Therefore, potential benefits are great while risks are small.

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APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- *Finders fees will not be paid to an individual as they are not allowed by UVa Policy*
- *All recruitment materials will be approved by the IRB-HSR prior to use. They will be submitted to the IRB after the IRB-HSR has assigned an IRB-HSR # to the protocol.*

- *Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.*

Retention Incentives

Any item used by the sponsor/ study team to provide incentive to a subject to remain in the study, other than compensation identified in the Payment section, will be submitted to the IRB for review prior to use. The IRB-HSR will provide the study team with a Receipt Acknowledgement for their records. Retention incentive items are such things as water bottles, small tote bags, birthday cards etc. Cash and gift cards are not allowed as retention incentives.

Clinical Privileges

The following procedures will be followed:

- *Investigators who are members of the clinical staff at the University of Virginia Medical Center must have the appropriate credentials and been granted clinical privileges to perform specific clinical procedures 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.*
- *Personnel on this protocol will have the appropriate credentials and clinical privileges in place before performing any procedures required by this protocol.*
- *Contact the Clinical Staff Office- 924-9055 or 924-8778 for further information.*

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.

- *No data will be shared outside of UVa, beyond using 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.*
- *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.*

Prisoners

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

Prisoner- Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.
For additional information see the OHRP website at http://www.hhs.gov/ohrp/policy/populations/index.html

APPENDIX: Recruitment

Recruitment includes identifying, review of records to determine eligibility or any contact to determine a potential subjects interest in the study.

****The UVa HIPAA covered entity is composed of the UVa VP Office of Research, the Health System, School of Medicine, School of Nursing, the Sheila C. Johnson Center, the Exercise and Sports Injury Laboratory and the Exercise Physiology Laboratory.***

1. **How do you plan to <u>identify</u> potential subjects?**
   To "identify" a potential subject refers to steps you plan to take to determine which individuals would qualify to participate in your study. This does NOT include steps to actually contact those individuals.
   If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being identified by the given method.

   a. __X__ Chart Review/ Clinic Schedule Review/ Database Review from a database established for health care operations (departmental clinical database) or quality improvement.

      DHHS: Study team requests Waiver of Consent to identify potential subjects.

      HIPAA- *Allowed under Preparatory to Research if PHI to be accessed.*

      IMPORTANT
      Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:
      - *a UVa student working in the UVa HIPAA Covered Entity**
      - a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity*

   b. __X__ Review of a database that was established to keep data to be used for future research such as the CDR, departmental research database or use of data from a separate current active research protocol.

      DHHS: Study team requests Waiver of Consent to identify potential subjects.

      HIPAA- *Allowed under Preparatory to Research if PHI to be accessed.*

      IMPORTANT
      Keep in mind that PHI in the medical record may only be accessed by individuals who work under the UVa HIPAA covered entity; which means they who meet one of the following criteria:
      - *a UVa student working in the UVa HIPAA Covered Entity**
      - *a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity**

NOTE: The information from which you are obtaining potential subjects must also have an IRB protocol approval.

IRB# 10797
If obtaining information from the Clinical Data Repository (CDR) insert IRB # 10797.

c. ____ Patients UVa health care provider supplies the UVa study team with the patients contact information without patients knowledge.

DHHS: Study team requests Waiver of Consent to identify potential subjects.

HIPAA- *Allowed under Preparatory to Research if PHI will be shared by the health care provider.*

IMPORTANT
Keep in mind that PHI may only be given to individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- *a UVa student working in the UVa HIPAA Covered Entity**
- *a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity**

d. _X___ Patient obtains information about the study from their health care provider. The patient contacts the study team if interested in participating.
DHHS: *NA*
HIPAA: *Allowed under Health Care Operations*
If this choice is checked, check 3d-INDIRECT CONTACT below.

e. __X__ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc.
If this choice is checked, check 3d- INDIRECT CONTACT below.
DHHS & HIPAA: *NA*

f. _____ Potential subjects have previously signed a consent to have their name in a registry/database to be contacted for future studies of this type.
IRB# of registry/ database: _____
DHHS & HIPAA: *NA*

If item # a, b or c is checked above and if this protocol involves the use of protected health information you confirm the following to be true:

- The use or disclosure is sought solely to review protected health information as necessary to prepare the research protocol or other similar preparatory purposes.
- No PHI will be removed from the UVa covered entity.
- The PHI that the researcher seeks to use or access is necessary for the research purposes.

2. How will potential subjects be <u>contacted?</u>

To "contact" a potential subjects refers to the initial contact you plan to take to reach a potential subject to determine if they would be interested in participating in your study. This may include direct contact by such methods as by letter, phone, email or in-person or indirect contact such as the use of flyers, radio ads etc.

If your study involves more than one group of subjects (e.g. controls and cases or subjects and caregivers) note below which groups are being contacted by the given method.

a.__X__Direct contact of potential subjects by the study team via letter, phone, direct e-mail. Members of study team ARE NOT health care providers of patients. Information will not be collected from psychotherapy notes.

Note: Letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

DHHS/HIPAA: Study team requests a Waiver of Consent and Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:

Keep in mind that if PHI was collected during the identification phase that contact with potential subjects may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- *a UVa student working in the UVa HIPAA Covered Entity**
- *a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity**

b._X___Potential subjects will be approached while at UVa Hospital or Health Clinic by a person who is NOT a member of their health care team. Information will not be collected from psychotherapy notes.

DHHS & HIPAA: Study team requests a Waiver of Consent and a Waiver of HIPAA Authorization to contact potential subjects.

IMPORTANT:

Keep in mind that contacting individuals in a clinical setting may only be performed by individuals who work under the UVa HIPAA covered entity; which means they meet one of the following criteria:

- *a UVa student working in the UVa HIPAA Covered Entity**
- *a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity**

You should share the following information with the potential subject:

1. *Your name*
2. *Who you are:* ***physician, nurse etc***. at the University of Virginia.

3. *Why you want to speak with them*
4. *Ask if you have their permission to explain the study to them*
5. ***If asked about how you obtained their information use one of the following as an option for response.***
   - ***DO NOT USE THIS RESPONSE UNLESS YOU HAVE OBTAINED PERMISSION FROM THEIR UVa PHYSICIAN:***
     Your doctor, Dr. ***insert name*** *wanted you to be aware of this research study and gave us permission to contact you.*
   - *We obtained your information from your medical records at UVa.* *Federal regulations allow the UVa Health System to release your information to researchers at UVa, so that we may contact you regarding studies you may be interested in participating. We want to assure you that we will keep your information confidential.*

IF THE PERSON SEEMS ANGRY, HESITANT OR UPSET, THANK THEM FOR THEIR TIME AND DO NOT ENROLL THEM IN THE STUDY. YOU MAY ALSO REFER THEM TO THE IRB-HSR AT 924-9634.

c.__X__Direct contact of potential subjects by the study team by approaching in person at UVa or via letter, phone, direct e-mail. Members of study team contacting potential subjects ARE health care providers of patients.

If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use. See IRB-HSR Website for templates.

DHHS: Study team requests a Waiver of Consent to contact potential subjects
HIPAA: *Allowed under Health Care Operations.*

d.__X__ Indirect contact (flyer, brochure, TV, broadcast emails, patient provided info about the study from their health care provider and either the patient contacts study team or gives their healthcare provider permission for the study team to contact them.)
The indirect method used (flyer, brochure, TV, broadcast emails) must be approved by the IRB prior to use. The IRB does not need to review any type of script to use when the potential subject responds to the indirect method.

DHHS & HIPAA: *NA*

e. ____ Potential subjects are not patients. The study does not include obtaining subjects health information. Subjects will be contacted directly via email, phone, letter or presentation in group setting with consent then obtained individually in a private setting.
If you are not approaching them in person but using a letter, phone call or direct email please note that the letter, phone, direct email scripts must be approved by IRB prior to use.
See IRB-HSR Website for templates.
DHHS: Study team requests a Waiver of Consent to contact potential subjects.
HIPPA: NA

3. Will any additional information be obtained from a potential subject during "prescreening"? Yes.

> ***Pre-screening*** *for IRB purposes is the term used to describe activities PRIOR to obtaining Informed Consent and may not include any research procedures.*
>
> *The activities may involve pre-screening of potential subjects over the telephone or in person is generally performed to determine their initial eligibility for, and, interest in a study and is a common strategy in the recruitment process.*
> *Questions appropriate for pre-screening address the specific inclusion/exclusion criteria for the study and other issues of suitability, for example, an individual's ability to come to the research site multiple times.*
> *It is not appropriate at this point in the process (i.e. prior to obtaining informed consent/enrollment) to gather information that is not directly related to assessing eligibility and suitability (e.g. obtaining complete medical histories, obtaining blood specimens for lab tests).*
> *An additional telephone script is not required, for this pre-screening process, in addition to any scripts required under Recruitment question # 2.*

IF YES, ***submit any documents that will be used to collect pre-screening information so that the IRB may confirm what questions will be asked.***
NOTE: To comply with HIPAA regulations only the minimum necessary information may be collected at this time. This means that only questions pertaining to the Inclusion and Exclusion Criteria may be asked.

IF YES,

DHHS: study team requests a Waiver of Documentation of Consent for Pre-screening questions.

HIPPA:

- ***HIPAA does not apply if :***
  - *no PHI is collected or*
  - *if PHI is collected from a potential subject by an individual from a department that is not part of the HIPAA covered entity*
- ***HIPAA does apply if*** *the collection occurs by individuals* who work in a department that is part of the HIPAA covered entity. In this case the collection will be covered under Health Care Operations/*
  - *These individuals are those that meet one of the following criteria:*
    - *a UVa student working in the UVa HIPAA Covered Entity**
    - *a faculty or staff member in a PAID appointment in the UVA HIPAA Covered Entity**

IF YES, Will any of the questions involve health information? Yes.

IF YES, will you collect HIPAA identifiers with the health information? Yes.
IF YES, which HIPAA identifiers will be recorded?

Name, MR#, date of birth, age, postal address, telephone number, email address (if applicable)

Do you confirm that health information with HIPAA identifiers will not be shared outside of UVa until a consent form is signed or only shared in a de-identified manner? Yes.

4. **Do you plan to ask the subjects to do anything, other than answering questions, for the study prior to signing a consent?** Yes.

►**IF YES, explain in detail what you will ask them to do**.

Tips to Study Team

- *You must document their verbal consent in the study records.*
- *If a subject is asked to stop taking a drug, document the date and name of the person on the study team giving the verbal order to stop medications (again- must be a person with a DEA#).*

DHHS: Study team requests the use of Verbal Consent (Waiver of Documentation of Consent) for minimal risk screening procedures.

HIPPA:
If the individual, obtaining consent, works under the HIPAA Covered Entity this is covered under Health Care Operations
If the individual obtaining consent does not work under the HIPAA covered entity, HIPAA does not apply.

Subjects will be asked to fast overnight prior to the screening visit. If subjects are on hormonal medications (such as oral contraceptive pills, spironolactone, and metformin), they will be told that in order to participate in the study, they must discontinue the hormonal medications for 3 months. They will be strongly urged to discuss the decision regarding whether or not to discontinue hormonal medications with their personal physician prior and to discontinue medications only with the agreement of their physician. Verbal consent for fasting and discontinuing medications will be documented in the study records, as will the discussion regarding consulting their personal physician.

5. How will the consenting process take place?

HIPPA:

- ***If the individual, obtaining consent, works under the HIPAA Covered Entity consenting is covered under Health Care Operations.***
- ***If the individual obtaining consent does not work under the HIPAA covered entity, HIPAA does not apply.***

An outpatient consenting and screening visit is scheduled for volunteers who express interest in 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 consent and screening visit is held in an outpatient examination room in the CRU or alternate UVA clinical unit. This allows a private conversation between the screening physician and/or study coordinator, 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 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 and/or study coordinator 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.

6. Will subjects sign a consent form for any part of the study? Yes.

7. Will the study procedures be started the same day the subject is recruited for the study? Yes.

►IF YES, explain in detail why the subject cannot be given more time to make a decision to consent.

Potential subjects are given a copy of the consent form prior to their screening visit. Subjects are instructed to review the consent form, and are encouraged to ask any questions prior to scheduling a screening visit. At the screening visit, subjects are lead through a discussion of the consent form. Subjects are given the opportunity to ask any additional questions during this portion of the screening visit. After the study team has read through the entire consent form with the subject, they are then given the opportunity to sign the consent form, decline to enroll in the study, or take more time to review the consent form before making a decision whether or not to enroll. If the subject decides to enroll in the study on the day of the screening visit, then we will proceed with the study procedures outlined in the study visit above, unless the subject objects.

Therefore, the study team feels that the subject is under no pressure to give consent at the screening visit without having ample opportunity to review the consent form. In addition, subjects are given the option to decline consent or delay study procedures at any point during this initial visit.

►IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision. See explanation above.

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

APPENDIX: Clinical Data Repository

1. Will you be obtaining data from the UVa Clinical Data Repository (CDR)? Yes

►If YES, check the categories of data elements below that you plan to obtain from the CDR. You are advised to talk to CDR personnel prior to completing this section.

CATEGORY	DATA ELEMENTS	CHECK ALL THAT APPLY
Demographics	e.g. Gender, race, age	X
Administrative	e.g. Includes payor, payscale, length of stay, fact of visits (inpatient or outpatient), locations of service (inpatient or outpatient), providers	X
Financial	e.g. Charges or costs associated with care	
Clinical Data	e.g. Diagnoses	X
	e.g. Procedures	x
	e.g. Mortality	
	e.g. Laboratory / Microbiology Results	X
	e.g. Medications	X
	e.g. Vitals, Height / Weight, Other Clinical Parameters	X
	e.g. Other (specify)	
Narrative Reports	e.g. Includes discharge summaries, pathology reports, operative notes, etc.	X

APPENDIX: Participation of Children

In the state of Virginia a person under the age of 18 is considered a child.

1. Explain why this research topic is relevant to children.
PCOS is a common clinical disorder affecting 6-8% of reproductive age women and significantly affects women's reproductive, metabolic, and cardiovascular health. PCOS is generally thought to begin in adolescence, and is increasingly recognized and diagnosed in this age group. Given the association between obesity and increased androgen levels in girls, there is concern that the childhood obesity epidemic may lead to a rise in the incidence of hyperandrogensim and PCOS. By studying the origins of PCOS in adolescence, we hope to develop better strategies for screening and prevention of PCOS in this patient population.

2. Is the knowledge being sought in this study already available for children or is it currently being acquired through another ongoing study?
No. Although other studies have treated hyperandrogenic girls with metformin, they have focused on clinical and metabolic parameters. This study is unique in that it is exploring the neuroendocrine effects of metformin in adolescent girls.

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.
Please see Drug Information for data regarding the use of metformin and micronized progesterone in both adults and minors.

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.

If the study will enroll subjects from patients at UVa, this question MUST be answered YES

►IF YES: If the caregiver is someone other than the person providing permission for the child to participate, the study team may wish to consider the use of an additional form for them. (example-a child is in foster care however the biological parent has not lost legal custody and provides their permission for the child to participate, but the foster parent will be the person involved in driving the child to their study visits. This form might address things such as who will receive the compensation for driving the child to the visits- the foster parent or the biological parent).
►IF YES and if neither of the items 4a or 4b listed below is answered YES, children who are wards of the state must be excluded from this protocol. Add" wards of state" as an additional exclusion criteria.

4a. Is the research in this protocol related to the child's 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.

If this study will be done at UVa, answer this question YES.

If you answered YES to # 4 and YES to EITHER 4a or 4b you may NOT exclude children who are wards of state.
If you answered YES to # 4 and you answered NO to both 4 a or 4b you must exclude children who are wards of the state from the protocol- Add " Wards of State" as an exclusion criteria.

4c. Are you aware of the following requirement? Yes.
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.

APPENDIX: 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?
John C. Marshall, MD, PhD

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

APPENDIX: 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?
John C. Marshall, MD, PhD

3. What is the phase or stage of this study? Not applicable.

APPENDIX: Drug Information

1 What is the drug name, manufacturer and IND# if available?
Metformin (generic metformin manufacturers); IND # 64, 126

2. If IND application has been submitted to the FDA, who is the Principal Investigator on the IND?
John C. Marshall, MD, PhD

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

APPENDIX: Pharmacy-Investigational Drugs/Biologics

1. What is the name of the investigational drug/biologic? Estrace (Warner-Chilcott, Rockaway, NJ) IND #64,126

2. Where will the subjects be seen for the administration/dispensing of the drug?
___X__ Inpatient Unit: Subject will be dispensed estrace when discharged from the first and third inpatient admissions. Subject will be instructed to take the estrace tablets once daily for 7 days after the first and third overnight admissions. (Thus subjects will take two rounds of estrace for 7 days). ___

3. What dose will be utilized in this study?
Estrace, 0.5-1 mg once a day

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

5. What will be the duration of dosing in this study?
7 days after the first overnight admission and 7 days after the second overnight admission (thus a total of 14 days)

6. What route of administration will be utilized?
PO

7. Will drug need to be prepared by the UVa Investigational Drug Service (IDS)?
__X___ NO- Drug will be prepared and/or administered per package insert

8. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)? No.

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

10. 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.

11. Will a comparator (active or placebo) be utilized in the protocol? No.

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

►IF YES, is this study investigator initiated? Yes.

If yes, answer questions # 13 and 14
If no, answer question # 13 only.

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

IF YES, answer questions 13a-13f
You may reference the non-IRB protocol to answer these questions.

13a. Describe pertinent animal data that is available regarding the toxicity/safety of this drug.
Not applicable as sufficient human data is available.

13b. Describe pertinent human data that is available regarding the toxicity/safety of this drug.
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.

13c. Have there been any human deaths associated with this drug?
None known.

13d. 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.

13e. 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.

14. 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:

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.

15. Is this a post-marketing study? No.

APPENDIX: Pharmacy-Investigational Drugs/Biologics

1. What is the name of the investigational drug/biologic?

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

2. Where will the subjects be seen for the administration/dispensing of the drug?

__X___ Inpatient Unit: Subject will be dispensed micronized progesterone when discharged from the first and third inpatient admissions. Subject will be instructed to take the progesterone suspension three times a day for 7 days after the first and third overnight admissions. (Thus subjects will take two rounds of progesterone for 7 days).

3. What dose will be utilized in this study?

20 mg/ml, 25-100 mg

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

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

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

7 days after the first overnight admission and 7 days after the second overnight admission (thus a total of 14 days)

6. What route of administration will be utilized?

PO

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

___X__ YES

►*IF YES, complete the following information under 7a-7d.*
If you need assistance completing this section contact the Investigational Pharmacists at 982-1048

7a. Concentration

__X___ Standard
_____ Non- Standard- *specify*

7b. Diluents

__X___ Standard
_____ Non- Standard- *specify*

7c. Stability after prepared

__X___ Standard
_____ Non- Standard- *specify*

7d. Special storage requirements

___X__ Standard
_____ Non- Standard- *specify*

8. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)? No.

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

10. 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.

11. Will a comparator (active or placebo) be utilized in the protocol? No.

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

►IF YES, is this study investigator initiated? Yes.

If yes, answer questions # 13 and 14
If no, answer question # 13 only.

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

IF YES, answer questions 13a-13f
You may reference the non-IRB protocol to answer these questions.

13a. Describe pertinent animal data that is available regarding the toxicity/safety of this drug.
Not applicable, as abundant human data is available.

13b. 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 over 30 adolescent girls and at least 12 adult women; no adverse events have occurred.

13c. Have there been any human deaths associated with this drug? None known.

13d. In how many humans has this drug been used previously?
The micronized progesterone suspension, as formulated by the UVa Investigational Drug Pharmacy, has been administered to over 30 adolescent girls and to at least 12 adults in the context of our clinical studies.

13e. 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 over 30 adolescent girls as part of our protocols. There have been no adverse effects.

14. 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 30 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.

15. Is this a post-marketing study? No.

APPENDIX: Pharmacy-Investigational Drugs/Biologics

1. What is the name of the investigational drug/biologic?
Metformin (generic metformin manufacturers); IND# 64,126

2. Where will the subjects be seen for the administration/dispensing of the drug?
__X___ Inpatient Unit:Subject will be given supply of metformin upon discharge from the second overnight study admission.

3. What dose will be utilized in this study?
Subject will start a 500 mg dose and gradually increase up to 2000 mg a day.

4. What will be the frequency of dosing in this study?
Upon discharge from admission 2 (day 8 of study), subjects will take 500 mg of metformin once daily.
On day 14 of study, subjects will begin taking 500 mg of metformin twice daily.
On day 21 of study, subjects will begin taking 1000 mg of metformin in the morning and 500 mg of metformin at night.
On day 28 of study, subjects will begin taking 1000 mg of metformin twice daily.

5. What will be the duration of dosing in this study?
Subjects will take metformin for at least 11 weeks.

6. What route of administration will be utilized?
PO

7. Will drug need to be prepared by the UVa Investigational Drug Service (IDS)?
__X___ NO- Drug will be prepared and/or administered per package insert

8. Are there any special handling instructions mandated by the study (e.g. weighing hazardous materials)? No.

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

►**IF YES, provide specifics.** Dose of metformin will be increased gradually (as outlined above).

10. 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.

11. Will a comparator (active or placebo) be utilized in the protocol? *No.*

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

►**IF YES, is this study investigator initiated? Yes.**

If yes, answer questions # 13 and 14
If no, answer question # 13 only.

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

IF YES, answer questions 13a-13f
You may reference the non-IRB protocol to answer these questions.

13a. Describe pertinent animal data that is available regarding the toxicity/safety of this drug.

Not applicable as sufficient human data is available.

13b. Describe pertinent human data that is available regarding the toxicity/safety of this drug.

Metformin is widely used for the treatment of Type 2 diabetes and polycystic ovary syndrome. In general, the medication is well tolerated. The most concerning adverse effect associated with metformin is lactic acidosis. This is a very rare effect, with a reported incidence of 0.03 cases per 1000 person-years of treatment. In over 20,000 person-years exposure to metformin in clinical trials, there were no reported cases of lactic acidosis. However, when it does occur, it is associated with a mortality rate of 50%. The majority of cases have been described in diabetics with impaired renal function, often in the context of multiple other medical and surgical issues and multiple other pharmacologic agents. Therefore, it is recommended that metformin be avoided in patients with other risk factors for lactic acidosis, including renal dysfunction, hepatic dysfunction, congestive heart failure, hypoxemia, and sepsis.

There have been 3 case reports of hepatotoxicity thought to be secondary to metformin in the literature. Liver function normalized following cessation of the drug, although causality was not definitively established.

Gastrointestinal adverse symptoms, including bloating, nausea, and diarrhea, are common, occurring in approximately 30% of patients taking metformin. The symptoms are generally mild and resolve with continued treatment. They can be minimized by starting with a low dose of metformin and

gradually increasing the dose. Metformin has not been associated with hypoglycemia when given in therapeutic doses.

13c. Have there been any human deaths associated with this drug?
Metformin has been associated with deaths secondary to lactic acidosis. As described above, lactic acidosis is a very rare complication of metformin use, with the rate of fatal lactic acidosis being estimated at 0.015 cases per 1000 patient-years. Reported cases occurred primarily in those with other risk factors for lactic acidosis, including renal insufficiency and congestive heart failure.

13d. In how many humans has this drug been used previously?
Metformin has been used in innumerable adults with Type 2 diabetes, as well as many women with PCOS. Metformin is used widely for the treatment of Type 2 diabetes and PCOS in adolescence, although the total number of children treated to date is unclear.

13e. If this protocol will be used in children describe any previous use of this drug with children of a similar age range.
Metformin is approved for use in children with Type 2 diabetes from ages 10 to 16 (ages 17 or older are considered "adult" for this FDA-approval), and has been evaluated for safety in that population. A number of small studies have evaluated Metformin as a potential treatment for adolescent girls with PCOS or its precursors, including hyperandrogenism and precocious puberty.

Number of girls treated with metformin for PCOS
Unfortunately, there is no registry documenting this information precisely. However, in a survey of pediatric endocrinologists published in 2005, 68% of surveyed pediatric endocrinologists said that they use metformin as first-line therapy for obese adolescents with PCOS ("Approach to adolescent polycystic ovary syndrome [PCOS] in the pediatric endocrine community in the U.S.A.," Guttmann-Bauman I, *Journal of Pediatric Endocrinology and Metabolism,* 2005). The prevalence of PCOS in of American young women is 5-10% ("Metformin for the Treatment of the Polycystic Ovary Syndrome," Nestler JE, *NEJM* 2008), and the onset of PCOS among these young women is commonly in adolescence (though exact numbers have not been published as to prevalence in adolescence). There are currently approximately 20 million girls in the US between 10-19 years old (http://en.wikipedia.org/wiki/Demographics_of_the_United_States). Thus, if even 25% of young women with PCOS developed it during adolescence and if just half of these saw a pediatric endocrinologist for treatment of their disease, and 68% of these endocrinologists started metformin as treatment, that would mean that at any given time 170,000 girls in this age range would be taking metformin for PCOS. Therefore, in our estimation, thousands of girls in this age range have been prescribed metformin off-label for PCOS.

Here at UVA, in Pediatric Endocrinology and the Children's Fitness Clinic, all of our providers use metformin as a first-line therapy for overweight adolescent girls with PCOS (which represents hundreds of patient-care visits here at UVA alone). Collectively, in our experience, this medication has been safe in children and we have seen no serious side effects, beyond mild and reversible GI disturbances (nausea, abdominal discomfort, loose stools).

14. 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:

Metformin is approved for use in children with Type 2 diabetes from ages 10 to 16, and has been evaluated for safety in that population. Therefore, as this medication will be given to a similar population in this study, we do not believe this represents increased risk.

__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.

15. Is this a post-marketing study? No.

APPENDIX: Privacy Plan for Studies With Consent

1. Answer the questions below (1a-1e) to describe your/central registry's plan to protect the identifiable data from improper use and disclosure.

1a. How will data be stored?

___X__ Data, which may include health information, or other highly sensitive data will be stored with HIPAA identifiers.
You MUST choose this option if case report forms will include such items as initials.

1b. Will specimens be stored by the UVa study team? Yes.

If YES, the following security precautions will be implemented:

- Specimens will be kept in a locked freezer/ or locked room
- __X___ Access to the freezer/room will be limited to authorized personnel. Specimens with HIPAA identifiers will never be shared outside of UVa without the written permission of the subject.

1c. Will any of the data be stored electronically by the UVa study team? Yes.

►IF YES, will it include any HIPAA identifiers with health information or other highly sensitive data?

►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.

1d. Will any of the data be collected or stored in hard copy format by the UVa study team (*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.

1e. 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.
- Each investigator will sign the University's Electronic Access Agreement 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. Identifiable data is considered to be "Highly Sensitive". A Limited Data Set is usually considered to be "Moderately Sensitive" and de-identified data is usually considered to be "Not Sensitive".
- 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 University's "Electronic Storage of Highly Sensitive Data Policy". Additional requirements may be found in the Universities Requirements for Securing Electronic Devices.
- If identifiable health information is taken away from the UVa Health System, Medical Center Policy # 0218 will be followed.
- The data will be securely removed from the server, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy.
- The data will be encrypted or removed if the electronic device is sent outside of UVa for repair according to the University's Electronic Data Removal Policy.
- If PHI will be faxed, researchers will follow the Health System Policy # 0194.
- If PHI will be emailed, researchers will follow the Health System Policy # 0193 and UVa Institutional Data Protection Standards .
- The data may not be analyzed for any other study without additional IRB approval.
- If you are using patient information you must follow Health System Policy # 0021.

Summary of Requirements to Comply with UVa Health System, Medical Center and University Policies and Guidance as noted above:

Highly Sensitive Data *is:*
-personal information that can lead to identify theft if exposed or
-health information that reveals an individual's health condition and/or history of health services use.

PHI- *a type of Highly Sensitive Data, is health information combined with a HIPAA identifier*

- LIMIT- Limit the HIPAA identifiers to the minimal amount needed- e.g. use initials instead of name, use a code instead of initials, limit amount/type of health information collected, and collect and share only those items you state you will in this protocol.
- SECURE- Secure Highly Sensitive Data
  - Because single-use electronic devices and media, such as desktops, laptops, memory sticks, CDs, smartphones etc., can be easily lost or stolen, the University strictly limits the circumstances under which Highly Sensitive Data may be stored on them. In accordance with the University's Electronic Storage of Highly Sensitive Data Policy, you must obtain written approval from your Department AND VP or Dean prior to moving data to single use devices or media by using the Highly Sensitive Data Storage Request Form.
    - *You additionally are responsible for applying all security safeguards covered in that policy, including but not limited to password protecting and encrypting any document on a single access electronic device.*
    - *If you use your smartphone to send email and your phone is not managed was not purchased and/or set up for you by the Health System, you cannot send Highly Sensitive Data via email.*
      - *In addition, do not use Outlook Web to send your email if it contains sensitive data.*
      - *Also, you are not allowed to auto forward your email to outside email systems like Gmail or Yahoo.*
      - *Do not save any email attachment containing Highly Sensitive Data to a single use device.*
    - *You are allowed to access Highly Sensitive Data stored on the University or Health Systems network via a VPN, however you cannot download any of the information onto your desktop or laptop.*
    - *Store files containing Highly Sensitive Data on a network drive specifically designated for storing this type of data, e.g. high-level security servers managed by Information Technology Services or the "F" and "O" managed by Heath Systems Computing Services. You may access it via a shortcut icon on your desktop, but you are not allowed to take it off line to a local drive.*
    - *If data will be collected and/or viewed via a website, it is critical that the website and associated data file are set up in a highly secured manner. Do not attempt without assistance from:*
      University Side: ITCmicrosystems@virginia.edu
      Health System: Web Development Center: (434-243-6702)
  - Encrypt any electronic file containing Highly Sensitive Data that is not on a network drive specifically designated for this purpose. . *See encryption solutions guidance.*

- Password protect any electronic device containing Highly Sensitive Data.
- Lock up hard copies of Highly Sensitive Data.

- PROTECT- Protect Highly Sensitive Data
  - Do not leave a hard copy file open on your desk when not using it and secure your computer when not attended.
  - Have discussions in private.
  - If you lose Highly Sensitive Data, you must report it in accordance with the Information Security Incident Reporting Policy.
  - Do not share Highly Sensitive Data with those not on the study team or those who do not have a need to know.
  - Do not share with sponsor unless subject has already signed a consent form or IRB has approved waiver of consent.
  - If faxing Highly Sensitive Data within UVa
    - Verify fax numbers before faxing, and use fax cover sheets with a confidentiality statement.
    - If printing to a central printer, ensure that names and identifiers on the documents are given to the correct patient.
  - Highly Sensitive Data may not be stored in a Drop Box.
  - If you plan to store data in the Cloud, you must consult with UVa Information Technology Services (ITS) to verify all essential security measures are in place. If you have a contract to use the cloud, the contract must include required security measures as outlined by ITS.
  - DO NOT email health information with name, medical record number or Social Security number to or from an email address that does not have an *HS in the address. May use subject initials if within the UVa HIPAA covered entity: The "UVA HIPAA covered entity" includes the hospital, health system, School of Medicine School of Nursing and the VP for Research Office.
  - Be aware: PHI collected without consent/ HIPAA authorization will NOT be allowed to leave UVa in an identifiable form unless the disclosure is tracked with Health Information Services.
  - Any Highly/Moderately Sensitive Data sent outside of UVa (e.g. to sponsor) that was obtained under a consent must be encrypted and password protected.
  - If your electronic device is sent outside of UVa for repair, all institutional data, whether Highly Sensitive or not, must be either encrypted or removed.
  - If transporting Highly/Moderately Sensitive Data in paper format from one UVa building to another, take the following steps to protect it:
    1. Put paper inside a closed container such as a briefcase, or sealed envelope to limit the chance of a losing a piece.
    2. Do not leave Highly Sensitive Data unattended in a public area if it is not locked up.
  - When the study is complete, all electronic files containing Highly/Moderately Sensitive Data must be stored on a network drive specifically designated for that purpose. They may not be stored on a single use device such as a CD.

- STOP, THINK and BE CAREFUL-
  - If this was your Highly Sensitive Data how would you want it protected?

- There are significant monetary fines to the individual and the institution for loss or misuse of sensitive data.
- Your job may also be on the line.

2. Describe your/central registry's plan to destroy the HIPAA identifiers at the earliest opportunity consistent with the conduct of the research and in accordance with any stipulations in the research sponsor contract and UVa records management guidelines.

__**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 (Limited Data Set)

1. Name
2. Postal address information, other than town or city, state, and zip code
3. Telephone numbers
4 Fax numbers
5. Electronic mail addresses
6. Social Security number
7. Medical Record number
8. Health plan beneficiary numbers
9. Account numbers
10. Certificate/license numbers
11. Vehicle identifiers and serial numbers, including license plate numbers
12. Device identifiers and serial numbers
13. Web Universal Resource Locators (URLs)
14. Internet Protocol (IP) address numbers
15. Biometric identifiers, including finger and voice prints
16. Full face photographic images and any comparable images
17. 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.)

APPENDIX: Sponsor

Sponsor Information

1. **Explain the sponsorship for this study.**

INSTRUCTIONS:

- List names of companies, institutes, foundations with which you have a grant or a contract from an entity that is not a support source.
- Example: This study is funded via a contract with the University of New York, which has a grant from the NIH to conduct this study. We will be receiving free drug from Glaxo. Glaxo will receive data prior to publication.
- If the outside entity will be monitoring the study or receiving data prior to publication enter them as a sponsor.
- If you are receiving things such as free supplies/ drug/ devices from a company who WILL NOT be monitoring the study or be receiving data prior to publication do NOT enter them here- enter this information under Support Source below.

Answer/Response: National Institutes of Health (NIH)

2. **Do you confirm that you will obtain a contract/ material transfer agreement with the sponsor via the School of Medicine Grants and Contracts Office or the Office of Sponsored Programs (OSP)** ospnoa@virginia.edu**?**

INSTRUCTIONS:

You should have answered YES to the following question in Protocol Builder:
--"Do you/will you have a contract with an outside entity to support this protocol?"

Answer/Response: Yes