Continuous Versus Cyclical OCP Use in PCOS (CCOUP)

NCT03819140

Document Date: 09/24/2021

Study Application (Version 1.11)

1.0 General Information

***Enter the full title of your study:**

Continuous versus Cyclical OCP Use in PCOS (CCOUP): A Pilot Study

***Enter the study alias:**

CCOUP Study
* This field allows you to enter an abbreviated version of the Study Title to quickly identify this study.

2.0 Add departments

2.1 and Specify Research Location:

Is Primary?	Department Name
◉	**UCSF** - *123027* - M_ObGyn-REI-Core
○	**UCSF** - *136219* - M_PEDS-ENDOCRINOLOGY

3.0 List the key study personnel: (Note: external and affiliated collaborators who are not in the UCSF directory can be identified later in the Qualifications of Key Study Personnel section at the end of the form)

3.1 *Please add a Principal Investigator for the study:

Huddleston, Heather G

Select if applicable

☐ Department Chair ☐ Resident

☐ Fellow

If the Principal Investigator is a Fellow, the name of the Faculty Advisor must be supplied below.

3.2 If applicable, please select the Research Staff personnel

A) Additional Investigators

Cedars, Marcelle MD
Other Investigator
Mody, Armaiti
Other Investigator
Morris, Jerrine R
Other Investigator
Pasch, Lauri
Other Investigator

B) Research Support Staff

Corley, Jamie
Study Coordinator
Lenhart, Nikolaus J
Study Coordinator
Mcgough, Alexandra M
Study Coordinator

3.3 *Please add a Study Contact

Mody, Armaiti
Morris, Jerrine R

The Study Contact(s) will receive all important system notifications along with the Principal Investigator. (e.g. The project contact(s) are typically either the Study Coordinator or the Principal Investigator themselves).

3.4 If applicable, please add a Faculty Advisor/Mentor:

Lodish, Maya B

3.5 If applicable, please select the Designated Department Approval(s)

Add the name of the individual authorized to approve and sign off on this protocol from your Department (e.g. the Department Chair or Dean).

4.0 Initial Screening Questions

Updated June 2017

4.1 * PROJECT SUMMARY: (REQUIRED) Give a brief overview of this project (250 words or less). Tell us what this study is about, who is being studied, and what it aims to achieve. If you have an NIH Abstract, paste it here: Click on the orange question mark to the right for more detailed instructions.

The mainstay treatment for females with Polycystic Ovary Syndrome (PCOS) has long been a combination of an oral contraceptive pill or OCP (containing both estrogen and progestin) along with an anti-androgen medication (such as spironolactone) to not only prevent chronic anovulation but also suppress elevated Testosterone levels and its clinical effects on the body. While there are multiple OCPs available on the market today and several studies that have looked at different progestins and their anti-androgenicity, not much is known about whether the length of active pills in OCP therapy (3 weeks versus 6 months) has any benefit in continued suppression of Testosterone and subsequently improvement in clinical findings of hyperandrogenism in the PCOS population. In this pilot, randomized clinical trial females between the ages of 15 and 40 years, diagnosed with PCOS based on the Rotterdam Criteria, not currently on medical therapy, but requiring an OCP for anovuatary menstrual cycles or hyperandrogenism, will be enrolled in the study and randomized to either a continuous 6 month OCP or cyclical 21 day active OCP therapy. Our aims are to conduct a pilot trial to determine the feasibility of such a study, as well as determine the effect (if any) of 6 months of active monophasic OCPs on Testosterone levels and cutaneous findings of hyperandrogenism (hirsutism and acne) as compared to a 21 day active/7day placebo OCP in women with PCOS. These findings will be compared over a period of 6 months.

4.2 * HUD DEVICE: (REQUIRED) Does this application involve a Humanitarian Use Device (HUD):

- (•) No
- ( ) Yes, and it includes a research component
- ( ) Yes, and it involves clinical care ONLY

4.3 * TYPE OF RESEARCH: (Click the Help link for definitions and guidance): (REQUIRED)

- (•) Biomedical research
- ( ) Social, behavioral, educational, and/or public policy research
- ( ) Hybrid - includes aspects of BOTH types of research (check this option if your research is mainly social/behavioral but also involves specimen collection or blood draws to look at biological measures)

4.4 * SUBJECT CONTACT: (REQUIRED) Does this study involve ANY contact or interactions with participants:

- (•) Yes (including phone, email or web contact)
- ( ) No (limited to medical records review, biological specimen analysis, and/or data analysis)

4.5 * RADIATION EXPOSURE: Does your protocol involve any radiation exposure to patients/subjects EITHER from standard care OR for research purposes (e.g., x-rays, CT-scans, DEXA, CT-guided biopsy, radiation therapy, or nuclear medicine including PET, MUGA or bone scans): (REQUIRED)

- ( ) Yes (•) No

4.6 * RISK LEVEL: (REQUIRED) What is your estimation of the risk level, including all screening procedures and study activities (Help Text updated 9/13):

- ( ) Minimal risk
- (•) Greater than minimal risk

4.7 * REVIEW LEVEL: (REQUIRED) Requested review level (Click on the orange question mark to the right for definitions and guidance):

- (•) Full Committee
- ( ) Expedited
- ( ) Exempt

4.11 * CLINICAL TRIAL: (REQUIRED) Is this a clinical trial? According to The World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) a clinical trial is:

- **Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.**

ICMJE requires registration of a clinical trial in a public database (such as ClinicalTrials.gov) prior to enrollment, for eventual publication of results in member biomedical journals. Guidance: Public Law 110-85 requires that all investigators who perform an *applicable clinical trial* must ensure that the trial is registered on a government web site called ClinicalTrials.gov. The FDA requires registration for "applicable clinical trials," defined as follows:

- **For any trials of drugs and biologics: controlled clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation.**
- **For trials of biomedical devices: controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post-market surveillance.**

For additional information on the ClinicalTrials.gov registration process at UCSF and the definition of a clinical trial for purposes of registration, visit the ClinicalTrials.gov section of the UCSF Clinical Research Resource HUB.

(•) Yes ( ) No

Clinical Trial Registration

"NCT" number for this trial:

03819140

If you don't yet have the NCT#, type 'Pending.'

4.12 * CLINICAL TRIAL PHASE (REQUIRED) Check the applicable phase(s) (Help Text updated 9/13):

- [ ] Phase I
- [ ] Phase II
- [ ] Phase III
- [x] Phase IV

4.13 * INVESTIGATOR-INITIATED: (REQUIRED) Is this an investigator-initiated study:

(•) Yes ( ) No

4.14 * CANCER: (REQUIRED) Does this study involve cancer (e.g., the study involves patients with cancer or at risk for cancer, including behavioral research, epidemiological research, public policy research, specimen analysis, and chart reviews):

( ) Yes (•) No

If you don't know if you should answer 'Yes' or 'No,' please **email** the Cancer Center's Protocol Review Committee for help.

4.15 SCIENTIFIC REVIEW: If this study has undergone scientific or scholarly review, please indicate which entity performed the review (check all that apply):

- [ ] Cancer Center Protocol Review Committee (PRC) (Full approval is required prior to final CHR approval for cancer-related protocols.)
- [ ] CTSI Clinical Research Services (CRS) Advisory Committee
- [ ] CTSI Consultation Services
- [x] Departmental scientific review
- [ ] Other:

* Which Department(s) provided review: **(REQUIRED)**

OBGYN Department - Reproductive Endocrinology and Infertility Division

4.16 * STEM CELLS: (REQUIRED) Does this study involve human stem cells (including iPS cells and adult stem cells), gametes or embryos:

(•) No
( ) Yes, and requires IRB and GESCR review
( ) Yes, and requires GESCR review, but NOT IRB review

4.17 * FINANCIAL INTERESTS: (REQUIRED) Do you or any other responsible personnel (or the spouse, registered domestic partner and/or dependent children thereof) have financial interests related to this study:

○ Yes ◉ No

5.0 Funding

5.1 * FEDERAL FUNDING: (REQUIRED) Is this study currently supported in whole or in part by Federal funding, *even by a subcontract*, OR has it received ANY Federal funding in the past:

◉ Yes ○ No

The IRB is required to compare the grant to the IRB application for studies with federal support. Indicate which portion of your grant you will be attaching:

- ☐ For NIH grants, the Research Plan, including the Human Subjects Section
- ☐ For other federal proposals (contracts or grants), the section of the proposal describing human subjects work
- ☐ The section of your progress report if it provides the most current information about your human subjects work
- ☑ The grant is not attached. The study is funded by an award that does not describe specific plans for human subjects, such as career development awards (K awards), cooperative agreements, program projects, and training grants (T32 awards) OR UCSF (or the affiliate institution) is not the prime recipient of the award

5.2 * DoD INVOLVEMENT: Is this project linked in any way to the Department of Defense (DoD): (REQUIRED)

○ Yes ◉ No

5.3 SPONSORS: Identify all sponsors and provide the funding details. If funding comes from a Subcontract, please list only the Prime Sponsor:

External Sponsors:

View Details	Sponsor Name	Sponsor Type	Awardee Institution:	Contract Type:	Project Number	UCSF RAS System Award Number ("A" + 6 digits)
⊟	NIH Natl Inst. Child Health & Human Dev.	01	UCSF			A133144

Sponsor Name:	NIH Natl Inst. Child Health & Human Dev.
Sponsor Type:	01
Sponsor Role:	Funding
CFDA Number:	
Grant/Contract Number:	
Awardee Institution::	UCSF

Is Institution the Primary Grant Holder:	No
if No, then who is the Primary Grantee?	
Contract Type:	
Project Number:	
UCSF RAS System Award Number ("A" + 6 digits):	A133144
Grant Number for Studies Not Funded thru UCSF:	
Grant Title:	
PI Name: (If PI is not the same as identified on the study.)	
Explain Any Significant Discrepancy:	

If the funding is coming through UCSF and you don't know the A or P number, you can search the eProposal side for the contract or grant (this does NOT replace adding the sponsor by name above AND entering the A or P number):

Project Status	Proposal Number	Project Title	Principal Investigator
No Projects are Linked to this IRB Study			

Other Funding Sources and Unfunded Research - Gift, Program, or Internal Funding (check all that apply):

- ☐ Funded by gift (specify source below)
- ☐ Funded by UCSF or UC-wide program (specify source below)
- ☐ Specific departmental funding (specify source below)
- ☑ Unfunded (miscellaneous departmental funding)
- ☐ Unfunded student project

You checked 'Yes' to federal funding or support in 5.1 above. If this study has ANY funding, uncheck the 'Unfunded' option. If it truly is unfunded, check 'No' in 5.1 above.

6.0 Sites, Programs, Resources, and External IRB Review

6.1 UCSF AND AFFILIATED SITES (check all that apply):

- ☑ UCSF (including Laurel Heights and all the other sites outside the main hospitals)
- ☐ Parnassus
- ☑ Mission Bay
- ☐ China Basin
- ☐ Mount Zion
- ☐ Helen Diller Family Comprehensive Cancer Center
- ☐ Langley Porter Psychiatric Institute

- [ ] San Francisco General Hospital (SFGH)
- [ ] SF VA Medical Center (SF VAMC)
- [ ] Blood Centers of the Pacific (BCP)
- [ ] Blood Systems Research Institute (BSRI)
- [ ] Fresno Community Medical Center
- [ ] Gallo
- [ ] Gladstone
- [ ] Jewish Home
- [ ] Institute on Aging (IOA)
- [ ] SF Dept of Public Health (DPH)

6.2 LOCATIONS: At what locations will study visits and activities occur:

UCSF PCOS Multidisciplinary Clinic (within the Reproductive Endocrine and Infertility Department) in Mission Bay

UCSF Center for Reproductive Health in Mission Bay

UCSF Pediatric Endocrinology Fellow's Clinic (within the Pediatric Endocrinology Department) in Mission Bay

6.3 OFF-SITE PROCEDURES: Will any study procedures or tests be conducted off-site by non-UCSF personnel:

- (•) Yes
- ( ) No

Please identify which procedures may be done off-site:

Patients will be expected to get labs drawn at an outside lab (Quest Diagnostics or LabCorp Laboratories).

6.4 RESEARCH PROGRAMS: Check any UCSF research programs this study is associated with:

- [ ] Cancer Center
- [ ] Center for AIDS Prevention Sciences (CAPS)
- [ ] Global Health Sciences
- [ ] Immune Tolerance Network (ITN)
- [ ] Neurosciences Clinical Research Unit (NCRU)
- [ ] Osher Center
- [ ] Positive Health Program

6.5 * CTSI CRS SERVICES: (REQUIRED) Will this study be carried out at one of the UCSF Clinical Research Services (CRS) units or utilize CRS services:

- ( ) Yes
- (•) No

6.6 * MULTI-CENTER TRIAL: (REQUIRED) Is this a multicenter research trial? By multi-center trial, we mean a study where the protocol is developed by an industry sponsor, consortium, a disease-group, etc., who then selects sites across the nation or in different countries to participate in the trial. The local sites do not have any control over the design of the protocol.

- ( ) Yes
- (•) No

6.7 OTHER SITE TYPES: Check all the other types of sites not affiliated with UCSF with which you are cooperating or collaborating on this project: Do NOT check any boxes below if this is a multi-center clinical trial, UCSF is just one of the sites, and neither UCSF nor its affiliates are the coordinating center.

- ☐ Other UC Campus
- ☐ Other institution
- ☐ Other community-based site
- ☐ Foreign Country
- ☐ Sovereign Native American nation (e.g. Navajo Nation, Oglala Sioux Tribe, Havasupai, etc.)

6.10 * RELYING ON AN EXTERNAL IRB: Does this application include a request to rely on an external IRB other than the NCI IRB (e.g. UC reliance, private/commercial IRB, or institutional IRB): (REQUIRED)

Check out the orange question mark to the right to find out if your study is eligible for external IRB review.

○ Yes ◉ No

7.0 Research Plan and Procedures

7.1 This new consolidated section requests information about:

- **Hypothesis**
- **Aims**
- **Study Design**
- **Background and Significance**
- **Preliminary Studies**
- **Procedures**
- **Statistical Methods**
- **References**

Later sections include:

- **Drugs and Devices**
- **Sample Size, Eligibility, and Subjects**
- **Recruitment and Consent**
- **Risks and Benefits**
- **Data and Safety Monitoring Plan**
- **Confidentiality, Privacy and Security**
- **Financial Considerations**
- **Qualifications of Personnel**
- **Other Approval and Registrations**

7.2 HYPOTHESIS: Describe the hypothesis or what the study hopes to prove (Help Text updated 9/13):

We propose that patients with Polycystic Ovary Syndrome (PCOS) on a continuous 6 month active oral contraceptive (OCP) preparation (no placebo pills for 6 months straight) will have improved Testosterone suppression as compared to patients taking cyclical (monthly) OCPs, who may have rebound ovarian function during days 21-28 of their menstrual cycle when receiving sugar pills. With continuous OCP use we also hypothesize that patients will have improved clinical findings of hyperandrogenism (acne and hirsutism) compared to cyclic OCP users.

7.3 AIMS: List the specific aims:

1. To conduct a pilot feasibility study observing the use of 2 formulations of an OCP (continuous 168 day active hormone pills vs. cyclical 21 day active/7day placebo pill packs) in patients with Polycystic Ovary Syndrome (PCOS).

2. To determine the effect of 6 months of continuous (168 days of active hormone pills) vs. cyclical (21 day active and 7 day placebo pills) OCP therapy on biochemical findings of hyperandrogenism (Testosterone levels and free androgen index).

3. To determine the effect of 6 months of continuous (168 days of active hormone pills) vs. cyclical (21 day active/7 day placebo pills) OCP therapy on cutaneous findings of hyperandrogenism (male pattern hair growth also known as hirsutism and acne).

4. To determine the effect of 6 months of continuous (168 days of active hormone pills) vs. cyclical (21 day active/7 day placebo pills) OCP therapy on self reported symptoms of anxiety and /or depression as collected from validated questionnaires.

7.4 DESIGN: Briefly describe the study design (e.g., observational, interventional, randomized, placebo-controlled, blinded, cross-over, cross-sectional, longitudinal, pharmacokinetic, etc.):

This is a pilot, randomized, open label clinical trial looking at the effects of different formulations of combined oral contraceptive pills (OCP) provided in therapy following the diagnosis of PCOS. Participants will be randomized in a 1:1 ratio to receive either a 21 day active hormone/7 day placebo pill pack (cyclical OCP) or an 168 day active hormone pill pack (6 month continuous OCP) and monitored with blood work and physical exams over the course of 6 months. Both groups will receive the same combined OCP component, containing 30mcg of ethinyl estradiol and 3 mg of Drospirenone (Yasmin).

7.5 BACKGROUND AND SIGNIFICANCE: Briefly provide the background and significance of this study (e.g. why is this study needed) (space limit: one half page):

If this is a first in humans study, please summarize the safety data from the animal studies. For pediatric drug or device studies, please identify if this is the first study in pediatric populations.

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder that affects 5-15% of women worldwide[1] and is associated with multiple comorbidities such as obesity, Type 2 Diabetes, infertility and cardiovascular events[2,3]. In the US, it is the most common endocrine abnormality of reproductive-aged women[3]. While the underlying cause remains unclear, women with PCOS are often found to have anovulatory cycles (menstrual dysfunction), clinical or biochemical signs of hyperandrogenism (such as elevated Testosterone levels, or male pattern hair growth and acne), and/or excessive follicle counts on ultrasound of the ovaries. Based on the Rotterdam Criteria (established in 2003) two out of the three above criteria must be met to diagnose PCOS[4]. While other definitions exist, the Rotterdam Criteria is widely used as an established diagnostic tool.

With chronic anovulation (where the ovaries do not release an oocyte during a menstrual cycle), women with PCOS have a greater risk of developing endometrial carcinoma, and thus combined oral contraceptive pills (OCPs) are the mainstay of initial therapy. While menstrual irregularity is a large concern in patients with PCOS, studies have also shown that many women with clinical findings of hyperandrogenism such as male pattern hair growth (hirsutism), hair loss and acne have significantly lower self-esteem and thus are looking for treatment that includes some anti-androgen effect[10]. OCPs pay a dual role of not only reducing bioavailable Testosterone in the body but also suppressing ovarian Testosterone production as well. While there are multiple clinical trials that have looked at different progestin containing OCPs in women with PCOS, most have shown 3rd and 4th generation progestins have significantly more anti-androgen

effect. Although no standard OCP therapy exists in this population, OCPs containing the 4th generation progestin Drospirenone have been shown to have strong anti-androgen activity in women with PCOS and thus is frequently used by clinicians.

Given these findings, the mainstay of treatment has long been an estrogen and progestin containing OCP and sometimes an additional anti-androgen medication (such as Spironolactone). What is noteworthy is that research is lacking considerably in the effect that continuous versus cyclical OCP use may have on patient's with PCOS as a monotherapy in treatment of hyperandrogenism. As previous research has shown that it is not necessary to have a period once a month, more clinicians are prescribing continuous OCPs as a matter of patient preference, but studies looking at the effect on sex hormones in women with existing hyperandrogenism are lacking.

7.6 PRELIMINARY STUDIES: Briefly summarize any preliminary studies relevant to your proposed research (space limit: one half page):

In a study by Legro et al (2008), healthy women with regular menses were followed over a period of 6 months on either a continuous (168 day active pill) or a cyclical (21 day active/7day placebo) OCP that contained 20 mcg of ethinyl estradiol and 1mg of Norethindrone acetate. Findings from this study showed no difference in overall bleeding between treatment arms but a significant decrease in moderate/heavy bleeding days in favor of the continuous regimen. Both OCP treatment arms showed significant estrogen and Testosterone suppression compared to baseline during the 3rd week of each monthly cycle. While sex hormones (estrogen and Testosterone) were not evaluated during the placebo week in the cyclical group, there was notable rebound ovarian function noted in the cyclical formulation resulting in breakthrough menstrual bleeding. While this study was specifically done on healthy women, only one study has looked at continuous versus cyclical OCPs in women with PCOS.

Ruchhoft et al (1996) showed in a fairly small study, that women with PCOS placed on a continuous OCP regimen for 3 months had significantly reduced Testosterone levels compared to baseline than those who were on cyclical preparations. Similarly, there was also a persistent reduction in LH, FSH and estradiol levels in the continuous treatment group throughout therapy. Alternatively, the study showed that individuals treated with a cyclical OCP had a significant rebound rise in their Testosterone, LH, FSH, and estradiol levels during the placebo week compared to mid-pill pack. These findings confirmed that it only takes a week off pills to (placebo week in cyclical OCPs) to cause rebound pituitary and ovarian activation resulting in increased hyperandrogenism. While having rebound ovarian function is not a bad thing in the general population as it allows for withdrawal bleeding, in patients with PCOS who require continuous suppression of ovarian function and Testosterone production, this could be an unwanted side effect.

7.7 * TREATMENT PROTOCOL: Is this a treatment study, i.e. does this study intend to provide treatment to individuals with a medical or psychological condition: (REQUIRED)

(•) Yes ( ) No

7.8 * BILLABLE PROCEDURES: Does this study involve any services or procedures (e.g. physical exams, surgeries, lab tests, imaging studies, or drugs) that could be billable to patients, their insurance, Sponsor, or any other entity (answer 'Yes' even if the study is going to pay for all the procedures): (REQUIRED)

(•) Yes ( ) No

If you are not sure if your study involves billable procedures, send an email to the **UCSF Office of Clinical Research (OCR)** for help answering this question.

7.9 * COMMON RESEARCH ACTIVITIES: Types of research activities that will be carried out. Check all that

apply and describe in more detail in the 'Procedures / Methods' section: (REQUIRED)

- [x] Interviews, questionnaires, surveys
- [ ] Educational or cognitive tests
- [ ] Focus groups
- [x] Observation
- [ ] Non-invasive imaging or testing (MRI, EEG, pulse oximetry, etc.)
- [ ] Administration of contrast agent
- [ ] Imaging procedures or treatment procedures that involve radiation (x-rays, CT scans, CT-guided biopsies, DEXA scans, MUGA or PET scan)
- [ ] Biopsy conducted solely for research purposes
- [ ] Use of placebo
- [ ] Sham surgical procedure
- [ ] Collection of data from wearable tech such as Fitbit, Apple Watch, Garmin, motion actigraphs, etc.)
- [ ] Fitness tests or other exertion activities
- [ ] Use of mobile health apps or other apps
- [ ] Social media-based research activities
- [ ] None of the above

7.10 * PROCEDURES / METHODS: (REQUIRED)

For clinical research, list all study procedures, tests and treatments required for this study, including when and how often they will be performed. If there are no clinical procedures, describe the research activities.

If some of the activities would occur even if the person were not in the study, as in the case of treatment or tests performed for diagnostic purposes, clearly differentiate between those activities that will be done solely for research purposes and those that are happening as part of routine care.

Examples may include:

- additional scans outside standard clinical diagnosis or monitoring
- additional biopsies to collect tissue for research
- extra clinic visits
- extra lab tests not required for clinical care

If you have a procedure table, attach it to the submission with your other study documents.

All potential participants in the study that go through the PCOS Multidisciplinary clinic have routine baseline blood work done (at least 1 month off any oral contraceptive pill) which includes total and free Testosterone levels, sex hormone binding globulin (SHBG), estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), Hemoglobin A1c (HbA1c), insulin, fasting glucose, and a lipid panel. If baseline blood work is done > 2 months prior to enrollment, we will repeat these levels to ensure accuracy prior to start of study. As part of the clinic visit, patients routinely fill out a lengthy survey which includes a quality of life assessment and self-assessments regarding acne and hair growth. Potential participants will also have a routine initial dermatological exam to evaluate for hirsutism (using the modified Ferriman Gallwey aka mFG

score) and acne which takes place on their initial visit to clinic, prior to enrollment in the study. This information will all be included in the information gathered about each participant who enrolls in the study as it will provide baseline values.

All potential participants that present to the clinic for a reassessment will fill out a lengthy survey which includes a quality of life assessment and self-assessments regarding acne and hair growth. Potential participants will also have a routine initial dermatological exam to evaluate for hirsutism (using the modified Ferriman Gallwey aka mFG score) and acne which takes place on their initial visit to clinic, prior to enrollment in the study. This information will all be included in the information gathered about each participant who enrolls in the study as it will provide baseline values. If the potential participant still meets criteria for PCOS and meets criteria for the CCOUP study (see below), they will have routine baseline blood work done as a part of the study which includes total and free Testosterone levels, sex hormone binding globulin (SHBG), estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), Hemoglobin A1c (HbA1c), insulin, fasting glucose, and a lipid panel.

Those who meet criteria to take part in the study (women between the ages of 15-40 years, diagnosed with PCOS and have findings of hyperandrogenism either by serum Testosterone levels above the normal reference range and/or by their mFG score (>/=5), are recommended to start an oral contraceptive pill for therapy), and give consent, will be randomized into either of two oral contraceptive (OCP) treatment groups. The two treatment groups consist of either 1.Ethinyl estradiol 30mcg-Drospirenone 3 mg: 21 day active/7day placebo pill pack or 2. Ethinyl estradiol 30 mcg-Drospirenone 3 mg:168 day active hormone pills. While this study involves an intervention, it is important to address that the hormonal contraceptive therapy being administered is routinely used in the care of women diagnosed with PCOS who are not acutely interested in fertility. Instructions will be given to participants in the continuous treatment arm to remove all placebo/sugar pills from each OCP pack so that they continuously take active hormone pills throughout the study time frame.

Study subjects will be expected to take their OCP pills at the same time each day for the length of the study (6 months). On the 4th, 12th and 24th week of therapy (roughly the 1st, 3rd and 6th month), repeat blood work will be drawn and is detailed below.

At 1 month into therapy, (near the end of the 4^{th} week on either OCP regimen) both treatment groups will be expected to come into the clinic for blood work (total Testosterone, SHBG, estradiol, LH, and FSH levels will be checked). As this is not considered routine labs, the study will cover the cost so that participants are not charged. At the time of the blood draw, subjects in the cyclical group should be on placebo/sugar pills and those in the continuous group on active hormone pills.

At 3 months into therapy, participants will come back to the PCOS clinic for routine care follow up and be seen by a Reproductive Endocrinology and Fertility specialist. This visit is considered routine and not specific to the study. However, during this visit a study investigator will also touch base briefly with the participants to see how they are doing. Four online surveys (through REDCap) will also be sent to participants that addresses if they have missed any doses of their medication, assess their quality of life, acne changes, screen for anxiety and depression. Patients will be asked to complete the BDI-II survey on their clinic day so that it can be evaluated by the study team immediately in the event that there are concerns for suicidal risk. In addition, participants will once again get blood work at their visit (including total Testosterone, SHBG, estradiol, LH, FSH) but will also go to their local lab (covered by their insurance) for additional routine labs including a fasting lipid panel, fasting serum glucose, insulin, and HbA1c. These labs are routinely done with follow up regardless of being in the study and should therefore be covered by each participant's insurance. Once again, the cyclical group should be on placebo/sugar pills at the time of blood draw and the continuous group on active hormone pills.

At 6 months into therapy, participants will come in for a study visit (this is not considered routine care) in which they will have their vitals taken, a physical exam that includes a re-evaluation of their mFG score, and an in-clinic pelvic ultrasound to assess ovarian volume and follicle counts performed by a Reproductive Endocrinology and Infertility specialist. They will also be emailed 5 post-study surveys through REDCap, that includes a quality of life questionnaire for PCOS, acne and hirsutism, as well as anxiety and depression screening, and includes questions regarding any missed doses of their medication. Patients will again be asked to complete the BDI-II survey on their clinic day so that it can be evaluated by the study team immediately in the event that there are concerns for suicidal risk. Lastly, participants will again have blood work drawn in the clinic (total Testosterone, SHBG, estradiol, LH, FSH). These labs are not considered standard of care and will be paid for by the study team.

Participants may also be called emailed reminders for follow up at least 2-3 times during the 6 month period.

CCOUP Study Timeline

	Screening	Enrollment	1 month	3 months	(routin
Questionnaires					
REDCap PCOS Multidisciplinary PCOS Clinic Pre-clinic Surveys (routine)	x				
REDCap Baseline Questionnaire		x			
REDCap 3 Month Follow Up Questionnaire /PCOS QOL				x	
REDCap 3 Month GAD-7 Questionnaire				x	
REDCap 3 month BDI-II Survey				x	
REDCap 3 Month Follow Up - Acne QOL Assessment				x	
REDCap 6 Month Follow Up Questionnaire /PCOS QOL					
REDCap 6 Month GAD-7 Questionnaire 2					
REDCap 6 Mond BDI-II Survey 2					
REDCap 6 Month Follow Up Questionnaire - Acne QOL Assessment					
REDCap 6 Month Follow Up Questionnaire - Hirsutism QOL Assessment					
Study Visits/Procedures					
Dermatologic Exam (mFG scoring)		x			
Pelvic Ultrasound		x			
Blood Work - Location	Patient's local lab - insurance covered	PCOS Clinic - study covers	PCOS Clinic - study covers	PCOS Clinic - study covers	Pa ins
Total Testosterone	x (routine)	* **	†	†	
Free Testosterone	x (routine)	**			
Sex Hormone Binding Globulin	x (routine)	* **	†	†	
LH	x (routine)	* **	x	x	
FSH	x (routine)	* **	x	x	
Estradiol	x (routine)	* **	x	x	
Fasting Lipid Panel	x (routine)	**			x (
HbA1c	x (routine)	**			x (
Fasting serum glucose	x (routine)	**			x (
Insulin	x (routine)	**	†	†	
Email Reminders			x		x

* if initial screening blood work done at the patient's outside lab is obtained >2 months from start of study, these select la enrollment to establish accurate baseline values.

**** If the patient is a return patient to the clinic looking to reestablish care and participate with the study, all she meets PCOS/CCOUP Study criteria and established as the patients new baseline levels.**

† indicates the select labs that will be sent from the PCOS clinic (where it is drawn) to the University of Virginia, Center fo Please refer to the attached study document "CCOUP Study Timeline" for the full procedure table.

7.11 STANDARD CLINICAL PRACTICE: To what extent, if any, do the planned research procedures differ

from the care that people would otherwise receive at this institution or the study site if not being done locally:

If the goal of therapy is management of hyperandrogenism and menstrual dysfunction, combined oral contraceptive pills (OCPs) are the mainstay of treatment based on *Endocrine Society* guideline s of PCOS. While there is no standard of care established regarding which combined OCP formulation and length of active pills that should be used in the treatment of women with PCOS, the mainstay of therapy has largely been monthly pill packs (21 days of active and 7 days of placebo pills) though continuous 3-6 month formulations have been used, with a 3rd or 4th generation progestin that provides some anti-androgen effect. Therapy with OCPs are individualized to each patient given the multitude of different formulations and their side effect profiles. In patients who have concerns for hirsutism an additional medication such as Spironolactone is often added to therapy. However, studies have shown that 4th generation progestins such as Drospirenone have a component of Spironolactone effect, limiting the need for dual therapy.

Comparatively, this study will use standard clinical practice guidelines in treating participants with an OCP that has a 4th generation progestin, Drospirenone. In addition, it is also standard clinical practice that patients seen at the PCOS Multidisciplinary clinic who are started on OCP therapy are followed up in 3 months for both a clinic visit and typically get routine blood work at this time as well.

Procedures that differ from the standard clinical practice in this study include: repeat blood work at 1 month and 6 months into OCP therapy, repeat pelvic ultrasound to assess ovarian volume and follicle counts at 6 months of therapy, and lastly a repeat modified Ferriman-Gallwey Hirsutism scoring done with a physical exam at he 6 month follow up.

7.12 INSTRUMENTS: List all questionnaires, surveys, interview, or focus group guides that will be used for this study:

	Screening	Enrollment	1 month	3 months	(routin
Questionnaires					
REDCap PCOS Multidisciplinary PCOS Clinic Pre-clinic Surveys (routine)	x				
REDCap Baseline Questionnaire		x			
REDCap 3 Month Follow Up Questionnaire /PCOS QOL				x	
REDCap 3 Month GAD-7 Questionnaire				x	
REDCap 3 Month BDI-II Survey				x	
REDCap 3 Month Follow Up - Acne QOL Assessment				x	
REDCap 6 Month Follow Up Questionnaire /PCOS QOL					
REDCap 6 Month GAD-7 Questionnaire 2					
REDCap 6 Month BDI-II Survey 2					
REDCap 6 Month Follow Up Questionnaire - Acne QOL Assessment					
REDCap 6 Month Follow Up Questionnaire - Hirsutism QOL Assessment					

Attach any unpublished instruments in the 'Other Study Documents' section of the Initial Review Submission Packet form after completing the study application. Published instruments should NOT be attached.

7.13 * BIOSPECIMEN COLLECTION: Are you drawing any blood or collecting other biosamples (e.g. tissue, buccal swabs, urine, saliva, hair, etc.): (REQUIRED)

(•) Yes ( ) No

* Could this study generate genetic data that may be broadly shared (e.g., submitted to NIH in compliance with **Genomic Data Sharing (GDS)/Genome-Wide Association Studies (GWAS)** requirements): **(REQUIRED)**

( ) Yes (•) No

Please check the Resource Sharing Plan section of your funding notice. You will not be able to share the data as required by your funding agency if the consent form doesn't include the required language.

7.14 * TYPE OF SPECIMENS (check all that apply): (REQUIRED)

- [x] Blood
- [ ] Tissue (describe below):
- [ ] Existing/archival materials (name source below): --
- [ ] Other (describe below):

7.15 * SPECIMENS ARE: (check all that apply): (REQUIRED)

- [ ] Leftover specimens from a clinical diagnostic or therapeutic procedure
- [x] Specimens collected for research purposes only (including extra samples taken during a clinical procedure)
- [ ] Other

7.16 * DESTINATION: Specimens will ultimately be stored (check all that apply): (REQUIRED)

Outside Entity:

- [ ] Cooperative group bank
- [ ] NIH
- [x] Other university
- [ ] Industry sponsor
- [x] Other

Specify to what institution, cooperative group, or company specimens will be transferred:

Balancing cost and ease, a select few blood samples will be sent to University of Virginia, Center for Research in Reproduction (to test for testosterone, sex hormone binding globulin and insulin). During routine follow up at the 3 month check we expect participants will also get fasting blood work at their insurance-covered lab of their choice.

UCSF:

- [ ] UCSF repository/bank being established under this protocol
- [ ] Existing UCSF specimen repository/bank with CHR approval
- [x] Other location at UCSF (please describe)

Provide the name of the bank and iRIS approval number (if not being banked at UCSF under this protocol). If you checked 'Other,' please provide the location or lab:

Center for Reproductive Health
Reproductive Heath Laboratories
499 Illinois St, 6th floor
San Francisco, CA 94158

7.18 SPECIMENS SENT OUTSIDE UCSF - IDENTIFIABILITY: Will direct identifiers be associated with specimens or shared with other researchers and/or outside entities:

- ○ Yes
- ◉ No
- ○ N/A - Specimens will not be shared with others

7.19 * FUTURE SPECIMEN USE: Will any specimens or portions of specimens be retained after the study is over for possible use in future research studies: (REQUIRED)

○ Yes ◉ No

7.21 * CLINICAL FOLLOW-UP DATA: Will clinical follow-up data be linked to specimens (i.e., will medical record information continue to be abstracted after the specimen is collected): (REQUIRED)

○ Yes ◉ No

Provide duration of follow-up or 'indefinitely':

7.26 STATISTICAL METHODS: Briefly summarize the methods and types of analyses that will be performed:

The means and standard deviation will be calculated for each of the blood tests within each treatment group and compared at the different time points to baseline measures. Additionally we will likely use a two sample t-test to estimate the difference in the mean Testosterone levels between the two treatment groups over the 6 month period. Analysis of covariance models, adjusted for the baseline measurement, will also likely be used to compare the treatment groups for metabolic parameters. Chi-Square analyses will be used to compare the treatment groups for reported anxiety and depression as analyzed categorically.

7.27 REFERENCES: List only the 5-10 most relevant references (a separate bibliography can be attached for reference purposes if this study involves novel approaches, agents, or an emerging technology that the IRB may not be familiar with):

1. Torres P.J., Siakowska M., Banaszewska B., Pawelczyk L., Duleba A.J., Kelley S.T., Thackray V.G. Gut microbial diversity in women with polycystic ovary syndrome correlates with hyperandrogenism. *The Journal of Clnical Endocrinology & Metabolism.*2018; 103 (4): 1502-1511.

2. Azziz R., Woods K. S., Reyna R., Key T. J., Knochenhauer E. S., Yildiz B. O. The prevalence and features of the polycystic ovary syndrome in an unselected population. *The Journal of Clinical Endocrinology & Metabolism*. 2004;89(6):2745–2749. doi: 10.1210/jc.2003-032046.
3. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004 Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 81:19–25.
4. Goodman N.F. et al. American Association of Clnical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society Disease State Clinical Review: Guide to the Best Pactices in the Evaluation and Treatment of Polycystic Ovary Syndrome – Part 1. Endocrine Practice 2015;21(11):1291-1300.
5. Legro R.S., Pauli J.G., Kunselman A.R., Meadows J.W., Kesner J.S., Zaino R.J., Demers L. M., Gnatuk C.L., Dodson W.C. Effects of Continuous *versus* Cyclical Oral Contraception: A Randomized Controlled Trial. *The Journal of Clinical Endocrinology & Metabolism*. 2008;93 (2):420-429.
6. Mendoza N, Simoncini T, Genazzani A. Hormonal contraceptive choice for women with PCOS: a systematic review of randomized trials and observational studies. *Gynecological Endocrinology*. 2014; 30(12): 850-860.
7. Roe AH, Dokras A. The Diagnosis of Polycystic Ovary Syndrome in Adolescents. *Reviews in Obstetrics and Gynecology*. 2011;4(2):45-51.
8. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clinical Epidemiology*. 2014;6:1-13. doi:10.2147/CLEP.S37559.
9. Legro et al. Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology & Metabolism*, 2013; 98(12): 4565–4592.
10. Rucchoft E.A., Elkind-Hirsch K.E., Malinak R. Pituitary function is altered during the same cycle in women with polycystic ovary syndrome treated with continuous or cyclic oral contraceptives or a gonadotropin-releasing hormone agonist. Fertil Steril. 1996;66:54-60.

8.0 Drugs and Devices

8.1 * DRUGS AND/OR BIOLOGICS: Are you STUDYING any drugs and/or biologics that are either approved or unapproved: (REQUIRED)

(•) Yes ( ) No

8.2 LIST THE DRUGS OR BIOLOGICS: List the drugs or biologics that will be studied. In the drug details screen you will be asked questions such as:

- **Whether the drug or biologic is FDA approved**
- **If the drug or biologic will be provided at no cost**
- **If an IND is necessary, the IND number, and who holds the IND**
- **If the drug or biologic is FDA approved and an IND is not required, the rationale for the decision**
- **If the Investigational Drug Service (IDS) is dispensing the drug or biologic (required unless a waiver is obtained from the IDS)**

Please see the UCSF IRB website for more details about the use of drugs and biologics in research, including the IND Decision Worksheet. Verification of IND numbers: If the sponsor's protocol does not list the IND number, you must submit documentation from the sponsor or FDA identifying the IND number for this study. Attach this documentation in the Other Study Documents section of the Initial Review Submission Packet. If you have any correspondence from the FDA or sponsor regarding this drug or biologic, please attach it to the application.

View Details	Drug Name		FDA Approved	A new drug or a new use of an already approved drug:	IND Number
	Trade Drug Name:	YASMIN			
	Generic Drug	DROSPIRENONE; ETHINYL	Yes	No	

⊟	**Name:** ESTRADIOL **Investigational Drug Name:**		

Trade Drug Name:	YASMIN
Generic Drug Name:	DROSPIRENONE; ETHINYL ESTRADIOL
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Bayer HealthCare Pharmaceuticals Inc.
Is the drug supplied at no cost?	No
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	

8.3 * MEDICAL DEVICES: Are you STUDYING any medical devices, in vitro diagnostics, or assays that are either approved or unapproved:(REQUIRED)

○ Yes ◉ No

8.6 * Is this an expanded access or compassionate use protocol, meaning the primary purpose is to diagnose, monitor or treat a patient's condition, rather than the collection of safety and efficacy data of the experimental agent: (REQUIRED)

○ Yes ◉ No

9.0 Sample Size and Eligibility Criteria

9.1 ENROLLMENT TARGET: How many people will you enroll:

60

If there are multiple participant groups, indicate how many people will be in each group:

As this is a pilot study we expect to enroll 30 participants into the cyclical OCP group and another 30 participants into the continuous 6 month OCP group with a total of sample size of 60.

9.3 SAMPLE SIZE JUSTIFICATION: Explain how and why the number of people was chosen. For multi-site studies, this is referring to the number that will be enrolled across all sites:

Since this is a feasibility or pilot study we expect to enroll 30 patients in each treatment arm for a total of 60 participants. Typically 7-9 new patients are seen in the PCOS Multidisciplinary clinic each month, however, due to COVID-19 there were restrictions on the number of individuals seen down to roughly 5-6 new patients are seen in the PCOS Multidisciplinary clinic each month. Now, there are new patients seen each month again. Given the protracted recruitment, any patient on chart review presenting to the Center for Reproductive Health with a complaint of PCOS seeking treatment, will also be considered for the study. **Additionally, all patients who met PCOS criteria in the last 2-10 years and present for a PCOS reassessment will be eligible for enrollment.** Assuming 2-3 outpatients seen in Multidisciplinary clinic and an additional 2-3 outpatients seen at the Center for Reproductive Health will meet criteria to participate in the study and will consent each month, we expect to reach our goal of at least 60 study subjects within the next 6 months.

9.4 * PARTICIPANT AGE RANGE: Eligible age ranges: (REQUIRED)

- [ ] 0-6 years
- [ ] 7-12 years
- [x] 13-17 years
- [x] 18-64 years
- [ ] 65+

9.5 * STUDY POPULATIONS: Data will be collected from or about the following types of people (check all that apply): (REQUIRED)

- [ ] Inpatients
- [x] Outpatients
- [ ] Family members or caregivers
- [ ] Providers
- [ ] People who have a condition but who are not being seen as patients
- [ ] Healthy volunteers
- [ ] Students
- [ ] Staff of UCSF or affiliated institutions
- [ ] None of the above

9.6 * SPECIAL SUBJECT GROUPS: Check the populations that may be enrolled: (REQUIRED)

- [x] Children / Minors
- [ ] Subjects unable to consent for themselves
- [ ] Subjects unable to consent for themselves (emergency setting)
- [ ] Subjects with diminished capacity to consent
- [x] Subjects unable to read, speak or understand English
- [ ] Pregnant women
- [ ] Fetuses
- [ ] Neonates
- [ ] Prisoners

☐ Economically or educationally disadvantaged persons
☐ None of the above

If not already addressed in the Background and Significance questions in the Research Plan section or elsewhere, explain why it is appropriate to include the types of subjects checked above in this particular study:

This is both a pediatric and adult study on females with PCOS. Adolescent females with PCOS will be included in the study as they are an equally affected population as are adult females, that utilize treatment with oral contraceptive pills. Subjects who are non English speaking may also benefit from therapy and should be included in this study when applicable. In this population consent will be obtained using an interpreter.

Describe the additional safeguards that have been included in the study to protect the rights and welfare of these subjects and minimize coercion or undue influence:

Here are some examples:

- evaluating capacity to consent for individuals who may be decisionally impaired (specify how)
- calibrating payment amounts to be non-coercive for the financially disadvantaged
- conducting more in-depth evaluations of subjects' understanding of the study and the voluntary nature of participation
- involving advocates in the consent process

More information and other safeguards are described here: **Vulnerable Subject Populations** and **Recruiting Staff and Students**.

To minimize coercion or undue influence, parental informed consent will be needed in patients who are younger than 18 years of age as well as assent from the participant if she chooses to participate in the study. For participants who are non english speaking, consent will be obtained using an interpreter who can go through the details of the study and consent form with the patient.

9.7 INCLUSION CRITERIA: Briefly describe the population(s) that will be involved in this study. Include anyone that data will be collected from or about (e.g. patients, healthy controls, caregivers, providers, administrators, students, parents, family members, etc.):

To be included in this study, participants must be:

1. Female, within 15-40 years of age

2. Diagnosed with Polycystic Ovary Syndrome based on the 2003 Rotterdam Criteria (must meet 2 out of 3 criteria):

a) Evidence of either biochemical or clinical hyperandrogenism (elevated free and or total Testosterone level above the normal reference range for assay, and/or a modified Ferriman-Gallwey Hirsutism score >/=5)

b) Oligo- or anovulation

c) Polycystic ovary morphology on ultrasound

3. Adolescents should be at least 2 years out from menarche (first menstrual period).

9.8 EXCLUSION CRITERIA: List any exclusion criteria (e.g. reasons why someone would not be included in the study):

1. Females with PCOS who are already on and currently using a form of contraceptive (oral, vaginal ring, or patch) will be excluded from the study as this will impact the study results and outcomes. **IUD has been removed as an exclusion criteria since we would not expect the Paragard (Copper) IUD to affect hormone profile and LNG IUD releases localized hormone and is thus without systemic effects.**

2. Females that are concurrently using or plan to use an antiandrogenic medication such as Spironolactone in the next 6 months.

3. Females currently or are planning to obtain permanent hair removal (ex. laser hair removal, electrolysis) in the concurrent 6 months of starting oral contraceptive (OCP) therapy will also be excluded from the study, as this is one of our secondary outcome measures (looking at cutaneous findings of hyperandrogenism) and will affect our results.

4. Women who are pregnant or have a contraindication for starting an OCP, including active smokers, history of clotting disorders, history of deep vein thrombosis or blood clots, neoplasia, vascular disease, migraines with aura, hypertension, or have renal/hepatic disease will be excluded from the study as OCP therapy would not be indicated or approved in this population.

5. Women with hyperkalemia (elevated potassium levels above the normal reference range for age) or history of blood clots will be excluded as this could pose added risk to a participant on this particular OCP therapy.

9.9 * RESEARCH CONDUCTED ON PATIENT CARE WARDS: Do any study activities take place on patient care units at UCSF medical facilities: (REQUIRED)

○ Yes ◉ No

10.0 Inclusion of Minors in Research

10.1 REGULATORY CATEGORIES OF RESEARCH: Select all the regulatory categories that apply:

- ☐ No greater than minimal risk (45 CFR 46.404, 21 CFR 50.51)
- ☑ Greater than minimal risk but presenting prospect of direct benefit (45 CFR 46.405, 21 CFR 50.52)
- ☐ Greater than minimal risk (though only a minor increase over minimal risk) and no prospect of direct benefit but likely to yield generalizable knowledge about the subjects disorder or condition (45 CFR 46.406, 21 CFR 50.53)
- ☐ Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407, 21 CFR 50.54)

Explain why the research in this study falls under the above category or categories:

Combined oral contraceptive pills (OCPs) are the mainstay of treatment in female minors with Polycystic Ovary Syndrome as they prevent the risk of endometrial carcinoma that can develop with prolonged anovulation. Both cyclical (monthly pill packs) and using OCPs continuously for several month on end are readily used for management of anovulation and thus as long as individuals with PCOS do not have a contraindication to starting this medication (such as active smokers, history of clotting disorders or blood clots, neoplasia, vascular disease, migraines, hypertension, or have renal/hepatic disease) they will receive the standard of care with a combined hormonal contraceptive (with both an estrogen and progestin component).

10.2

MINORS CONSENTING: Will this study enroll minors who can legally consent for themselves (as in the case of emancipated minors or minors being treated for pregnancy or drug use without their parents knowing). This is different from agreeing to be in the study even when their parents are the ones providing 'official' consent, which we refer to as 'providing assent':

Note: This is very rare and the answer is usually 'No.'

○ Yes ◉ No

10.3 PARENTAL PERMISSION VS. WAIVER: Please review the guidance to see under what circumstances the IRB can waive parental permission.

- ☑ Parental permission will be obtained
- ☐ Waiver of parental permission is requested: The waiver meets the provisions for a waiver of consent (i.e., the research poses minimal risk, it could not practicably be carried out without the waiver of parental permission, AND the waiver will not adversely affect the rights and welfare of the minor participants (45 CFR 46.116(d))
- ☐ Waiver of parental permission is requested: Parental permission is not a reasonable requirement to protect the minor (e.g. neglected or abused children) or parental knowledge of the study may endanger the health or welfare of the minor (45 CRF 46.408(c))

Provide details on the other protections that will be in place:

10.4 ASSENT OF MINORS OR WAIVER: Please review the guidance to see under what circumstances the IRB can waive assent.

- ☑ Assent of children developmentally and psychologically able to provide assent will be obtained
- ☐ Waiver of assent is requested: The capability of some or all of the children is so limited that they cannot reasonably be consulted
- ☐ Waiver of assent is requested: The research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research
- ☐ Waiver of assent is requested: The activities involving the minor are limited to chart review or the something equally innocuous
- ☐ Waiver of assent is requested: It is not culturally appropriate to involve the minor in the decision to participate (e.g. some foreign research)

10.5 DOCUMENTATION OF PERMISSION AND ASSENT: (select all that will be used):

- ☑ Permission form addressed to the parents
- ☐ Simplified assent form addressed to the child, 7-12 years old (parents get separate form)
- ☑ Assent form addressed to the child, 13 years and older (for subjects and parents)
- ☐ Assent form addressed to the child, 13 years and older (parents get separate form)

Check one:

- ◉ One parent's signature will be obtained
- ○ Two parents' signatures will be obtained

If this study is approvable under regulatory category .405 and you plan to get permission from only one parent, explain why you think one parent's permission is sufficient:

As this study will involve late adolescent teenagers, to participate in a minimal risk study with direct benefit to the participant, one parent or legal guardian's signature may be sufficient. We will also obtain assent from the minor as well on the same consent form. Furthermore it is likely that participants approached about the study will be present with one parent in clinic.

10.6 WARDS OF THE STATE: Might this study enroll wards of the state:

○ Yes ◉ No

11.0 Recruitment and Consent

11.1 * RECRUITMENT METHODS: What kinds of methods will be used to identify potential participants for recruitment (check all that apply): (REQUIRED)

- [x] Medical records review
- [x] Recruitment registry
- [ ] Re-contact of participants from the investigators' previous studies
- [x] Referrals from colleagues (attach the 'Dear Colleague' letter or other recruitment materials you will provide to colleagues)
- [x] Referrals from the community / word of mouth
- [x] Advertisements (flyers, brochures, radio or t.v. ads, posting on clinical research sites or social media, presentation of the study at community events/media, etc.)
- [ ] Online recruiting tool such as TrialSpark
- [ ] CTSI Recruitment Services unit
- [ ] Other method (describe below)

Attach your recruitment materials (e.g., flyers, ads, recruitment letter templates, email text, etc.) in the Other Study Documents section of the Initial Review Submission Packet Form.

* Provide the name of the recruitment registry. If approved in iRIS, provide the Study Number: **(REQUIRED)**

Former UCSF patients found to meet criteria for PCOS and seen at the UCSF Multidisciplinary Clinic in the prior 2-10 years will also be identified as potential participants for recruitment.

11.2 * SEARCHING OF MEDICAL RECORDS: (REQUIRED)

Whose patients are they:

- [x] Investigators' own patients or patients seen within the same practice
- [ ] Patients not under the care of the investigators

How and by whom will records be accessed and searched (check all that apply):

- [x] Self-search in APeX or other medical records source
- [ ] Self-search using UCSF's Research Cohort Selection Tool
- [ ] CTSI Consultation Service Recruitment Services
- [ ] UCSF Academic Research Services (ARS)
- [ ] University of California Research Exchange (UC ReX)
- [x] Other method (describe below)

Describe the other ways medical records may be accessed and searched to identify prospective participants:

The REDCap database will also be utilized aside from accessing the participant's medical records. Prior to enrollment in this study, all patients who are seen at the UCSF PCOS Multidisciplinary clinic in Mission Bay or at the UCSF Center for Reproductive Health with a complaint of PCOS complete an online survey and questionnaire which includes concerns about hair growth, weight, eating, body shape and a psychological assessment. The study investigator will review both the EMR records and REDCap survey for each potential participant who may meet eligibility requirements for the study prior to their initial clinic visit.

11.3 DETERMINATION OF ELIGIBILITY: How, when, and by whom will eligibility for recruitment be determined:

New referrals to the PCOS Multidisciplinary clinic or the Center for Reproductive Health with a concern for PCOS will be screened by the study team or clinical investigator just prior to their initial clinic visit by reviewing their EMR (APeX) chart and REDCap pre-clinic surveys. A screening form (attached to this IRB) will be used to see if the patient meets eligibility criteria to be included in the study and will be completed by either the clinical research coordinator or clinical investigator either at the patient's initial referral visit or second visit, when they come for routine follow up. After the patient has been seen in clinic, diagnosed with PCOS, and meets eligibility requirements will we approach the patient about our study and obtain informed consent if interested.

11.4 * INITIATION OF CONTACT: Who initiates contact (check all that apply): (REQUIRED)

- [x] Investigators/study team
- [ ] UCSF recruitment unit (e.g. CTSI Consultation Services)
- [ ] Potential participant
- [ ] Other (explain below)

11.5 * HOW IS CONTACT INITIATED: (check all that apply): (REQUIRED)

- [x] In person
- [x] Phone
- [x] Letter / email
- [ ] Website or app
- [ ] Other (explain below)

Attach the telephone recruitment script in the Other Study Documents section of the Initial Review Submission Packet Form. If potential participants will initiate contact, attach the telephone screening script that will be used to provide more information about the study and determine if callers are eligible to participate.

Attach the recruitment letter or email template in the Other Study Documents section of the Initial Review Submission Packet Form.

11.6 RECRUITMENT PLAN: Based on the checkboxes you chose above, please provide a narrative describing your recruitment plan. We want to know:

- **Who is conducting the search for potential participants, and how?**
- **How are potential subjects being approached for recruitment? By whom, and when?**

If there will be more than one participant group (e.g. patients, healthy controls, caregivers, family members, providers, etc.), provide details about the recruitment plans for each group. (Recommended length - 100-250 words)

All new referrals sent to the UCSF PCOS Multidisciplinary clinic will be screened prior to their clinic visit by the clinical investigator(s), by reviewing APeX medical charts and REDCap database pre-clinic surveys that are routinely sent to patients prior to their first visit. There are 2 days each month in which the PCOS clinic sees new patients. Typically, at the first visit patients are evaluated by several multidisciplinary providers who come together at the end of the clinic day to discuss if the patient 1) meets criteria for the diagnosis of PCOS and 2) what medications or interventions they should be started on. At the second clinic visit, the same patients from earlier in the month are seen again for follow up to discuss the results of the previous visit and whether they will need to start any medication(s) or other therapeutic interventions.

All patients presenting for a PCOS re-evaluation will complete the same REDCap database pre-clinic surveys and routine labs as they would if they were presenting to the UCSF PCOS Multidisciplinary clinic. When they present for a reassessment, they will be seen for one visit in which they undergo the usual history and physical asssessment. At the end of this evaluation, the patient will learn if they still meet criteria for PCOS and the medications or interventions they should be started on.

In terms of recruitment, the investigator(s) and/or clinical research coordinator will approach potential patients during their first or second clinic visit to discuss the study details, assess the patient's interest in research and possibility of enrollment. A screening form will be filled out by the clinical investigator and/or clinical research coordinator that determines whether the patient meets criteria to participate in the study. Consent forms will be provided to patients if interested as well as a sheet highlighting the important details of the study which the clinical research coordinator or clinical investigator will review with the patient prior to signing. Once consent has been obtained and if the patient meets criteria (which can only take place at the second clinic visit), will they be randomized to either of two treatment groups (monthly or 6 month OCP therapy) and can be started on their medication thereafter.

In addition to the above recruitment plan, a letter/email may be sent out to community physicians and/or colleagues at UCSF who may be providers of patients with PCOS (see study flyer). This email will give some details about the PCOS Multidisciplinary Clinic and when to refer but also provide a brief outline of the CCOUP study, the types of participants we are trying to recruit and general eligibility requirement in case they are interested in referring. Outside physicians can then decide whether to refer to our clinic a potential participant on their own, but the actual process of screening to see if a patient is eligibile to enroll will only occur once they are referred to the PCOS clinic (to be seen by either Dr. Huddleston or Dr. Cedars). We will also provide flyers for patients with similar information which providers can give to assess their interest in the study.

As the CCOUP study is listed on ClinicalTrials.gov, potential participants and physicians alike can also reach out to the PI or co-investigators separately regarding further information about the study via email or phone listed online. Patients and physicians would then be given instructions that if they would like to participate they need a referral placed to the Multidisciplinary PCOS clinic so that they or their patients can be screened before recruitment.

11.7 * CONSENT METHODS: How will permission to participate (i.e., informed consent) be obtained from each potential participant. If there will be multiple groups and different plans for consenting each, check all that apply. See the orange Help bubble to the right for more detailed guidance. Participants will (check all that apply): (REQUIRED)

- [x] Sign a consent form at the end of the consent discussion (signed consent)
- [ ] Provide online 'eConsent' using DocuSign or another E-Signature system
- [ ] Click through a link in a survey or email after reading about the study and then complete the study online (electronic consent)
- [ ] Be told about the study and be given a handout/information sheet and be asked if they agree to participate (verbal consent)
- [ ] Complete the study activities and turn in materials, as in the case of a completed survey that is placed in a drop box or mailed to the study team (implied consent)
- [ ] Not be able to provide consent and will have a family member consent for them, as in the case of a critically ill or unconscious patient (surrogate consent)

- [ ] Not be able to provide consent (emergency waiver of consent - allowed for minimal risk research or greater than minimal risk research with an approved community consultation plan)
- [ ] Not know about the study, as in the case of chart reviews or observations of public behavior (waiver of consent)
- [ ] Other method (describe below)

Attach your consent form, information sheet, or electronic consent text in the Informed Consent Documents section of the Initial Review Submission Packet Form.

11.8 * CONSENT PROCESS: Describe the process for obtaining informed consent, including details such as who will have the consent discussion and when participants will be asked to sign the consent form in relation to finding out about the study: (REQUIRED) We encourage researchers to review our guidance on obtaining and documenting informed consent.

- **If there are multiple groups being consented differently, provide details about the consent process for each group.**
- **If you are relying on verbal or implied consent, provide details about how that will happen.**
- **For studies using online recruitment and consent or consent via mail, provide details here.**

A member of the study team or clinical investigator will sit down with potential participants who are seen at the **UCSF PCOS Multidisciplinary clinic, seen for a reassessment as an established patient, or seen through the Center for Reproductive Health clinic** to discuss details of the study and be given a consent form if interested. This will either occur during the patient's first or second clinic visit in the month that they are seen as a new patient. An informed consent form will be given to each potential participant and/or parent (in the case that the participant is < 18 years old) detailing the significance of the study, length of study, methods, randomization process, as well as risks and benefits. Assessment of the subject's and/or parental comprehension will be done prior to the participant signing the consent form. In the event that the subject is a minor, a parental guardian will need to give signed consent and child will need to give assent for her to participate. At the time of obtaining consent or at the 2nd clinic visit, participants will be evaluated to see if they meet criteria and have no exclusion criteria using the CCOUP Study Screening Form. Recruitment and informed consent will be done in person to ensure full comprehension and thereafter discuss with providers which treatment arm the participant has been randomized into. For individuals who are non-English speaking, consent will be obtained with an interpreter present.

* It is important that the people obtaining consent are qualified to do so. Briefly describe the training and experience these individuals have in obtaining informed consent: **(REQUIRED)**

The study investigator or research coordinator will obtain consent. The study investigator has obtained training through the Responsible Conduct of Research course through the UCSF TICR Summer Clinical Research Workshop and has completed CITI training. The research coordinator has also completed CITI training as well.

11.9 * CONSENT COMPREHENSION: Indicate how the study team will assess and enhance the subjects' understanding of study procedures, risks, and benefits prior to signing the consent form (check all that apply): (REQUIRED) Tip: Review the Consent Comprehension - Learning Notes in the Help bubble at the right for specific questions that can be asked to assess comprehension, consider using the UCSF Decision-Making Capacity Assesment Tool, and review our guidance on obtaining written or verbal informed consent for more detail on how to conduct the assessment.

- [x] The study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study or the experimental treatment, the risks and benefits of participating, and the voluntary nature of participation
- [x] Potential participants will be asked or shown a series of questions to assess their understanding of the study purpose, procedures, risks and benefits, as well as the voluntary nature of participation (especially appropriate when the consent process happens online or

through a mobile health app)

☐ Other method (describe below):

Provide details of the other approaches that will be used, if using another method to assess comprehension:

The study team will assess each subject's comprehension of the trial by asking a series of questions regarding the study's purpose, study design, risks, and benefits as well as participant rights. Also, a handout will be provided to patients that are interested in enrolling, which highlights by bullet point important details regarding the study (CCOUP Study Recruitment Materials).

11.11 * NON-ENGLISH CONSENT METHOD: Indicate which method(s) you will use to consent non-English speaking subjects: (REQUIRED)

☐ Preferred Method—Consent form and other study documents will be available in the subject's primary language Personnel able to discuss participation in the patient's language will be present for the consent process.

☑ Short-Form—A qualified interpreter will translate the consent form verbally, and subjects will be given the Experimental Subject's Bill of Rights in their primary language, following instructions in Those Who do not Read, Speak or Understand English for required witnessing and signatures

* Explain how you will maintain the ability to communicate with non-English speakers throughout their participation in the study: **(REQUIRED)**

Throughout the study, subjects and/or their parents (in the case of adolescents under 18 years of age) who are non-English speakers will be addressed with an interpreter to ensure that they understand all recommendations and requirements of participating in the study. A phone interpreter will be used for scheduling follow up visits, blood draws. Questionnaires are in English, but can be done using an interpreter at the time of a study visit or over the phone with the help the study investigator and an interpreter.

11.13 TIME: What is the estimated time commitment for participants (per visit and in total):

Each participant will be followed over the course of the study for 6 months but can withdraw at any time. The estimated time commitment for each participant per clinic visit is roughly 30 minutes to 1 hour, which may either be a routine follow up visit meeting with a physician and/or a physical exam/pelvic exam. Additionally, we expect there will be some time commitment needed by each participant for blood draws when going to their local Quest Diagnostics lab. We will recommend participants call ahead and schedule a time to go to the lab so that they do not have a long wait time. In total, the estimated time commitment for participants that involves clinic study visits and getting blood work done is roughly 5 hours or less over the course of 6 months.

IMPORTANT TIP: Ensure this information is consistent with the information provided in the consent form.

11.14 ALTERNATIVES: Is there a standard of care (SOC) or usual care that would be offered to prospective participants at UCSF (or the study site) if they did not participate in this research study:

◉ Yes ○ No

Describe the care that patients would ordinarily receive at the medical center if they did not participate in this study (provide details, assuming that some of the IRB members are not specialists in this field):

Patients who do not wish to participate in this study will be provided with standard of care therapy based on their medical needs. This could include but is not limited to the following: starting an OCP of the same or different brand as the study, an IUD, placement of a vaginal ring and/or starting an anti-androgen medication such as Spironolactone.

11.15 OFF-STUDY TREATMENT: Is the study drug or treatment available off-study:

- (•) Yes
- ( ) No
- ( ) Not applicable

12.0 Waiver of Consent/Authorization for Recruitment Purposes

This section is required when medical records may be reviewed to determine eligibility for recruitment.

12.1 * PRACTICABILITY OF OBTAINING CONSENT PRIOR TO ACCESS: Study personnel need to access protected health information (PHI) during the recruitment process and it is not practicable to obtain informed consent until potential subjects have been identified: (REQUIRED)

- (•) Yes

If **no**, a waiver of consent/authorization is NOT needed.

12.2 * RISK TO PRIVACY: A waiver for screening of health records to identify potential subjects poses no more than minimal risk to privacy for participants:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

12.3 * RIGHTS/WELFARE: Screening health records prior to obtaining consent will not adversely affect subjects' rights and welfare:

- (•) Yes

If **no**, a waiver of authorization can NOT be granted.

12.4 * IDENTIFIERS: Check all the identifiers that will be collected prior to obtaining informed consent:

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [ ] Fax numbers
- [x] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers

- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

Note: HIPAA rules require that you collect the minimum necessary.

12.5 * HEALTH INFORMATION: Describe any health information that will be collected prior to obtaining informed consent:

Information about potential participants including age, whether or not they meet criteria for PCOS and hyperandrogenism, as well as blood test review (which may include total and free Testosterone, estradiol, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), insulin, hemoglobin A1c, fasting serum glucose, lipid panel, and sex hormone binding globulin levels), as well as medication history if available will be collected prior to obtaining informed consent.

Note: HIPAA requires that you collect the minimum necessary.

12.6 * DATA RETENTION/DESTRUCTION PLAN: Describe your plan to destroy any identifiable data collected to determine eligibility for recruitment. This should be done at the earliest opportunity. If you plan to retain identifiable recruitment data, provide the justification for doing so:

Any paperwork with identifiable data regarding potential participants in the study used to determine eligibility will be destroyed using the secured shredder boxes located in clinic immediately after the patient's second clinic visit (as after this time point patients will have either consented to the study or not).

All baseline blood work is typically done prior to clinic visit and so no blood samples will be collected or stored in the clinic for this study or recruitment purposes. Recruitment data for the study (questionnaires, blood work, pelvic ultrasound findings and modified Ferriman-Gallwey scores) are all stored on REDCap on a secured network. Any information with identifiable information that is obtained on paper will be inputted into REDCap and copies destroyed thereafter.

13.0 Risks and Benefits

13.1 RESEARCH-RELATED RISKS: Check if your study involves any of these specific research-related risks to participants that may need to be disclosed in the consent form:

- [ ] For interventional studies, risk that the regimen may be more harmful or less effective than other available interventions
- [ ] Risks associated with radiation exposure for imaging studies specifically for research purposes
- [ ] Risks associated with the administration of contrast agent for imaging studies
- [ ] Risks associated with withholding of treatment or discontinuation of current treatment (e.g., washout period is required by the study protocol)
- [ ] For randomized, placebo-controlled trials, possible temporary or permanent health consequences from the deprivation of effective therapies during the placebo administration period
- [ ] For studies involving a sham surgical procedure, the risk that participants may experience increased morbidity without the possibility of benefit
- [ ] Risks associated with modification or extension of a surgical procedure primarily for research purposes (e.g. risks associated with prolonging anesthesia, time in the operating room, etc.)
- [x] Risk of pain or physical discomfort caused by the research intervention

☑ Possible personal discomfort due to sensitive topics (stress, embarassment, trauma)

13.2 RISKS: Describe any anticipated risks and discomforts not listed above:

Aside from the above mentioned risks, participants may be at risk for any of the number of adverse side effects that are seen with OCP therapy (listed below).

Likely side effects: Premenstrual syndrome (13.2%), headache/migraine (10.7%), breast pain /tenderness/discomfort (8.3%), nausea/vomiting (4.5%), abdominal pain/tenderness/discomfort (2.3%), mood changes (2.3%).

Less likely side effects: Gallbladder disease, hypertension, hepatic adenomas, elevation in lipid levels

Rare but serious side effects: Venous thromboembolism (risk is greatest during the first year of use and less than the risk associated with pregnancy), hepatocellular carcinoma. Women over 35 years of age who smoke have an increased risk of serious cardiovascular events from OCP use including heart attack, blood clots or stroke.

Side effects specific to Yasmin: There may be a slight increase incidence of Deep Vein Thrombosis (a very rare side effect of all OCPs) for Yasmin as compared to some other OCPs.

Randomization risks: Subjects will be assigned to a treatment program by chance, and the treatment the subject receives may prove to be less effective or to have more side effects than the other study treatment or other available treatments. Subjects assigned to the continuous OCP treatment group are likely to have more irregular bleeding than those randomized to cyclical use.

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, infection and fainting.

Pelvic Ultrasound risks: There can be some discomfort and or pressure experienced with the pelvic ultrasound as this is done transvaginally.

Questionnaires: Several of the questionnaires ask detailed questions regarding the participants mental health (anxiety, depression), and quality of life regarding the diagnosis of PCOS and how it may or may not cause some distress or discomfort. If a subject is identified to be at risk or currently reporting suicidality, following the study protocol, the investigator as well as a dedicated psychologist will be notified and will determine if that patient should be placed on a secured medical hold (likely taken to an Emergency Room for further evaluation). Details of the protocol are located in the CCOUP Study Suicide Ideation Protocol.

13.3 MINIMIZING RISKS: Describe the steps you have taken to minimize the risks/discomforts to subjects. Examples include:

- **designing the study to make use of procedures involving less risk when appropriate**
- **minimizing study procedures by taking advantage of clinical procedures conducted on the study participants**
- **mitigating risks by planning special monitoring or conducting supportive interventions for the study**
- **having a plan for evaluation and possible referral of subjects who report suicidal ideation**

As we do not anticipate significant changes in hormone levels each month, we have limited blood draws to 1 month, 3 months and 6 months post start of OCP therapy; thereby reducing procedures that may cause distress and or pain to the participant. While there are a number of adverse side effects associated with OCP therapy (Yasmin) this is the same as what would be expected if they were not in the study and started on the medication for management of anovulation or contraception in PCOS. If an adverse reaction were to take place, procedures will

be set in place for participants to contact the study team and determine if this was in fact related to the medication. In the event that there is a true drug reaction, we would immediately stop the patient from continuing this mediation.

13.4 RESOURCES: Describe the resources in place to conduct this study in a way that assures protection of the rights and welfare of participants: These resources typically include appropriately trained and qualified personnel (in terms availability, number, expertise and experience), funding, space, equipment, and time to devote to study activities. Depending on the nature of the research study, investigators should consider the proximity or availability of critical resources that may be essential to the safety and welfare of participants, such as

- **the proximity of an emergency facility for care of participant injury**
- **availability of psychological support after participation**
- **resources for participant communication, such as language translation services**

Information will be provided in the consent forms that includes contact information for participants to call in if they have questions regarding the study or their rights.

13.5 * BENEFITS: (REQUIRED) Note: These are the benefits that the IRB will consider during their review. They are not necessarily appropriate to include in the consent form.

Possible immediate and/or direct benefits to participants and society at large (check all that apply):

- [x] Positive health outcome (e.g. improvement of condition, relief of pain, increased mobility, etc.)
- [x] Closer follow-up than standard care may lead to improved outcomes or patient engagement
- [ ] Health and lifestyle changes may occur as a result of participation
- [x] Knowledge may be gained about their health and health conditions
- [x] Feeling of contribution to knowledge in the health or social sciences field
- [x] The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- [ ] Other benefit (describe below)
- [ ] None

13.6 RISK TO BENEFIT RATIO: Explain why the risks to subjects are reasonable in relation to anticipated benefits, if any, to the participant or society:

Participants in this study will be provided with current standard of care therapy for PCOS. The only difference is that they may have more frequent blood draws to check hormone levels and will have a re-evaluation of the hirsutism and ovarian morphology at the end of the study.

14.0 Data and Safety Monitoring Plan

14.2 * DATA AND SAFETY MONITORING PLAN: (REQUIRED)

All greater than minimal risk studies are required to provide a plan. Lack of an adequate plan is one of the most common reasons why IRB approval is delayed.

Instructions:

Describe the plan for monitoring data quality and participant safety. Key areas that should be included in the plan are:

- An explanation of the plan to monitor data collection, study progress, and safety
- A description of who will perform the monitoring and at what frequency (e.g., the PI only, a contract research organization, a Data and Safety Monitoring Board or Data Monitoring Committee, etc.)
- The type of data and events that will be reviewed (e.g., adverse events, breaches of confidentiality, unanticipated problems involving risk to participants or others, unblinded efficacy data, etc.)
- Procedures and timeline for communicating monitoring results to the UCSF IRB, the study sponsor, and other appropriate entities
- Assurance that the research team will adhere to the **UCSF IRB reporting requirements**

As appropriate:

- A plan for conducting and reporting interim analysis
- Clearly defined stopping rules
- Clearly defined rules for withdrawing participants from study interventions

Internal (on-site) Adverse Events: These will be monitored by the PI who will determine whether a definite, probable or possible related AND serious or unexpected event has occurred. If an event has occurred it will be reported within 5 working days of PI's awareness or immediately (in the event of related deaths or life-threatening events) using the iRIS Adverse Event Reporting Form.

Monitoring of data collection and study progress: This will be performed by the study investigator along with the PI every 2 weeks with a chart review of the current enrolled participants to ensure labs, questionnaires and procedures have been done in a timely manner in accordance to the protocol, there are no breaches of confidentiality or unanticipated problems involving risk to participants or others if an adverse event has occurred.

Trial Stopping Rules: In the event that a rare but serious side effect such as a thromboembolism or hepatocellular carcinoma occurs within multiple subjects within a study group, the PI will investigate this adverse event (AE) to determine the safety of continuing the trial further. As this pilot study will be recruiting individuals over a long period of time, the PI and investigators will meet to discuss on an on-going basis patient AE to determine if there is a need to stopping the trial due to patient safety concerns.

A suicidal ideation and depression protocol has also been set in place in case a patient is found to have answered Question 9 of the BDI-II surveys with a score greater than zero or a total score over 19. The protocol details specific steps that need to be taken immediately including contacting Dr. Pasch and following up with the patient immediately. Details of the protocol have been attached to this application as a separate document.

14.3 * DATA AND SAFETY MONITORING BOARD (DSMB): Will a Data and Safety Monitoring Board (DSMB) be established: (REQUIRED)

- ○ Yes
- ◉ No

Guidelines

A Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) is a formal, independent committee that is specifically established to conduct interim monitoring, oversight and analysis of study information and data to assure the continuing safety, efficacy, appropriateness, relevance,

and integrity of the study.

The UCSF IRB reserves the right to request a DSMB/DMC for any study. However, the following are factors that the IRB will consider when making this determination:

- There is a significant likelihood of a serious adverse event to subjects
- The study is conducted at multiple sites and the level of risk is greater than minimal
- The study generates data that are blinded or randomized
- The study involves a large number of patients randomized to one of two or more interventions
- A study for which the performance of an interim analysis is crucial for the protection of the subjects
- First use in humans
- First use in children
- The study involves gene transfer, stem cell therapy, or other novel interventions for which long-term outcome data are not known or available

15.0 Confidentiality, Privacy, and Data Security

15.1 PROTECTING PRIVACY: Indicate how subject privacy will be protected:

- [x] Conduct conversations about the research in a private room
- [x] Ask the subject how they wish to be communicated with – what phone numbers can be called, can messages be left, can they receive mail about the study at home, etc.
- [x] Take special measures to ensure that data collected about sensitive issues do not get added to their medical records or shared with others without the subject's permission
- [ ] Other methods (describe below)

15.2 SENSITIVE DATA: Do any of the instruments ask about illegal or stigmatized behavior:

(•) Yes ( ) No

IMPORTANT NOTE: Indicate in the consent form what kinds of sensitive information will be collected.

15.3 CONSEQUENCES OF A LOSS OF PRIVACY OR CONFIDENTIALITY: Could a breach of privacy or confidentiality result in any significant consequences to participants, such as criminal or civil liability, loss of state or federal benefits, or be damaging to the participant's financial standing, employability, or reputation:

( ) Yes (•) No

15.4 EXTRA CONFIDENTIALITY MEASURES: Explain any extra steps that will be taken to assure confidentiality and protect identifiable information from improper use and disclosure, if any:

Study ID #s will be created for each participant as an extra confidentiality measure, as it is an extra layer of protection for participants and does not link any PHI to the study data.

15.5 * REPORTABILITY: Do you anticipate that this study may collect information that State or Federal law requires to be reported to other officials, such as elder abuse, child abuse, or threat to self or others: (REQUIRED)

(•) Yes ( ) No

The confidentiality and privacy section of the consent form should include this as a possible risk of participation.

* Describe the types of reportable information the research team may encounter and provide the details of the reporting plan: **(REQUIRED)**

At two separate time points during this study a questionnaire will be sent to participants to evaluate for signs/symptoms of Depression. At any point whether on questionnaire or on verbal report there is concern that a participant is at risk for becoming suicidal, this will be reported immediately (both in the patient's medical record and study file) and steps will be followed based on the Suicidal Ideation Protocol. To ensure the safety of the individual, Dr. Pasch (clinical psychologist at UCSF) will be notified immediately so that further evaluation and management can be taken. A set of questions are available on the protocol to evaluate imminent risk of harm. Of note, the study file with the reported event will not contain the name or any identifying information of the participant.

15.6 CERTIFICATE OF CONFIDENTIALITY: Will this study obain a Certificate of Confidentiality:

( ) Yes (•) No

15.7 SHARING OF RESEARCH RESULTS: Will there be any sharing of EXPERIMENTAL research test results with subjects or their care providers:

( ) Yes (•) No

15.8 * IDENTIFIERS: Will any personal identifiers be collected: (REQUIRED)

(•) Yes ( ) No

Check all the identifiers that may be included:

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [ ] Fax numbers
- [x] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [ ] Account numbers
- [ ] License or certificate numbers
- [ ] Vehicle ID numbers
- [ ] Device identifiers or serial numbers
- [ ] Web URLs
- [ ] IP address numbers
- [ ] Biometric identifiers
- [ ] Facial photos or other identifiable images
- [ ] Any other unique identifier

* Could study records include *ANY* photos or images (even 'unidentifiable' ones): **(REQUIRED)**

○ Yes ◉ No

15.9 DATA DISCLOSURE: Will identifiable information be shared with outside groups:

○ Yes ◉ No

15.11 * DATA COLLECTION AND STORAGE: (check all that apply): (REQUIRED)

Collection methods:

- ☐ Paper-based (surveys, logs, diaries, etc.)
- ☐ Electronic case report forms (CRFs), such as OnCore or another clinical trial management portal
- ☑ Web-based online surveys or computer-assisted interview tool
- ☐ Mobile applications (mobile or tablet-based)
- ☐ Wearable devices
- ☐ Audio/video recordings
- ☐ Other:

* What online survey tool will you use: **(REQUIRED)**

- ☐ Qualtrics (Recommended)
- ☑ RedCAP (Recommended)
- ☐ Survey Monkey (NOT recommended and may require UCSF ITS Security review)
- ☐ Other

* Data will be collected/stored in systems owned by (check all that apply): **(REQUIRED)**

- ☑ UCSF
- ☐ SF VAMC
- ☐ Amazon (Amazon Cloud)
- ☐ Other academic institution
- ☐ 3rd party vendor (business entity)
- ☐ Other (explain below)

15.12 DATA SECURITY: Indicate how data are kept secure and protected from improper use and disclosure (check all that apply): NOTE: Whenever possible, do not store subject identifiers on laptops, PDAs, or other portable devices. If you collect subject identifiers on portable devices, you MUST encrypt the devices.

- ☐ Data are stored securely in My Research
- ☑ Data are coded; data key is destroyed at end of study
- ☑ Data are coded; data key is kept separately and securely
- ☐ Data are kept in a locked file cabinet
- ☐ Data are kept in a locked office or suite
- ☑ Electronic data are protected with a password
- ☑ Data are stored on a secure network
- ☑ Data are collected/stored using REDCap or REDCap Survey
- ☐ Data are securely stored in OnCore

15.13

*** DATA SECURITY: Confirm below that you will keep data confidential: (REQUIRED) I will keep any data sets that include identifiers secure and protected from improper use and disclosure by using methods such as:**

- **Physical Security – Keeping data in locked file cabinets, locked offices, locked suites, and physically securing computers and servers.**
- **Electronic Security – Following UCSF minimum security standards for electronic information resources, which includes (but is not limited to): not storing identifiers on portable devices like laptops or flash drives if they are unencrypted, encrypting portable devices, and storing data in password-protected files and on secure networks.**

(•) Yes

15.15 HIPAA APPLICABILITY: Study data will be:

- [ ] Derived from the Integrated Data Repository (IDR) or The Health Record Data Service (THREDS) at SFGH
- [x] Derived from a medical record (e.g. APeX, OnCore, etc. Identify source below)
- [x] Added to the hospital or clinical medical record
- [x] Created or collected as part of health care
- [x] Obtained from the subject, including interviews, questionnaires
- [ ] Obtained ONLY from a foreign country or countries
- [ ] Obtained ONLY from records open to the public
- [ ] Obtained from existing research records
- [ ] None of the above

Unless a waiver of Authorization is granted, in addition to the consent form, participants will need to sign UCSF Research Subject Authorization Form (HIPAA Form). NEW REQUIREMENT - This form should be uploaded in the Other Study Documents section of the Initial Review Submission Packet Form. Failure to obtain HIPAA Authorization for research is one of the most common findings from QIU Routine Site Visits. Your IRB approval letter will include instructions about HIPAA requirements specific to your study.

If derived from a medical record, identify source:

APeX

15.16 * HIPAA - PERMISSION TO ACCESS SENSITIVE DATA: Does the research require access to any of the following types of health information from the medical record: (check all that apply) (REQUIRED)

- [ ] Drug or alcohol abuse, diagnosis or treatment
- [ ] HIV/AIDS testing information
- [ ] Genetic testing information
- [x] Mental health diagnosis or treatment
- [ ] None of the above

Important note: Ensure that participants initial the corresponding line(s) in Section C of the HIPAA authorization form during the consent process.

16.0 Financial Considerations

16.1 * PAYMENT: Will subjects be paid for participation, reimbursed for time or expenses, or receive any other kind of compensation: (REQUIRED)

(•) Yes ( ) No

16.2 PAYMENT METHODS: Subjects payment or compensation method (check all that apply):

Payments will be (check all that apply):

- [ ] Cash
- [ ] Check
- [x] Gift card
- [ ] Debit card
- [ ] UCSF Research Subject Payment Card
- [ ] Reimbursement for parking and other expenses
- [ ] Other:

16.3 PAYMENT SCHEDULE: Describe the schedule and amounts of payments, including the total subjects can receive for completing the study:

- **If there are multiple visits over time, explain how payments will be prorated for partial completion**
- **If deviating from recommendations in Subject Payment Guidelines, include specific justification below**

Patients will be eligible to receive up to $100 through the form of an Amazon gift card by participating in the study.

· At the end of the 1st clinic visit (Month 1 – blood draw), participants will receive a $25 gift card.

· At the end of the 2nd clinic visit (Month 3 – follow up visit, blood draw and online surveys), participants will receive another $25 gift card.

· At the end of the 3rd and final clinic visit (Month 6 – follow up visit, pelvic ultrasound, skin exam and online surveys), those who have completed all study procedures will receive a $50 Amazon gift card.

16.4 COSTS TO SUBJECTS: Will subjects or their insurance be charged for any study activities:

(•) Yes ( ) No

Describe the costs that may be incurred by subjects or 3rd party payers as a result of participation:

- Explain why it is appropriate to charge those costs to the subjects
- If this is a therapeutic study, compare subjects' costs to the charges that would typically be associated with receiving care off-study (e.g. is it more expensive to participate in this study than to receive care off-study?)

Depending on each participants insurance carrier there can be a cost associated with obtaining the specific oral contraceptive pill that will be utilized in this study. This would be typical even if the patient is not in the study. We do also anticipate at the 3 month time point that the patient's

insurance will cover certain follow up labs to be done at their insurance recommended laboratory that are considered routine in clinic follow up visits and not uniquely specific to this research study. In general however, most follow up labs throughout the 6 months are for research purposes, and will be paid for by the study team so that participants will not incur any cost.

17.0 Qualifications of Key Study Personnel

17.1 **NOTE: This information is required and your application will be considered incomplete without it. If this study involves invasive or risky procedures, or procedures requiring special training or certification, please identify who will be conducting these procedures and provide details about their qualifications and training. Also identify each person who will be involved in the consent process. Click the orange question mark for more information and examples.** **Under qualifications, please include:**

- **Academic Title**
- **Institutional Affiliation (UCSF, SFGH, VAMC, etc.)**
- **Department**
- **Certifications**

November, 2015 - NEW Definition of Key Study Personnel and CITI Training Requirements:

UCSF Key Study Personnel include the Principal Investigator, other investigators and research personnel who are directly involved in conducting research with study participants or who are directly involved in using study participants' identifiable private information during the course of the research. Key Personnel also include faculty mentors/advisors who provide direct oversight to Postdoctoral Fellows, Residents and Clinical Fellows serving as PI on the IRB application. **The IRB requires that all Key Study Personnel complete Human Subjects Protection Training through CITI prior to approval of a new study, or a modification in which KSP are being added. More information on the CITI training requirement can be found on our website.**

KSP Name	Description of Study Responsibilities - Briefly describe what will each person be doing on the study. If there are procedures requiring special expertise or certification, identify who will be carrying these out. Also identify who will be obtaining informed consent.	Qualifications, Licensure, and Training
Mody, Armaiti	Fellow investigator who is primarily involved in writing up the protocol, IRB application, and consent forms. She will be involved in obtaining informed consent, contacting participants through phone calls /emails, seeing participants at study visits, evaluating each participants modified Ferriman-Gallwey	MD physician, affiliated with UCSF, within the Pediatric Endocrinology Department, Completed Citi training

	hirsutism score at study visits, analyzing data outcomes, write up	
Huddleston, Heather G	Primary Investigator overseeing the study protocol, IRB application, grant proposals, study methods/procedures and data analysis.	MD physician, affiliated with UCSF, within the Ob /Gyn, Reproductive Sciences Department, Completed Citi training
Mcgough, Alexandra M	Oversees recruitment and enrollment, coordinates study visits and subject remuneration.	Clinical Research Coordinator, research support staff
Cedars, Marcelle MD, MD	Co-investigator overseeing the study protocol, study methods /procedures and data analysis.	MD physician, affiliated with UCSF, within the Ob /Gyn, Reproductive Sciences Department
Wong, Jenise MD, PhD	Research personnel overseeing the study protocol, study methods and data analysis	MD, PhD, affiliated with UCSF, within the Pediatric Endocrinology department
Lenhart, Nikolaus J	Will be helping with obtaining informed consent of participants, contact person for participants with regards to procedures and study visits during the study.	Clinical Research Coordinator UCSF Center for Reproductive Health
Pasch, Lauri	Contact person in the BDI-II Protocol in the event a participant endorses concern for suicidal ideation or intent.	Clinical Psychologist with the UCSF Center for Reproductive Health
Corley, Jamie	Will be helping with obtaining informed consent of participants, contact person for participants with regards to procedures and study visits during the study. Help with processing blood.	Clinical Research Coordinator UCSF Center for Reproductive Health
	Fellow investigator who will be helping with screening, recruitment /enrollment, and following up on patient tasks/procedures, including contacting participants through	MD physician, affiliated with UCSF, within the Reproductive

Morris, Jerrine R	phone calls/emails, seeing participants at study visits, evaluating each participants modified Ferriman-Gallwey hirsutism score at study visits, and analyzing data outcomes.	Endocrinology and Infertility Department, completed Citi training
Lodish, Maya B	Research mentor overseeing the study from the Pediatric Endocrinology division. Also providing miscellaneous departmental/divisional funding as needed for e-gift cards to participants.	MD physician, affiliated with UCSF, within the Pediatric Endocrinology division, completed Citi training.

18.0 Other Approvals and Registrations

18.1 * ADMINISTRATION OF RECOMBINANT DNA: Does this study involve administration of vaccines produced using recombinant DNA technologies to human subjects (Help Link added Aug '15): (REQUIRED)

○ Yes ◉ No

18.2 * HUMAN GENE TRANSFER: Does this study involve human gene transfer (NOTE: Requires NIH Recombinant DNA Advisory Committee (RAC) review prior to IRB approval): (REQUIRED)

○ Yes ◉ No

18.4 OTHER APPROVALS: Indicate if this study involves other regulated materials and requires approval and/or authorization from the following regulatory committees:

☐ Institutional Biological Safety Committee (IBC)

Specify BUA #:

☐ Institutional Animal Care and Use Committee (IACUC)

Specify IACUC #:

☐ Controlled Substances

19.0 End of Study Application

19.1 End of Study Application Form **To continue working on the Study Application: Click on the section you need to edit in the left-hand menu. Remember to save through the entire Study Application after making changes. If you are done working on the Study Application: Important: Before proceeding, please go back to Section 4.0 Initial Screening Questions and Save and Continue through the form to make sure all the relevant sections and questions have been included. If you've changed any answers since you started, the branching may have changed. Your application will be incomplete and it will have to be returned for corrections. Once you are sure the form is complete, click**

Save and Continue. If this is a new study, you will automatically enter the Initial Review Submission Packet form, where you can attach consent forms or other study documents.
Review the Initial Review Submission Checklist for a list of required attachments.
Answer all questions and attach all required documents to speed up your approval.

The UCSF IRB wants your feedback about this new form. Please click the link to take a brief survey about the new application form.