PennState

HRP-591 - Protocol for Human Subject Research

Protocol Title:

Therapeutic Effect of Sonographic Hysterosalpingography: Oil vs Water Based Media: The SHOW Pilot Trial

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Important Instructions for Using This Protocol Template:

1. Add this completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page, item 7.
2. This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.
3. **Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.**
4. **For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB** (http://irb.psu.edu)**. For all other research, do not delete the instructional boxes from the final version of the protocol.**
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1.0 Objectives

1.1 Study Objectives

The primary objective is to collect the ongoing pregnancy rate among subjects in the study. The co-primary objective is observe the safety and tolerability of Lipiodol UF®. Secondary objectives will be to document the relative pain during the Sono HSG procedure and any changes in quality of life as a result of the procedure according to the contrast agent. Exploratory outcomes will be the feasibility of blinding the patient and observer to the type of contrast medium injected at the end of the Sono HSG procedure and the prevalence of Anti-Chlamydial antibodies and association with outcomes. The results from this pilot trial will guide the design of a larger multi-center clinical trial examining Lipiodol UF® as a contrast agent during Sono HSG.

1.2 Primary Study Endpoints

Ongoing pregnancy rate (8 week viable intrauterine pregnancy) on all pregnancies conceived within 6 months(+2 weeks) of Sono HSG.

1.3 Secondary Study Endpoints

Procedural related pain on visual analogue scale (VAS) score, echogenicity of Lipiodol UF® with ultrasound, accuracy of patient and investigator assessment of type of contrast medium received during the study, prevalence of anti-chlamydial antibodies, live birth rate.

2.0 Background

2.1 Scientific Background and Gaps

Hysterosalpingography is a common test in women with primary and secondary infertility to establish a normal uterine cavity and tubal patency and traditionally has been done under fluoroscopy. There is no standardized way of performing the test nor is there agreement on the best contrast media. However there is evidence that this test may have therapeutic benefit as many couples conceive after the female has undergone the test, prior to initiating treatment. The use of oil-based vs water-based contrast media for hysterosalpingography has been an ongoing subject of debate dating into the 1950's and before. Oil based media have been theorized to have greater benefit on facilitating pregnancy after the test (both spontaneously and after treatment) compared to water based agents. There have been a number of randomized trials to support this and serial meta-analyses have documented a benefit of oil-based contrast media over water-based on pregnancy rates.(1-3) The exact mechanisms for the improvement of fertility are unknown, but it is theorized that oil based method may better unclog blocked or obstructive fallopian tubes of accumulated debris. There may also be immune modulated effects that improve fertilization. It has also been suggested that women with unexplained infertility may receive the greatest therapeutic benefit from the use of oil-based contrast agents.

We plan to study a specific oil based contrast medium, Lipiodol UF® (Guerbet LLC, Princeton, NJ). This product is FDA approved for infusion during hysterosalpingography in the U.S. There have been a number of small published RCTs documenting a pregnancy benefit with this specific contrast agent vs water-based contrast(4,5) with long term follow up of safety and efficacy.(6)

The major controversy about the use of oil-based contrast agents are concerns about the safety with reports of granuloma formation in the pelvis and concerns about intravasation of oil-based dye and related morbidity including at least one reported case of a coma which eventually resolved spontaneously.

There are multiple public health issues that could benefit from further study of oil-based agents. We have seen an increasing utilization of in vitro fertilization in the U.S. and throughout the world. The indications for IVF which were originally tubal disease, have now expanded to any infertility diagnosis, and we are seeing increasing utilization of this technology for ovulatory disorders and unexplained infertility which used to be managed with less expensive therapies.(7) Additionally IVF in the U.S. is associated with a high risk of multiple pregnancy, currently approaching 30% because of the habit of transferring multiple embryos (up to 2 in most patients).(8) While the introduction of guidelines limiting the number of embryos transferred has lowered the high order multiple pregnancy rate (i.e. triplets or higher), this twinning rate has remained high. Twinning remains an undesirable treatment outcome due to its associated increased risk of maternal and fetal morbidity (through increased maternal rates of pre-eclampsia, abnormal placentation, abruption, etc and through increased prematurity, either iatrogenic or spontaneous due to preterm delivery on the fetus). Identifying a fertility test that also has therapeutic benefit, would increase the number of pregnancies conceived naturally or with low cost, low multiple pregnancy-associated fertility treatments (i.e. mainly oral based ovarian stimulation agents for the female factor and intrauterine inseminations for male factor). Reducing preterm delivery rates and fetal prematurity is the number one perinatal health issue in the United States.

Unrecognized tubal disease remains a leading cause of infertility in the world. Many have recommended using serum tests to document a history of pelvic infection and potential tubal disease. One of the tests that is used world-wide but remains experimental are tests for anti-chlamydial antibodies. Chlamydia remains a common sexually transmitted disease and a major cause of pelvic inflammatory disease, tubal damage, and infertility. We have previously shown that anti-chlamydial antibodies (specifically anti-Chlamydial trachomatis IgG3 seropositivity) is associated with lower pregnancy rates and higher rates of ectopic pregnancy in an infertile population undergoing first line infertility treatment with oral ovarian stimulation agents combined with either timed intercourse or intrauterine insemination.(9) We are further interested in incorporating this test into the fertility testing regimen and it may also select patients who may be more likely to conceive after Sono HSG testing (i.e. by the absence of anti-chlamydial antibodies).

2.2 Previous Data

Recently a large multi-center trial using this agent compared to a water-based agent was conducted in the Netherlands and the results were reported at the Annual Meeting of the European Society of Human Reproduction and Endocrinology (ESHRE) in 2015. The trial (H2OIlie study) randomized 1119 women primarily with unexplained infertility in a 1:1 ratio to the agents and found a significantly higher ongoing pregnancy rate 6 mos after HSG (the primary outcome) with Lipiodol UF® compared to the water-based agent, i.e. 39.2% vs. 28.5%, Relative Risk (RR) and 95% Confidence Intervals (CIs) RR = 1.38, 95% CIs 1.16 to 1.63. These data to date have only been published in abstract form.

2.3 Study Rationale

The rationale for this trial is to further explore the use of oil based contrast media, specifically Lipiodol UF® both in the context of a contrast agent and as a potential treatment agent for women from couples with infertility. We specifically propose, eventually, to both build on and replicate the H2Oilie trial conducted in the Netherlands. We will build on the H2Oilie trial by utilizing ultrasound instead of fluoroscopy to conduct our HSG. Ultrasound based hysterosalpingography, i.e. Sono HSG, can be conducted in an outpatient setting by a single physician. It avoids patient and physician exposure to radiation, in many cases the additional trip to an inpatient hospital, the requirement of staffing by both radiologic and gynecologic personnel, and the greater expense of fluoroscopic HSG. We will expand the patient population from primarily women with unexplained infertility, to all women with infertility who will receive expectant management or conventional first line therapies. We will excluded women who will be going on to in vitro fertilization (IVF) as the chosen infertility therapy, because IVF as a first line

therapy is only applicable to women with tubal occlusion/tubal disease or couples with severe oligospermia requiring oocyte insemination or intracytoplasmic sperm injection (ICSI).

Our specific hypothesis is that tubal patency testing by Sono HSG with an oil-based contrast medium, Lipiodol UF®, will lead to higher ongoing pregnancy rates compared to the use of normal saline as a contrast medium with equal safety as a saline contrast agent.

The intervention will involve injection of 10 cc of Lipiodol UF® versus saline at the time of Sono HSG as a control. Lipiodol UF® is approved as an injection agent for HSG by the U.S. FDA.

The underlying rational for the pilot trial is to obtain preliminary data and to pilot the methodology to conduct a larger multi-center trial definitively powered to document the safety and efficacy of Lipiodol UF® as a primary contrast agent during Sono HSG.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Female, age 18-40 years
2. Eligible for Sono HSG for fertility testing
3. In good general health
4. Willing and capable of complying with the study procedures
5. At least one patent tube and no endometrial pathology on Sono HSG
6. Ready to undergo infertility treatment immediately after the test
7. Not planning on IVF therapy in the next 6 mos

3.2 Exclusion Criteria

1. Known tubal or endometrial (polyp, submucous fibroid, etc.) pathology
2. At high risk for tubal disease due to history of Pelvic Inflammatory Disease
3. Known hypersensitivity to Lipiodol UF®or known allergy to iodine containing contrast media or shellfish
4. Endometrial pathology on Sono HSG requiring further evaluation (as per the performing physician)
5. Bilateral tubal occlusion on Sono HSG
6. Unable to tolerate potential pain associated with the study.
7. Requiring IVF due to severe male factor, known pelvic adhesions, etc.
8. Couples with decreased male factor fertility rate (i.e., low sperm count or motility, i.e. less than 5 million/mL concentration on semen analysis

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Patients are free to withdraw from participation in the study at any time upon request. We do not anticipate a reason for termination.

3.3.2 Follow-up for withdrawn subjects

We will follow all subjects even if they discontinue fertility treatment, either voluntarily or because of an adverse event (AE) or severe adverse event (SAE) related to the Sono HSG procedure.

4.0 Recruitment Methods

4.1 Identification of subjects

Patients will be identified via chart review and recruited from the practice at Penn State Hershey by the investigators and study personnel.

4.2 Recruitment process

Patients will be recruited from the practice at Penn State Hershey by the investigators and study personnel. They will be provided with the study information from their clinician when presented all options currently available for infertility treatment. Participants who are potentially interested will contact the study staff for more information/screening.

4.3 Recruitment materials

Phone Screening Eligibility Form will be used to pre-screen interested subjects.

4.4 Eligibility/screening of subjects

A screening script will be designed and utilized to use in response to a potential subjects interest in the study. This will include a script to follow as well as a list of general inclusion/exclusion questions to be asked as part of the pre-screening process.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

After the subject has completed a pre-screening and has agreed to participate in the study, consent will be obtained. If the participant has an upcoming clinic visit, the informed consent process will take place in our infertility clinic, located at 35 Hope Drive with one of the study investigators or a study coordinator. If the participant does not have an upcoming clinic visit, this will be done over the phone with the subject and a study coordinator along with a witness on the study coordinator's end. The participant, along with the study coordinator and witness will sign the consent documents. Participants will then mail, scan, or fax the signed consent form back to the study staff. Study staff will then attach the witness signature page to the signed consent form then provide a copy of all pages to the subject. No study procedures will be conducted before the patient signs the informed consent and any investigators who are not authorized to perform consenting procedures will not do so.

5.1.1.2 Coercion or Undue Influence during Consent

Study subjects will be provided the study information from their clinician along with all other options currently available for infertility treatment. It will be the subject's decision to pursue the study. If the subject completes the pre-screening process and is interested in the study, the subject can opt to proceed with the study. If the subject decides to not participate, they will not be swayed otherwise. The subject's decision to participate or not to participate in the study will not affect their care.

5.1.2 Waiver or alteration of the informed consent requirement

A partial waver of consent has been requested for recruitment purposes in order to use chart review to identify patients who are potentially eligible for the study so that they can be approached to determine if they are interested in participating.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

The subject will review the ICF with an approved member of the investigative team. Each section of the ICF will be reviewed and after each section the subject will have an opportunity to ask questions. All questions will be answered. At the end of the verbal review of the consent form, the subject will have time to read the entire consent form thoroughly. If the subject agrees to study participation and all questions have been answered, the subject will sign, date and time the ICF. The person providing the ICF as well as a witness to the verbal consent process if completed over the phone will also sign, date and time the ICF. A copy of the signed ICF will be provided to the subject.

Written consent will be obtained over the phone for those participants who do not have an upcoming clinic visit, willutilize a witness on the study coordinator's end and will be faxed/scanned/mailed by the participant to the researcher. This will lessen the burden on the subject so that they do not have to come in solely to sign the consent form and allow researchers the ability to randomize the patient prior to their arrival for the procedure so as to minimize delays in the visit.

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

A waiver of documentation of consent is requested for recruitment purposes. Verbal consent will be obtained from potential subjects prior to asking the Pre-Screening questions.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

The inclusion of non-English speaking subjects is not planned.

5.3.2 Cognitively Impaired Adults

NOT APPLICABLE

5.3.2.1 Capability of Providing Consent

5.3.2.2 Adults Unable To Consent

5.3.2.3 Assent of Adults Unable to Consent

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

NOT APPLICABLE

5.3.3.1 Parental Permission

5.3.3.2 Assent of subjects who are not yet adults

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

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

Check all that apply:

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

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

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

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

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

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

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

6.2.1.1 Plan to protect PHI from improper use or disclosure

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

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

At the end of the study, all study databases will be de-identified and archived at the Penn State Department of Public Health Sciences server.

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

We will need access to the medical record in order to identify patients who are potentially eligible for the research study. Participant medical records will also need to be reviewed in order to obtain data in the follow-up period regarding pregnancy outcomes and adverse events.

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

We will need a partial waiver in order to identify potentially eligible subjects using the electronic medical record prior to consent.

6.3 Waiver or alteration of authorization statements of agreement

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

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

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

7.0 Study Design and Procedures

7.1 Study Design

The study will be a double blind randomized controlled trial of Lipiodol UF® vs Normal Saline as a Sono HSG contrast medium. It will be a single center trial with a 1:1 randomization ratio.

7.2 Study Procedures

	Screening	Enrollment/Study Visit Time = 0	Post Procedure = 2 – 4 weeks	Final Study Contact Time = 6 mos (+2 weeks)	Pregnancy Follow up Up to 15 mos
Inclusion/Exclusion Criteria	**X**				
Review Informed Consent and Obtain Per Telephone	**X**				
Schedule Sono HSG	**X**				
Collect Written Informed Consent		**X**			
Randomize		**X**			
Perform Urine Pregnancy Test		**X**			
Perform Sono HSG with Saline and then Study Agent		**X**			
Administer FertiQol Questionnaire		**X**		**X**	
Assess Patient VAS score		**X**			
Assess echogenicity of study media		**X**			
Assess adequacy of blinding by patient and physician		**X**			
Obtain Blood for Anti-Chlamydial Antibodies		**X**			

	Screening	Enrollment/Study Visit Time = 0	Post Procedure = 2 – 4 weeks	Final Study Contact Time = 6 mos (+2 weeks)	Pregnancy Follow up Up to 15 mos
Obtain blood for TSH and Free T4		**X**	**X**		
Collect adverse events since test				**X**	
Obtain Release of Pregnancy Records as necessary					**X**
Collect all pregnancy outcomes					**X**

7.2.1 Screening

When patients are offered Sono HSG as part of fertility testing, they will be given a study brochure and a copy of the consent form. Because this test is performed in the follicular phase prior to ovulation, the test is scheduled for some future date allowing screening of the potential participants and time for participants to review the consent and decide whether to participate. An initial screening with the study coordinator will occur to ensure eligibility based on patient desire and meeting inclusion and avoiding exclusion criteria. All questions about the consent will be answered during screening.

7.2.2 Randomization

Randomization will be performed after written consent is obtained and prior to any study procedures taking place. Contrast media will be prepared in stable opaque syringes and picked up from the Investigational Pharmacy. Randomization will occur using the REDCap randomization module.

7.2.3 Baseline Assessments/Study Intervention

Case report forms documenting the history will be obtained, the Ferti-QOL (12) quality of life survey will be obtained. Serum for Anti-Chlamydial antibodies as well as Free T4 and TSH will be drawn before or after the Sono HSG depending on the patient's reason for visit, as often a baseline progesterone and hCG level are obtained prior to the Sono HSG if the patient is to go on immediately to treatment. The rationale for the Anti-Chlamydial antibodies is that we have shown they are associated with failure to conceive and pregnancy loss including ectopic pregnancies in our prospective randomized controlled trials (9). Samples drawn for anti-chlamydial antibodies will be sent to the study sponsor's laboratory for analysis. Free T4 and TSH will be collected in order to assess thyroid function. A urine pregnancy test will be performed. We will then proceed with the Sono HSG. This begins first with a routine pelvic ultrasound. Then a speculum is inserted into the vagina and then the Sono HSG catheter is inserted through the cervical canal into the uterine cavity and the balloon is inflated to maintain a seal at the cervical canal. A special device, i.e. the FemVue system, will then be used to infuse normal saline while at the same time creating bubbles to ease ultrasound visualization. The speculum is removed and the transvaginal ultrasound probe is inserted. The Sono HSG begins with infusion of normal saline via the FemVue catheter. After a patient has had an SHG with a normal cavity and at least one patent tube as determined by the performing physician, the patient will receive the study contrast or control saline which will be in an opaque glass syringe and connected to the uterine catheter via opaque tubing to allow double blinding of physician and patient. The study agent will be shaken vigorously to induce turbulence and air bubbles to ease tracking of the agent and then infused in 2 cc increments under ultrasound

visualization while the physician again visualizes the uterine cavity and patency of the fallopian tube(s). Infusion will cease with documentation of a normal cavity and tubal patency or when 10 cc have been infused. The amount of contrast infused will be recorded. After infusion the patient will be asked to assess the degree of pain she experienced by the VAS scale and both physician and patient will be asked to document a guess as to what contrast medium was used as study agent.

7.2.4 Post-Procedure Visit (2-4 weeks)

Participants will have a blood draw completed 2-4 weeks after the Sono HSG procedure to re-test TSH and Free T4.

7.2.5 Follow Up (up to 15 months)

Follow up will take place via review of medical records. Patients will follow American Society of Reproductive Medicine (ASRM) guidelines for treatment.(13) Currently, based on Level I evidence that would be clomiphene/IUI for unexplained infertility (14) and letrozole with timed intercourse for polycystic ovary syndrome.(15) The initial consent will allow access to all medical records in the Electronic Health Record including any resulting pregnancy. Data collected will include any potential adverse events as well as information on the participant's course of infertility treatment/any resulting pregnancy outcomes up to 15 months after the procedure. If a patient seeks infertility or pregnancy care outside the institution we will obtain a release of records form from the patient at their last visit to our infertility clinic to obtain release of these records at the end of the 6 month participation in the study (or longer if a patient conceives at the end of the 6 month window of study participation). We will not follow any conceptions that occur more than 6 months after performing the Sono SHG. A conception is defined as a positive urine or serum pregnancy test for hCG. All conceptions will be followed up to the completion of that pregnancy.

7.2.6 Final Study Contact (6 months + 2 weeks)

The final study contact will take place by mail. If the patient has not become pregnant, the patient will be mailed the follow up Ferti-QOL questionnaire to fill out with a self addressed prepaid return envelope. Any pregnancies that occur up to 6 months after randomization will be followed to completion and will not receive a FertiQol questionnaire.

7.3 Duration of Participation

Study duration will typically be 6 months(+2weeks), but can be up to 15 months if conception occurs at the end of study period.

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

7.4.1 Description

Lipiodol UF® is an FDA- approved oil-based radiopaque contrast agent indicated for: hysterosalpingography in adults, lymphography in adult and pediatric patients selective hepatic intra-arterial use for imaging tumors in adults with known hepatocellular carcinoma (HCC).

7.4.2 Treatment Regimen

The physician will dose at 2 cc increments into the uterine cavity via the Sono HSG Catheter, visualizing the endometrial cavity via ultrasound and ruling out filling defects as well as visualizing the left and the right fallopian tube to document patency. Up to 10 cc can be instilled into the uterine cavity.

7.4.3 Method for Assigning Subject to Treatment Groups

The randomization scheme for this study will use 1:1 group allocation via variable-size, random permuted blocks to ensure that the number of participants in each treatment arm is balanced after each set of B randomized participants, where B is the block size. The study coordinator will use the randomization module in the password protected, secure REDCap database software to randomize the participant. Participants will be entered consecutively. The Penn State Investigational Pharmacy will have access to the randomization scheme and perform the preparation of study contrast to maintain double blinding.

7.4.4 Subject Compliance Monitoring

The drug will be administered to the subject under the supervision of the physician performing the procedure.

7.4.5 Blinding of the Test Article

The drug will be prepared and blinded by Investigational Drug Services at Penn State Hershey. They drug will be dispensed in an opaque syringe and opaque tubing will be used during the procedure to maintain the double blind.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The study agent, Lipiodol UF®, will be purchased from Guerbert LLC, Princeton, NJ and shipped to the Investigational Pharmacy at Penn State Hershey which will store and dispense the product for the study. The study agent will be ordered in 10cc vials. The Investigational Pharmacy at Penn State Hershey will also prepare the normal saline control for Sono HSG.

7.4.6.2 Storage

The study agent Lipiodol UF® will be stored at room temperature 15°-30°C (59°-86°F) and protected from light in the investigational pharmacy until prepared for use.

7.4.6.3 Preparation and Dispensing

The study agent Lipiodol UF® or the control normal saline will be re-packaged prior to administration in a 10 cc opaque glass syringe by the Penn State Investigational Pharmacy and will be coded in a de-identified fashion. It will be dispensed upon physician prescription to study personnel.

7.4.6.4 Return or Destruction of the Test Article

All unused Lipiodol UF® will be returned to Guerbet, LLC at the end of the study.

7.4.6.5 Prior and Concomitant Therapy

Participants who are planning to undergo IVF therapy in the next six months will not be included in the study.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Fifty-six subjects will be randomized and receive study intervention, twenty-eight per randomization arm. We estimate that we will need to screen one hundred patients in order to meet this goal.

8.2 Sample size determination

For pilot studies it has been suggested that sample sizes ranging anywhere from 12 to 60 subjects per group would provide sufficient data to obtain estimates of the primary outcome in order to power a future definitive clinical trial, as well as provide sufficient evidence to assess feasibility, blinding safety, and regulatory considerations.(16) A sample size of 50 evaluable subjects (25 per group) should be sufficient in order to satisfy the goals of this pilot study (i.e., feasibility of binding the contrast medium, obtaining estimates for a formal power calculation of a future trial, and evaluating the safety of the contrast medium). We anticipate, however, that 10% of the subjects will either drop-out prior to study completion or be randomized but not be able to have a Sono HSG performed because they change their minds during the procedure and opt out or they have bilateral tubal occlusion or a hydrosalpinx. Also, subjects may not be evaluable as result of technical errors associated with manipulation of the required glass syringe for study drug administration. Therefore, we will recruit a minimum of 60 subjects up to a maximum of 72 subjects, terminating enrollment once we have reached the goal of 50 evaluable subjects.

8.3 Statistical methods

The analysis dataset will follow a modified intention to treat (mITT) where all evaluable subjects will be analyzed. For the pilot study, an evaluable subject is a subject that has been randomized and has completed the Sono HSG.

Descriptive statistics for continuous data will be reported as the mean (standard deviation) or as the median (25th percentile, 75th percentile) if the distribution is not normally distributed. Descriptive statistics for categorical will be reported as a frequency and percentage. All hypothesis tests will be two-sided and tested at a significance level of 0.05. All analyses will be conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC) or R software, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

8.3.1. Primary Endpoint Analysis

A Pearson's chi-square test, or Fisher's exact test if the expected cell counts are <5, will be used to compare the proportion of subjects with an ongoing pregnancy (for all pregnancies identified by 6 mos after Sono HSG) between the Lipiodol UF® and saline groups. A relative risk and 95% confidence interval will be used to quantify the effect size.

8.3.2. Secondary Endpoint Analysis

A two-sample t-test will be used to compare the Lipiodol UF® to saline groups with respect to continuous outcomes, such as VAS scores, change in Ferti-QOL scores from baseline to 6 mos after Sono HSG, and anti-chlamydial antibody levels. The effect size from the two-sample t-tests will be quantified using the difference in means and 95% confidence interval. In the event the data do not meet parametric assumptions, the data will either be transformed (e.g., a logarithmic transformation) in order to satisfy parametric assumptions or a non-parametric Wilcoxon rank-sum test will be used to compare the treatment groups.

A Pearson's chi-square test, or Fisher's exact test if the expected cell counts are <5, will be used to compare the live birth proportions, as well as detectability (yes/no) for anti-chlamydial antibodies, between the Lipiodol UF® and saline groups. A relative risk and 95% confidence interval used to quantify the effect size.

9.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

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

10.2 Data that are reviewed

The primary safety parameters we will collect are patient discomfort as determined by VAS scores, any serious sequelae to Sono HSG including allergic reactions, infection, development of adhesions, subsequent related surgeries or hospitalizations.

10.3 Method of collection of safety information

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor, Allen Kunselman. All AEs will be captured on the appropriate CRF and include event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

10.4 Frequency of data collection

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

10.5 Individuals reviewing the data

The safety review will be performed by the Steering Committee. The Steering Committee will be composed of the Study PI, Dr. Legro, participating co-investigators in the Division of Reproductive Endocrinology, the Biostatistician, Allen Kunselman, and the study coordinator. The Steering Committee will meet in person regularly during the departmental research meeting to review progress and study issues.

10.6 Frequency of review of cumulative data

Annual reports will be made to the Penn State IRB as per the current protocol. Data will also be monitored by the Public Health Sciences department periodically.

10.7 Statistical tests

A Pearson's chi-square test, or Fisher's exact test if the expected cell counts are <5, will be used to compare each reported AE between the Lipiodol UF® and saline groups, provided there are sufficient AEs to obtain inference.

10.8 Suspension of research

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Guerbet LLC, Princeton, NJ. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the involved party (i.e. investigators, IRB, sponsors). There are no planned stopping rules as we are using an FDA approved contrast agent for its approved indication.

11.0 Risks

The immediate risks of Lipiodol UF® for HSG are lower than the other indicated uses, since the major risks are related to intravasation and associated anaphylactic and/or embolism events. While there is evidence of intravasation during conventional fluoroscopic HSG(10), there has been only one case report of a cergral embolization event related to this, with a 12 day coma and ICU stay after HSG that resolved without sequelae. (11). The immediate risks include discomfort or pain from the infusion into the uterine cavity, an anaphylactic or allergic reaction to Lipiodol UF®, and embolization after intravasation. The long term risks include formation of granulomas and/or pelvic adhesions and late sequelae of intravastion.

There is a risk of loss of confidentiality if information is obtained by someone other than the investigators. Precautions will be taken to prevent this as described in Section 9.

There is a risk that the questionnaires may make participant uncomfortable.

Risks of standard venipuncture include slight pinch or pin prick, discomfort, black and blue mark at the site of puncture, small blood clot, infection or bleeding at the site, and fainting during the procedure.

Risks associated with Sonohysterogram/Hysterosalpingogram include pain, bleeding, damage to the uterus, pelvic infection, interrupting an unrecognized pregnancy, small amount of radiation exposure, and allergic reaction to the radio-opaque dye.

Risks associated with randomization. One treatment may be less effective or have more side effects than the other research treatment or other available treatments.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

There is no guarantee that subjects will benefit from this research. The potential benefit is an increased chance for ongoing pregnancy and live birth for women desiring children who undergo the test.

12.2 Potential Benefits to Others

The results of this research may guide the future practice of this test by establishing a more effective and tolerable procedure by using lipid based oil medium for sonographic based hysterosalpingography (Sono HSG) compared to water based contrast for women seeking fertility.

13.0 Sharing Results with Subjects

We will share the overall results of the study and the study agent assignment with all patients at study closure.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Participants who complete the FertiQol at final study contact, will receive a $10 gift card. .

15.0 Economic Burden to Subjects

15.1 Costs

Participants will not be charged for the cost of any tests or procedures that are required as part of the research and are outside the standard of care including all study required blood tests and the lipid oil which will be provided by the sponsor at no cost. Participants and/or their insurance companies will be responsible for costs of medical services for care they would receive even if they were not in this study including routine medications, tests and procedures, co-payments/co-insurance/deductibles. Routine tests and procedures will be billed in the usual manner and participant will be responsible for any charges not reimbursed by their insurance company.

15.2 Compensation for research-related injury

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

16.0 Resources Available

16.1 Facilities and locations

Participant visits and Sono HSG will occur at the infertility clinic at 35 Hope Drive on the Hershey Medical Center campus.

16.2 Feasibility of recruiting the required number of subjects

Patients will be recruited from the practice at Penn State Hershey by the investigators and study personnel. We perform 10-15 Sono HSGs per month for fertility testing and it is anticipated that almost all patients will be eligible as the criteria for study inclusion overlap with our criteria for fertility testing. We project a high rate of recruitment of eligible patients into the trial. However with a conservative estimate that 50% of patients undergoing Sono HSG for fertility testing opt to participate in the study we estimate 5-7 patients per month will be enrolled. Thus it will take conservatively 7-10 months to recruit the cohort and according to our best estimate, 6 months. We do not anticipate difficulty in following patients since they will be receiving fertility treatment immediately after the Sono HSG through our practice.

16.3 PI Time devoted to conducting the research

The PI is the Vice Chair of Research in the Department of OB/GYN and has one full day per week dedicated to research.

16.4 Availability of medical or psychological resources

Participants will be receiving routine care and infertility treatment.

16.5 Process for informing Study Team

There are 2 weekly meetings within the Division of Reproductive Endocrinology attended by the physicians and research coordinators. One is dedicated entirely to research, and the other is dedicated to clinic. Research recruitment and updates are covered at both of these meetings. Study coordinators are cross trained on the REI study protocols.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not Applicable

17.2 Internal PSU Committee Approvals

Check all that apply:

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

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

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

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

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

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

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

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

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

18.0 Multi-Site Research

Not Applicable

19.0 Adverse Event Reporting

19.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

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

20.0 Study Monitoring, Auditing and Inspecting

20.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored

N/A

21.2 Location of storage

N/A

21.3 Duration of storage

N/A

21.4 Access to data and/or specimens

N/A

21.5 Procedures to release data or specimens

N/A

21.6 Process for returning results

N/A

22.0 References

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