Comparing Intra-vaginal Culture of Embryos to In-vitro Culture of Embryos with Minimal Stimulation

NCT02802176

Document Date: 6/27/2016

Study Application (Version 1.10)

1.0 General Information

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

Comparing intra-vaginal culture of embryos using INVOcell device to in-vitro culture of embryos

***Enter the study alias:**

INVOcell embryo culture
* 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

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:

Cedars, Marcelle MD

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

Ahmad, Asima
Co-Principal Investigator
Noel, Martha W
Other Investigator

B) Research Support Staff

Anaya, Yanett

Research Assistant
Hoskin, Elena
Study Coordinator
Lenhart, Nikolaus J
Study Coordinator
Morris, Jerrine R
Research Assistant
Wong, Rebecca S
Study Coordinator

3.3 *Please add a Study Contact

Ahmad, Asima
Cedars, Marcelle MD
Hoskin, Elena
Lenhart, Nikolaus J
Wong, Rebecca S

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:

Cedars, Marcelle MD

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

Giudice, Linda MD, PhD
Department Chair

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.

BACKGROUND:
There is a need for cost-effective infertility treatments. For women requiring in-vitro fertilization (IVF), intra-vaginal culture (IVC) of embryos can be used as a lower-cost alternative, using the INVOcell® device.

HYPOTHESIS:
In women with infertility requiring IVF, we will see similar clinical pregnancy rates (CPR) with minimal gonadotropin or oral medication stimulation using the INVOcell device compared with conventional IVF.

PRIMARY AIM:
To determine outcomes of IVC with INVOcell device versus conventional IVF while using oral stimulation or minimal gonadotropins stimulation protocols:

a. Implantation rate

SECONDARY AIMS:
To determine the effect of IVC with INVOcell device versus conventional IVF while using oral stimulation or minimal gonadotropins stimulation protocols on:

a. Fertilization rate
b. Embryo quality
c. Clinical pregnancy rate
d. Live birth rate

DESIGN
Non-blinded prospective randomized controlled trial pilot study

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:

NCT02802176

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 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
- [ ] Departmental scientific review
- [ ] Other:

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

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

4.16 * 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

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)
No Sponsor has been added to this IRB Study						

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

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
- [x] Mission Bay
- [ ] China Basin
- [x] 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 Center for Reproductive Health - Mission Bay
499 Illinois St, 6th Floor
San Francisco, CA 94158

UCSF Center for Reproductive Health - Mount Zion
2356 Sutter St, 7th Floor
San Francisco, CA 94115

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

- ( ) Yes
- (•) No

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 a central IRB (other than the NCI CIRB) or an external IRB (UC, commercial, or institutional): (REQUIRED)

○ 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):

In women with infertility requiring IVF or same-sex couples requiring IVF, we will see similar clinical pregnancy rates (CPR) with minimal gonadotropin or oral medication stimulation using the INVOcell device compared with conventional IVF.

7.3 AIMS: List the specific aims:

PRIMARY AIM:
To determine the outcomes of IVC with INVOcell device versus conventional IVF while using oral stimulation or minimal gonadotropins stimulation protocols on:

a. Implantation rate

SECONDARY AIMS:
To determine the outcome of IVC with INVOcell device versus conventional IVF while using oral stimulation or minimal gonadotropins stimulation protocols on:

a. Fertilization rate
b. Embryo quality
c. Clinical pregnancy rate
d. Live birth rate

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

Non-blinded prospective randomized controlled trial pilot study

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.

The focus of global reproductive health initiatives has traditionally placed an emphasis on improving maternal/child health (maternal mortality, neonatal mortality) as well as broadening the reach of contraception. Along these lines of fertility and family planning, we often forget that "family planning" includes the concept of fertility as well as *in*fertility. Although there has been a reduction in child-seeking behavior amongst couples over time (meaning a decreased proportion), the prevalence of infertility has not changed very much from 1990-2010. In 2010, a World Health Organization (WHO) study found an estimated 48.5 million couples were infertile [1]. For women aged 20-44 attempting to conceive, 1.9% experienced primary infertility and 10.5% experienced secondary infertility [1]. Also, given the limitations with conducting population-based surveys in resource-limited settings and developing nations, these numbers may be drastically underestimated.

There is a great deal of stress and anxiety couples facing infertility experience. In developing nations and resource-limited settings, there is a significant level of stigma women suffering from infertility may also experience including: being ostracized from the community, verbal abuse and even physical abuse sometimes resulting in permanent injury or death [2]. The burden extends further, as those in remote areas have limited access to care in addition to the extensive costs required for workup and treatment [3]. For this reason, there is a need for cost-effective treatments that can be available for these women that do not rely on high-level technologies and 24-hour electricity availability [4]. Treatment can be as simple as ovulation induction with oral medications to as complicated and expensive as in-vitro fertilization (IVF) with the use of additional technologies (ie preimplantation genetic diagnosis).

For those patients requiring IVF treatment for management of their infertility, intra-vaginal culture (IVC) of embryos as a lower-cost alternative, which was first introduced in the 1980s, can be considered[4]. This can be performed using the INVOcell® device. There is a reduction in the cost of the treatment due to the following: 1) only one technician needed, 2) entire procedure including oocyte retrieval to placement of device can be completed in 60-90 minutes, 3) can be performed in a doctor's office/clinic setting and does not require lab or operating room, 4) does not rely on constant electricity to maintain laboratory and can be performed in load-shedding areas with unreliable electricity. There is also a psychological benefit as the woman can participate in the fertilization of the embryos first-hand in a more "natural" environment, as opposed to fertilization in a lab. In addition, this eliminates any chance of and reduces anxiety around embryo mix-ups [4].

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

IVC, also called INVO, was developed by Claude Ranoux in 1988 as another method for culturing oocytes or embryos when compared to the conventional laboratory culture method [5]. Since then, the device has been used and studied in multiple countries including: Austria, Bolivia, Brazil, Canada, Ecuador, India, Mexico, Nicaragua, Pakistan, Panama, Spain, Turkey, and Venezuela [5-8]. In addition, INVOcell was FDA approved for use in the United States in November of 2015.

There have been numerous studies on the INVO procedure and INVOcell device including evaluation and optimal conditions of the culture such as pH, pCO2 and pO2 [8] to optimal time of intra-vaginal culture [9]. Garcia-Ferreyra et al performed a prospective, non-randomized study that evaluated INVO using intracytoplasmic sperm injection (ICSI) with INVOcell versus conventional ICSI to day 3 and found no significant differences between embryo quality (77% INVO-ICSI versus 86.8% ICSI), pregnancy rate (54.2% INVO-ICSI versus 58.1% ICSI) and implantation rate (31.7% INVO-ICSI versus 33.6% ICSI) [10]. To control for factors between patients, a pilot study performed in 2015, compared sister oocytes (INVO vs IVF) and found similar cleavage rates (93% ± 1.5% IVF versus 97% ± 6% INVO) and a clinical pregnancy rate of 43% per embryo transferred from INVO procedure.

In the United States, the device has been FDA approved for IVC for three days, but there is currently research being done to investigate whether IVC for five days (to blastocyst stage) can lead to improved embryo quality and live birth rates. Doody et al performed a randomized controlled trial comparing IVF to IVC that showed no significant differences in the percentage quality of blastocysts transferred when compared to IVF (87.9% IVC, 97.2%, p = 0.09) and live birth rate (55 % IVC, 60 % IVF) [9]. In fact, the implantation and birth rates per blastocyst transferred was actually higher with INVOcell versus IVF (54.5 versus 44.4% and 48.5 versus 41.7%) [9].

These findings are promising and show that INVOcell may be a good alternative to IVF in resource-limited settings or as a cost-effective alternative to IVF in developing nations, as the cost of one IVF cycle is equivalent to 3-4 INVO cycles. Most studies thus far have evaluated the use of INVOcell with normal or mild stimulation protocols, which can result in the production of numerous eggs. For resource-limited settings, especially where there is no embryology lab and acute care, one would want to limit the number of eggs produced per cycle, such that all are used for transfer into the uterus in addition to preventing ovarian hyperstimulation syndrome (OHSS). There is no randomized controlled trial that compares INVO versus conventional IVF using oral-only and minimal stimulation protocols – protocols that would lead a smaller number of eggs and also reduced costs, as oral medication is more cost-effective.

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 * 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)

- [ ] Interviews, questionnaires, surveys
- [ ] Educational or cognitive tests
- [ ] Focus groups
- [x] Observation
- [x] 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

7.9 * 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.

Patients will be randomized to intra-vaginal culture (IVC) of embryos using INVOcell or traditional in-vitro fertilization (IVF) of embryos. Both groups of patients will receive the same initial workup, consultation and evaluation, ovarian stimulation, cycle monitoring, oocyte retrieval, and embryo transfer. The only difference between the two groups will be the culturing/growth of the embryos, which will be randomized to IVC or IVF. All embryos will be transferred on day 3. The IVC protocol is attached for reference.

7.10 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:

The only difference in clinical practice the "cases" from this randomized controlled trial would have that differed from the "control" population, would be the use of intravaginal culture (IVC) using the INVOcell device instead of the standard in-vitro fertilization (IVF) for fertilization and growth of embryos.

7.12 * 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

Based on current research trends, we strongly recommend including the genomic data sharing language in the consent form to allow future sharing, even if you don't anticipate it now. It's easier than trying to reconsent all the specimen donors!

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

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

Describe and/or name source:

Because patients will not be randomized to either arm of the study (IVC versus IVF) until the day of trigger, they will receive the standard of care and workup that all infertility patients receive when they come to UCSF Center for Reproductive Health for their care. No additional blood tests, tissue collection or biopsies will be performed beyond the standard of care. Therefore, all patients will have their blood drawn for evaluation of the etiology of their infertility, possible tracking hormone levels during their stimulation cycle, and have embryo transfers performed.

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

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

Explain **Other**:

Specimens collected will be the same that are all part of standard care for patients under infertility evaluation. These include: blood samples and embryos (that will belong to patient and be transferred to uterus or frozen for later use by patient).

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

Outside Entity:

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

UCSF:

- [ ] UCSF repository/bank being established under this protocol
- [x] Existing UCSF specimen repository/bank with CHR approval
- [ ] 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:

University of California San Francisco - Center for Reproductive Health - Embryology Lab

7.16 UCSF-BANK PHYSICAL LOCATION: The repository/bank is physically located at (list the address and room number for all locations):

Embryology Lab - 6th floor
Center for Reproductive Health
499 Illinois Street
San Francisco, CA 94158

7.18 * 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

7.20 * 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':

Indefinitely, as patients may return for use of their embryos for next child.

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

This study will be a pilot study which will potentially lead to a larger randomized controlled trial. We expect N=20 to each group (cases and controls, respectively) and given low-stimulation protocols, expect 1-3 embryos per patient. Given these low numbers, summary statistics will be used.

For categorical outcomes, frequency tables will be provided. For continuous outcomes, full summary statistics will be provided. This will include mean, standard deviation, minimum, maximum, median and quartiles.

To determine the effect of IVC with INVOcell device versus conventional IVF while using oral stimulation or minimal gonadotropins stimulation protocols on:

a. Fertilization rate, which is defined by the total number of fertilized oocytes divided by total number of mature oocytes retrieved. This comparison will take place on day-3, as that is when the IVC embryos will be assessed.
b. Embryo quality. This is measured by the Gardner grading system.
c. Implantation rate, which is defined by number gestational sacs seen on early pregnancy 6-week ultrasound divided by number of embryos transferred
d. Clinical pregnancy rate, which is defined by the number of fetal poles with heartbeat seen on ultrasound divided by the number of embryos transferred
e. Live birth rate, which is defined by the number of living babies delivered divided by the number of transfers

To determine the effect of IVC with INVOcell device versus conventional IVF while using oral stimulation or minimal gonadotropins stimulation protocols on:

a. Live birth rate, which is defined by the number of live births divided by the number of transfers

7.26 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. Mascarehas, M.N., et al., *National, Regional, and Global Trends in Infertility Prevalence Since 1990: A Systematic Analysis of 277 Health Surveys.* PLOS Medicine, 2012. 9(12): p. e1001356.
2. Unisa, S., *Childlessness in Andhra Pradesh, India: Treatment-seeking and consequences.* Reproductive Health Matters, 1999. 7(13): p. 11.
3. Asemota, O.A. and P. Klatsky, *Access to infertility care in the developing world: the family promotion gap.* Seminars in Reproductive Medicine, 2015. 33(1): p. 6.
4. Khan, M., S. Zafar, and S. Syed, *Successful intravaginal culture of human embryos for the first time in Pakistan — An experience at the Sindh Institute of Reproductive Medicine, Karachi.* Journal of Pakistan Medical Association, 2013. 63(5).
5. Ranoux, C., et al., *A new in vitro fertilization technique: intravaginal culture.* Fertility Sterility, 1988. 49(4): p. 4.
6. Lucena, E., et al., *INVO Procedure: Minimally Invasive IVF as an Alternative Treatment Option for Infertile Couples.* The Scientific World Journal, 2012. 2012 (571596): p. 6.
7. Mitri, F., et al., *A pilot study to evaluate a device for the intravaginal culture of embryos.* Reproductive BioMedicine Online, 2015. 31(6): p. 7.
8. Fukuda, M., K. Fukuda, and C. Ranoux, *Unexpected low oxygen tension of intravaginal culture.* Human Reproduction, 1996. 11(6): p. 3.
9. Doody, K.J., E.J. Broome, and K.M. Doody, *Comparing blastocyst quality and live birth rates of intravaginal culture using INVOcellTM to traditional in vitro incubation in a randomized open-label prospective controlled trial.* Journal of Assisted Reproductive Genetics, 2016. 33(4): p. 6.
10. Garcia-Ferreyra, J., et al., *In Vivo Culture System Using the INVOcell Device Shows Similar Pregnancy and Implantation Rates to Those Obtained from In Vivo Culture System in ICSI Procedures.* Clinical Medicine Insights: Reproductive Health, 2015. 10(9): p. 5.

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

Note: This question is frequently answered incorrectly. If any drugs or biologics, approved or unapproved, are being administered under this protocol, you should check 'Yes' unless you are *absolutely* sure that NONE of the drugs are part of the research protocol. Tip: Ask the PI or the sponsor if you are not sure how to answer this question.

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

◉ Yes ○ No

8.4 * NSR: Are you requesting a Non-Significant Risk (NSR) determination for an investigational device: (REQUIRED) Note: an NSR determination is different from an Investigational Device Exemption (IDE). Check the Help link for more guidance on what types of devices can qualify for an NSR determination.

○ Yes ◉ No

8.5 LIST THE DEVICES: List the medical devices or in vitro diagnostics to be studied or used. In the device details screen you will be asked questions such as:

- **Whether the device is FDA approved or investigational**
- **Medicare device category**
- **If the device will be provided at no cost**

- **If an IDE is necessary, the IDE number, and who holds the IDE**
- **Risk category of the device**
- **FDA status of the device**

Please see the UCSF IRB website for more details about the use of devices in research, including the Investigator Checklist for Significant Risk, Non-Significant Risk, and/or IDE Exempt Device Studies

Verification of IDE numbers: If the sponsor's protocol does not list the IDE number, you must submit documentation from the sponsor or FDA identifying the IDE 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 device, please attach it to the application.

View Details	Device Name	Is the Device FDA Approved	Is this a new device or a new use of an already approved device	IDE Number
⊟	INVOcell	Yes	No	

Manufacturer/Supplier of Device	INVO Bioscience
Medicare Category	☐ A ☐ B
Where will the Devices Be Stored	In clinic
Will Devices be supplied at no Cost	No
Is this a HUD (HDE)	No
HDE Number	
Is the Device FDA Approved	Yes
Is this a new device or a new use of an already approved device	No
Is an IDE necessary	No
IDE Number	
Who holds the IDE	N/A
IDE details	
In the opinion of the sponsor, select the level of risk associated with this device	No Significant Risk

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:

50

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

The enrollment target is 32 patients total. There are two groups and 16 patients will be randomized to each group: (1) intravaginal culture with INVOcell device (cases) versus (2) in-vitro fertiilzation and culture of embryos (controls). However, we want to consent up to 50 patients to account for any possible attrition (i.e. IVF cycle gets cancelled, lost to follow up, etc)

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:

As this is a pilot study, we chose to limit the number of participants enrolled. The goal is to enroll 32 participants, with 16 randomized to each group. Given the inclusion and exclusion criteria, we estimate that it will take us approximately 6 months to enroll the necessary number of patients. Participants will be enrolled on a rolling basis.

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

- [ ] 0-6 years
- [ ] 7-12 years
- [ ] 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)

- [ ] 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:

Given our patient population, women who have a diagnosis of infertility or couples requiring donor sperm, there may be some individuals from different backgrounds and those that do not speak English. For those participants, we will be providing an interpreter for their native language, in addition to study documents printed in their native language.

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**.

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.):

Inclusion Criteria:
-Normal uterine cavity
-One or more years of infertility
-Normal male partner (or donor) semen analysis

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

Exclusion Criteria:
-Age < 18 or >37 years old
-AFC < 8
-Abnormal male partner (or donor) semen analysis
-Vaginal inflammation or genital (vaginal, uterine, tubal) infection -Uncontrolled chronic disease (such as uncontrolled diabetes or hypertension)

-Uterine anatomic abnormalities
-Allergy to plastics or inability to use diaphragm retention device
-Untreated hydrosalpinx
-Drug of alcohol abuse (defined by >14 drinks/week)
-Prior history of IVF cycle where fertilization did not occur
-History of recurrent pregnancy loss

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 Recruitment and Consent

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

- [x] Medical records review
- [ ] Recruitment registry
- [ ] Re-contact of participants from the investigators' previous studies
- [ ] 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
- [x] 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 details about the other recruitment methods: **(REQUIRED)**

Participants will be recruited from the Center for Reproductive Health at the University of California at San Francisco. All eligible women will be identified by the clinician at the time of their initial infertility evaluation and approached about the study.

10.2 * 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 IDEAS electronic medical record system used by the Center for Reproductive Health will also be used.

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

Inclusion Criteria:
-Normal uterine cavity
-One or more years of infertility
-Normal male partner (or donor) semen analysis

Exclusion Criteria:

-Age < 18 years old or >38 years old
-AFC < 8
-Abnormal male partner (or donor) semen analysis
-Vaginal inflammation or genital (vaginal, uterine, tubal) infection
-Uncontrolled chronic disease (such as uncontrolled diabetes or hypertension)
-Uterine anatomic abnormalities
-Allergy to plastics or inability to use diaphragm retention device
-Untreated hydrosalpinx
-Drug of alcohol abuse (defined by >14 drinks/week)
-Prior history of IVF cycle where fertilization did not occur
-History of recurrent pregnancy loss

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

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

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

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

10.6 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)

Participants will be recruited from the Center for Reproductive Health at the University of California at San Francisco. All eligible women will be identified by the clinician at the time of their initial infertility evaluation and approached about the study. Women who are interested in participating will receive consent forms to review. They will then be approached by the research team for further information regarding the study. At that time, informed consent will be performed by the research team.

The enrollment target is 40 patients with 20 patients randomized to each group: intravaginal culture with INVOcell device versus in-vitro fertiilzation and culture of embryos. We expect enrollment to take at least 6 months given the inclusion and exclusion criteria for this study.

10.7 * 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.

10.8 * 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.**

At their first visit to the Center for Reproductive Health at the University of California at San Francisco, all eligible women will be identified by the clinician at the time of their initial infertility evaluation and approached about the study. At this time they can indicate participation or decline participation. They may consent at this visit or they will be given materials to take home and consider (patient information sheet and consent form).
If they have not done so already, when patients are ready to start their stimulation cycle, they will confirm whether or not they wish to participate in the study and sign the consent forms.

A study-specific research assistant or healthcare affiliate involved in the care of the patient will obtain informed consent at the first or second clinical visit. Or, if the prospective subject wishes, she may return at a later time to consent to study participation as long as this all occurs prior to oocyte retrieval day.

* 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)**

All people obtaining informed consent are medical affiliates who have years of experience in the field of obstetrics and gynecology in addition to obtaining consent with other IRB-approved studies. In addition, they have taken required courses through the CHR regarding protection of human subjects.

10.9 * 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.

- [ ] 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
- [ ] 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)
- [x] Other method (describe below):

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

The consenting research assistant or investigator will be responsible for determining whether subjects understand the consent process. If a participant asks questions that the research assistant (or other healthcare affiliate obtaining consent) cannot answer, the question will be directed to research supervisor or Principal Investigator.

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

- [x] 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)**

Non-English speakers, as always, will be provided with an interpreter of their native language. In addition, they will receive study documents in their native language for review.

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

The study will not require the patient to devote any additional time beyond what their time commitment is for the standard IVF treatment.

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

10.14 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):

The patients included in the study would be either randomized to the standard, in-vitro fertilization (IVF) technique of embryo culture, versus the newer intra-vaginal culture (IVC) technique. If a patient decides not to participate in the study, they will receive the standard IVF treatment.

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

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

11.0 Waiver of Consent/Authorization for Recruitment Purposes

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

11.1 * 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.

11.2 * 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.

11.3 * 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.

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

- [x] Names
- [x] Dates
- [x] Postal addresses
- [x] Phone numbers
- [x] Fax numbers
- [x] Email addresses
- [ ] Social Security Numbers*
- [x] Medical record numbers
- [ ] Health plan numbers
- [x] Account numbers
- [x] License or certificate numbers
- [ ] Vehicle ID numbers
- [x] Device identifiers or serial numbers
- [x] Web URLs
- [x] IP address numbers
- [x] Biometric identifiers
- [x] Facial photos or other identifiable images
- [ ] Any other unique identifier
- [ ] None

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

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

The patient's full medical history will be updated prior to obtaining informed consent. This will include prior infertility treatments and medical records from prior treatments, labs, imaging, and

operative reports. This is essential to determine if patients meet inclusion/exclusion criteria for the study.

Note: HIPAA requires that you collect the minimum necessary.

11.6 * 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:

The identifiable data collected to determine eligibility for recruitment will be removed from the database as soon as it is determined that the patient (1) does not meet criteria for the study (2) does not want to participate in the study. The only reason to keep this information in the study database would be if a patient would like to be contacted to participate in the study in their subsequent IVF cycle if they do not get pregnant during the current cycle.

12.0 Risks and Benefits

12.1 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.)
- ☑ Risk of pain or physical discomfort caused by the research intervention
- ☐ Possible personal discomfort due to sensitive topics (stress, embarassment, trauma)

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

Randomization risk: You will be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.
Side effects risk: You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. As with anyone undergoing fertility treatments, side effects may be mild or serious.
Fertility treatment risks (either Group 1 or Group 2 participants):

- You will be receiving fertility medications to stimulate your ovaries to grow multiple eggs. Some of the more common side effects from this treatment include: bloating, cramping, nausea, headache, visual changes, hot flashes, and mood changes.
- You also have a small risk of more serious side effects or complications including ovarian hyperstimulation syndrome (OHSS), dehydration, lightheaded/dizziness, and abdominal discomfort.
- From the egg retrieval process, there are risk associated with anesthesia and procedural risks such as bleeding, infection and injury that your treatment physician will describe to you in more detail during the consenting process.
- Your ovaries will be stimulated using the minimal stimulation protocol. This is a lower cost stimulation and sometimes can produce a smaller quantity of eggs than full stimulation. Due to the smaller number of eggs, there may be a reduced pregnancy rate.

INVOcell device risks (Group 1 participants):

- There is a small risk that the placement and retention of the INVOcell device may be slightly uncomfortable for the patient, though studies have shown there has been no significant report of discomfort. During the device retention studies performed, 14/15 women reported no or mild discomfort.
- There is also a chance that the device may be expulsed from the vagina. This has never occurred with the device, and if it were to occur, you will have been trained on how to replace the device into the vagina.
- There is a small risk of failure of embryo development that may occur regardless of which study group you are in. This risk may be slightly increased with the INVOcell device.

Unknown Risks: The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

12.3 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**

Patients will be shown the INVOcell device and vaginal retention device prior to randomization into the IVF or IVC group. They will be educated on its use, instructed to call the on-call physician if there is any discomfort or questions and also instructed on how to replace the device if it is expulsed. They will also be given an informational packet regarding the device and its use.

12.4 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**

As with all other patients at CRH, certified phlebotomists will perform all blood draws in order to minimize risk and discomfort associated with venipuncture. Safety monitoring procedures are in place for clinical phlebotomy procedures, and wherever adverse events are noted, the Principal Investigator will take appropriate action. No additional blood will be drawn for study patients besides what is routinely performed for infertility patients.

In order minimize risk to privacy and confidentiality, access to the research database will be limited to authorized personnel, including the principal investigator, co-investigators and research staff. Subject identities will not be revealed in any publication that may result from the proposed project. The master list for linking samples and clinical information to a particular subject will be considered high-security, and access will be limited to the principal investigator and co-investigators. Consent forms and PHI release forms will be kept in locked files. The confidentiality of all study-related records will be maintained in accordance with State and Federal Laws.

12.5 * 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):

☑ Positive health outcome (e.g. improvement of condition, relief of pain, increased mobility, etc.)

- [ ] 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
- [ ] Knowledge may be gained about their health and health conditions
- [x] Feeling of contribution to knowledge in the health or social sciences field
- [ ] The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children
- [x] Other benefit (describe below)
- [ ] None

Briefly discuss the other possible benefits:

This study will provide more concrete evidence about the use of this device for oral-only or minimal-stimulation protocols. This information will be highly valuable, as these protocols are more likely to be feasible in low-resource settings and may help set a standard protocol for use of INVOcell in resource-limited settings. In addition, this will be offered at a reduced price ($4000 for minimal stimulation cycle) compared to traditional IVF and will provide more access to care.

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

There is only a small risk of possible minimal discomfort with placement of the vaginal device for infertility patients. However, this device allows patients to have their embryos fertilize and grow inside them and potentially result in them becoming pregnant, which is their ultimate goal.

13.0 Data and Safety Monitoring Plan

13.2 * 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

Subjects who participate in the study are assigned a unique ID number that is maintained in a separate database only accessible to the Investigators and Research Staff. Any clinical data that is abstracted for the research database will not contain personally identifying variables (PHI). Data will be continuously monitored by research staff. Results on the progress of the study will be reported annually to the IRB and also upon the study completion.

There will also be a safety monitoring committee formed to oversee the study. The committee will meet monthly to review any safety concerns raised by the study.

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

- (•) Yes
- ( ) No

13.4 DSMB DETAILS: Provide details from the DSMB's charter, including meeting frequency, and affiliations and qualifications of members: If the DSMB has not yet been established, submit these details to us as they become available.

We will assemble a Data and Safety Monitoring Board, comprised of Mitchell Rosen (Reproductive Endocrinologist), Hakan Cakmak (Reproductive Endocrinologist) and Stephanie Jeniches, NP. The committee will meet monthly during the study and review any safety violations or concerns generated by patients completing the exercise protocols.

14.0 Confidentiality, Privacy, and Data Security

14.1 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.
- [ ] 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)

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

- ( ) Yes (•) No

14.3 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

14.4 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:

None

14.5 * 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

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

○ Yes ◉ No

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

○ Yes ◉ No

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

◉ Yes ○ No

Check all the identifiers that may be included:

- ☑ Names
- ☑ Dates
- ☑ Postal addresses
- ☑ Phone numbers
- ☐ Fax numbers
- ☑ Email addresses
- ☐ Social Security Numbers*
- ☑ 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

If publications from this study may include ANY photos or images of patients - even without faces - either collected for research or from the medical records, you are required to have each patient sign the 'Consent for Photography / Authorization for Publication' form prior to submittal for publication. Failure to obtain consent for publication may result in a finding of Serious Non-compliance by the IRB and civil and criminal penalties, *including fines up to $1.5 million dollars* for violation of the HIPAA privacy protections if a participant complains.

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

(●) Yes ( ) No

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

( ) Yes (●) No

14.11 * 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
- [x] Other:

* Specify what other methods will you use to collect data: **(REQUIRED)**

Medical records

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

- [x] UCSF
- [ ] SF VAMC
- [ ] Amazon (Amazon Cloud)
- [ ] Other academic institution
- [ ] 3rd party vendor (business entity)
- [ ] Other (explain below)

14.12 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
- [x] Data are kept in a locked file cabinet
- [ ] Data are kept in a locked office or suite
- [x] Electronic data are protected with a password
- [x] Data are stored on a secure network
- [ ] Data are collected/stored using REDCap or REDCap Survey
- [ ] Data are securely stored in OnCore

14.13 * 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

14.15 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
- [ ] 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, IDEAS

14.16 * 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)

- [x] Drug or alcohol abuse, diagnosis or treatment
- [x] HIV/AIDS testing information
- [x] 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.

15.0 Financial Considerations

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

○ Yes ◉ No

15.4 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?)

There is no cost for participating in the study. You will not be charged for any of the study treatments or procedures, as that will be free of cost. Therefore, there will be no difference in cost based on what treatment group you are in.

The cost of the associated fertility treatments, however, will be charged to your insurance carrier. If your insurance company does not cover these costs, then you will be responsible for these costs. You will be paying for the cost of the minimal stimulation protocol treatment and associated treatments at a reduced price.

The regular cost of the minimal stimulation protocol at the time of IRB submission is: $5885 + anesthesia cost + medications (not included). The reduced price for participation in the study is: $4000 + anesthesia cost + medications (not included).

16.0 Qualifications of Key Study Personnel

16.1 **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
Cedars, Marcelle MD, MD	Principal Investigator	Marcelle Cedars, MD, is a Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences. She serves as Director of the Division of Reproductive Endocrinology and Vice Chair for Clinical Programs of the Department of Obstetrics, Gynecology and Reproductive Sciences.
Dr. Giudice, Linda MD, PhD	Departmental Reviewer (Department Chair)	Linda Giudice, MD, PhD, is a Professor in the Department of Obstetrics, Gynecology and Reproductive Sciences.
Ahmad, Asima	Principal Co-Investigator Data collection at initial and follow- up patient visits (history, physical examination, ultrasound examination); participant recruitment; primary physician for patient contact; data compilation and analysis	MD, MPH (Reproductive Endocrinology & Infertility fellow)
Noel, Martha W	Other Investigator Data collection at initial and follow- up patient visits (history, physical examination, ultrasound examination); participant recruitment; data analysis	MD (Reproductive Endocrinology and Infertility Clinical Fellow)
Lenhart, Nikolaus J	Study coordinator Assist in recruiting and consenting study participants; assist in participant randomization	Study coordinator UCSF Center for Reproductive Health
Wong, Rebecca S	Study coordinator Assist in recruiting and consenting study participants; assist in participant randomization	Study coordinator UCSF Center for Reproductive Health

Hoskin, Elena	Study coordinator Assist in recruiting and consenting study participants; assist in participant randomization; answer study related questions as necessary	Research Coordinator Supervisor in the UCSF Center for Reproductive Health

17.0 Other Approvals and Registrations

17.1 * 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

17.2 * 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

17.4 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

18.0 End of Study Application

18.1

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.