Evidence-based Practice Center Methodology Report Protocol

Project Title: Transparency of Reporting Requirements
Report Topic: Management of Infertility

I. Background

Selective reporting can bias estimates of effect, yet methods to detect such biases are limited.[1,2] Statistical methods for detecting publication bias (e.g., funnel plots, Beggs rank correlation) are underpowered.[3] Comparing outcomes listed under Methods versus those reported under Results in published manuscripts is an expedient but crude method for detecting reporting bias.[4] Another method is to search ClinicalTrials.gov (CT.gov) and compare studies identified there to published studies (to detect publication bias) and to compare planned analyses and outcomes reported in CT.gov to those reported in the final publication (to detect reporting bias).[4,5] The EPC guidance recommends this approach.[6] While conceptually sound, this approach may be labor-intensive, and its utility uncertain.

II. Project Goals

The overall goal of this project is to determine whether selective reporting introduces biased estimates of effect in the Duke "Management of Infertility" systematic review. A secondary goal is to estimate the skills and person-hours required to detect these biases.

By comparing results from a search of CT.gov and studies included in the Infertility review, we will determine if selective reporting and/or reporting bias exists. Importantly, if selective reporting is detected, we will estimate its impact by revising the Strength of Evidence (SOE) Tables to determine if the SOE ratings are changed.

III. The Ongoing Systematic Review (Management of Infertility)

The ongoing "Management of Infertility" systematic review, RFTO #2, poses six draft key questions (KQs), four addressing the comparative effectiveness and safety of treatment strategies for subfertile/infertile women by etiology (e.g., endometriosis), one addressing treatment strategies for male factor infertility, and one addressing health outcomes of oocyte and semen donors. Treatments evaluated will be broad-ranging, including procedures (e.g., *in vitro* fertilization), fertility-enhancing drugs (e.g., clomiphene), and surgical interventions (e.g., treatment of endometriosis). The problem and range of etiologies and treatments will provide opportunities to explore different approaches to searching in CT.gov. The broad range of interventions is advantageous because they are evaluated by scientists with different training and traditions regarding publication, and the clinical trial registration and results submission requirements described in Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) applies only to a subset of interventions. Finally, the review has sufficient breadth

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to allow our team to focus on a subset of KQs, where clinical trials are applicable, and a range of interventions indicated for different etiologies (i.e., KQ 1, polycystic ovarian syndrome; KQ 2, endometriosis; KQ 4, tubal factor infertility). This will enhance the generalizability of our results to other EPC projects.

IV. Methods

Our general approach will be pragmatic, using methods that could be readily incorporated into future systematic reviews. For feasibility reasons and to apply our methods to a range of interventions, we will include only KQ 1, KQ 2 and KQ 4 in this analysis (Appendix 1). Three of our key personnel (E. Myers, J. Gierisch, J. Eaton) and 4 EPC staff (M. von Isenburg, M. Chobot, R. Gray, A. McBroom Brooks) are participating in both the Infertility systematic review and this transparency project. These team members will ensure coordination between the two projects.

Searching CT.gov

We will conduct a search in CT.gov for each KQ with the assistance of our search librarian. Because CT.gov does not use MeSH-based search terms, we will adapt the search strategies developed for the Infertility systematic review (Appendix 2) to language appropriate for CT.gov. We will conduct two searches, a broad search using the basic interface and a more specific search using the advanced interface in CT.gov. We will use the fields, "recruitment," "study results," "study type," "conditions," "interventions," "age group," and "first received" to narrow the search using the advanced interface. Results of the two searches will be imported into an EndNote library. This may involve developing a customized import filter for EndNote, and if so, this will be developed in collaboration with our librarian.

Matching Studies

We will match randomized controlled trials (RCTs) identified in CT.gov with those identified for the Infertility review at several levels:

First, we will determine whether all studies included in the Infertility review have a matching record in CT.gov using results from the narrow search executed with the CT.gov advanced interface. Matching will be performed initially in EndNote using the NCT identifier. For unmatched studies, we will conduct a manual match using the condition, intervention, sample size, and author/investigator as matching variables. The goal of this match is to determine if all eligible studies have a matching record in CT.gov. Matching will be performed initially for the narrow CT.gov search. For any unmatched studies, we will determine if they were captured in the broad CT.gov search.

Second, for eligible studies with a CT.gov record, we will abstract selected variables from the CT.gov record to determine whether key study design variables match information in the published manuscript (Appendix 3). Variables abstracted will be:

- Date of completion

- Number of study arms
- Intervention description
- Study design
- Outcomes measures
- Analysis approach
- Subgroup analyses

Data from CT.gov will be compared to published data. For each variable, the data will be classified as: matching, discrepant, or possibly discrepant. Discrepant data are defined as cases where information is absent in one source but reported in another, or when the information given in the two sources is contradictory. Discrepancies will be summarized quantitatively across studies (e.g., % agreement, kappa) and narratively by study.

Third, we will screen the remaining CT.gov citations for potentially eligible completed studies. Eligibility criteria for each KQ are given in Appendix 4. We will use author names and intervention terms to search for a matching publication in PubMed. We will classify studies into two groups: completed study without a published manuscript, and completed study with a matching published manuscript that was not identified in the systematic review search. We will report the studies by time elapsed since study completion and identify whether the study was identified from the broad search, narrow search, or both searches.

All matching will be constrained to studies published since the 2005 ICMJE policy requiring trial registration. Manual matching will be performed initially by a research assistant, who will rate her confidence in the match as: confident or not confident. A study investigator will review the matching classification for any studies or variables rated as "not confident," and for a sample of matches rated as "confident." Team members involved in matching will pilot the forms and process in order to refine our data collection forms and procedures.

Estimate of Person-hours to Complete the Project

EPC staff routinely log the time spent working on projects using project specific codes. Co-investigators do not log project time routinely. Therefore, our project coordinator will send weekly queries to co-investigators asking for estimates of time spent (to nearest 15 minutes) completing project specific tasks. These estimates will be tracked in an excel spreadsheet. We will use the staff logs and co-investigator weekly reports to estimate the total staff time and co-investigator time dedicated to completing project related activities.

Impact on Systematic Review Conclusions

Study conclusions will flow from the strength of evidence (SOE). We will use the GRADE framework for evaluating SOE, a framework that includes assessment of risk of bias, consistency, precision, directness, and publication bias. The EPC risk of bias tool explicitly considers reporting bias. Therefore, risk of bias and publication bias are the domains most likely to be affected by supplemental data from CT.gov. In collaboration with authors of the Infertility systematic review, we will generate a revised SOE table and determine qualitatively whether

study conclusions would change. We will pay particular attention to whether conclusions change by intervention type (e.g., procedure, drug, surgical intervention), as selective reporting may vary by intervention.

References

1. Borenstein M, Hedges LV, Higgins JPT, et al. Publication Bias. *Introduction to Meta-Analysis*: John Wiley & Sons, Ltd; 2009:277-92.
2. Song F, Parekh S, Hooper L, et al. Dissemination and publication of research findings: an updated review of related biases. Health Technology Assessment. 2010;14(8):iii, ix-xi, 1-193. PMID: 20181324.
3. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002. PMID: 21784880.
4. Dwan K, Altman DG, Clarke M, et al. Evidence for the selective reporting of analyses and discrepancies in clinical trials: a systematic review of cohort studies of clinical trials. PLoS Med. 2014;11(6):e1001666. PMID: 24959719.
5. Hartung DM, Zarin DA, Guise JM, et al. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. Ann Intern Med. 2014;160(7):477-83. PMID: 24687070.
6. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2014.

APPENDIXES

Appendix 1. Infertility KQs

KQ 1: What are the comparative safety and effectiveness of available treatment strategies for women with polycystic ovary syndrome (PCOS) who are subfertile/infertile and who wish to become pregnant?

a. Does the optimal treatment strategy vary by patient characteristics such as age, ovarian reserve, race, body mass index (BMI), presence of other potential causes of female infertility, or presence of male factor infertility?

KQ 2: What are the comparative safety and effectiveness of available treatment strategies for women with endometriosis who are subfertile/infertile and who wish to become pregnant?

a. Does the optimal treatment strategy vary by patient characteristics such as age, ovarian reserve, race, BMI, stage of endometriosis, presence of other potential causes of female infertility, or presence of male factor infertility?

KQ 3: What are the comparative safety and effectiveness of available treatment strategies for women who are subfertile/infertile for unknown reasons and who wish to become pregnant?

a. Does the optimal treatment strategy vary by patient characteristics such as age, ovarian reserve, race, BMI, presence of other potential causes of female infertility, or presence of male factor infertility?

KQ 4: What are the comparative safety and effectiveness of available treatments for women with tubal or peritoneal factors (e.g., pelvic adhesions) who are subfertile/infertile and who wish to become pregnant?

a. Does the optimal treatment strategy vary by patient characteristics such as age, ovarian reserve, race, BMI, presence of other potential causes of female infertility, or presence of male factor infertility?

KQ 5: What are the comparative safety and effectiveness of available treatment strategies for couples with male factor infertility and no evidence of an underlying diagnosis associated with infertility in the female partner?

a. Does the optimal treatment strategy vary by characteristics in either partner such as age, ovarian reserve, race, or BMI?

KQ 6: What are the short- and long-term health outcomes of donors in infertility?

a. For female oocyte donors:
    i. What is the most appropriate evaluation prior to donation?
    ii. Do short- and long-term outcomes differ among different induction/retrieval protocols?

b. For male semen donors:

    i. Are there long-term health, quality-of-life, or other adverse outcomes associated with donation?

Appendix 2: Infertility SR – PubMed Search Strategy

Set #	Terms
#1	"Infertility"[Mesh] OR "Anovulation"[Mesh] OR “infertility”[tiab] OR “infertile”[tiab] OR “subfertility”[tiab] OR “subfertile”[tiab] OR “sub-fertility”[tiab] OR “sub-fertile”[tiab] OR “anovulation”[tiab] OR “aspermia”[tiab] OR “asthenozoospermia”[tiab] OR “azoospermia”[tiab] OR “oligospermia”[tiab] OR “sertoli cell-only syndrome”[tiab]
#2	"Reproductive Techniques, Assisted"[Mesh] OR "Polycystic Ovary Syndrome/therapy"[Mesh] OR "Endometriosis/therapy"[Mesh] OR "Nutrition Therapy"[Mesh] OR "Weight Loss"[Mesh] OR "Exercise"[Mesh] OR "Exercise Therapy"[Mesh] OR "Fertility Agents"[Mesh] OR "Clomiphene"[Mesh] OR "Gonadotropin-Releasing Hormone"[Mesh] OR "Metformin"[Mesh] OR "Hormone Antagonists"[Mesh] OR "Gonadotropins"[Mesh] OR “Watchful Waiting"[Mesh] OR “Natural Family Planning Methods “[MeSH] OR “Ovulation Detection”[MeSH] OR "Fallopian Tubes/surgery"[Mesh] OR "Fallopian Tube Diseases/surgery"[Mesh] OR "Gynecologic Surgical Procedures"[Mesh] OR “Arginine/therapeutic use”[MeSH] OR “Aspartic Acid/therapeutic use”[MeSH] OR “Citrulline/therapeutic use”[MeSH] OR “Flavonoids/therapeutic use”[MeSH] OR “Adrenal Cortex Hormones”[MeSH] OR “Ejaculatory Ducts/therapy”[MeSH] OR "Varicocele/surgery"[Mesh] OR “Laser Therapy”[MeSH] OR “Dexamethasone”[MeSH] OR “Vasovasostomy”[MeSH] OR “Urofollitropin”[MeSH] OR “electrocoagulation”[MeSH] OR “Preimplantation Diagnosis”[MeSH] OR "Insemination"[Mesh] OR "Uterine Diseases/surgery"[Mesh] OR "Reproductive Techniques"[Mesh:NoExp] OR "Ovulation Prediction"[Mesh] OR "Genetic Testing"[Mesh] OR "letrozole"[Supplementary Concept] OR “cetrorelix”[Supplementary Concept] OR “ganirelix”[Supplementary Concept] OR “follitropin beta”[Supplementary Concept] OR “follitropin alfa”[Supplementary Concept] OR “Crinone”[Supplementary Concept] OR “Ovidrel”[Supplementary Concept] OR “reproductive techniques”[tiab] OR “reproductive technology”[tiab] OR “reproductive technique”[tiab] OR “reproductive technologies”[tiab] OR “assisted reproductive”[tiab] OR “ivf”[tiab] OR “in vitro”[tiab] OR invitro[tiab] OR “sperm injection”[tiab] OR “ICSI”[tiab] OR “IUI”[tiab] OR “intrauterine insemination”[tiab] OR “intrauterine implantation”[tiab] OR “embryo transfer”[tiab] OR “artificial insemination”[tiab] OR “assisted pregnancy”[tiab] OR “assisted reproduction”[tiab] OR “ovulation induction”[tiab] OR “ovarian stimulation”[tiab] OR “ovarian hyperstimulation”[tiab] OR “clomiphene”[tiab] OR “serophene”[tiab] OR “clomiphene citrate”[tiab] OR “letrozole”[tiab] OR “metformin”[tiab] OR “gonadotropins”[tiab] OR “gonadotropin releasing hormone”[tiab] OR “hormone antagonists”[tiab] OR “menotropins”[tiab] OR “menopur”[tiab] OR “repronex”[tiab] OR “goserelin”[tiab] OR “Zoladex”[tiab] OR “leuprolide”[tiab] OR “Lupron”[tiab] OR “nafarelin”[tiab] OR “Synarel”[tiab] OR “cetrorelix”[tiab] OR “Cetrotide”[tiab] OR “degarelix”[tiab] OR “Firmagon”[tiab] OR “ganirelix”[tiab] OR “antagon”[tiab] OR exercise[tiab] OR diet[tiab] OR “weight loss”[tiab] OR “natural family planning”[tiab] OR “timed intercourse”[tiab] OR “Billings”[tiab] OR “Creighton”[tiab] OR “rhythm method”[tiab] OR “standard days method”[tiab] OR “calendar method”[tiab] OR “basal body temperature method”[tiab] OR “hysteroscopy”[tiab] OR “hysteroscopic”[tiab] OR “microhysteroscopy”[tiab] OR “microhysteroscopic”[tiab] OR “ovarian drilling”[tiab] OR “donor oocytes”[tiab] OR “oocyte retrieval”[tiab] OR “sperm donation”[tiab] OR “sperm donor”[tiab] OR “semen donation”[tiab] OR “semen donor”[tiab] OR “sperm extraction”[tiab] OR “sperm retrieval”[tiab] OR “sperm aspiration”[tiab] OR “tesa”[tiab] OR “micro tese”[tiab] OR “mesa”[tiab] OR “pesa”[tiab] OR “ejaculatory duct resection”[tiab] OR “recombinant human follicle stimulating hormone”[tiab] OR “rhFSH”[tiab] OR “rFSH”[tiab] OR “hormone therapy”[tiab] OR “laser vaporization”[tiab] OR “laser vaporisation”[tiab] OR “dexamethasone”[tiab] OR “vasectomy reversal”[tiab] OR “sterilization reversal”[tiab] OR “superovulation”[tiab] OR “follistim”[tiab] OR “Gonal F”[tiab] OR “Gonal-F”[tiab] OR “Bravelle”[tiab] OR “crinone”[tiab] OR “endometrim”[tiab] OR “prometrium”[tiab] OR “fulguration”[tiab] OR “endometriosis excision”[tiab] OR “endometrioma excision”[tiab] OR “ovarian cystectomy”[tiab] OR “tubal ligation reversal”[tiab] OR “tubal cannulation”[tiab] OR

Set #	Terms
	“therapeutic donor insemination”[tiab] OR “ovulation prediction”[tiab] OR “ovidrel”[tiab] OR “assisted hatching”[tiab] OR “preimplantation diagnosis”[tiab] OR “preimplantation genetic diagnosis”[tiab] OR “preimplantation screening”[tiab] OR “preimplantation genetic screening”[tiab] OR “preimplantation testing”[tiab] OR “preimplantation genetic testing”[tiab]
#3	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR randomly[tiab] OR Clinical trial[pt] OR “clinical trial”[tiab] OR “clinical trials”[tiab] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention studies"[MeSH Terms] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH Terms] OR "case-control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal”[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab] OR "follow up"[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])
#4	#1 AND #2 AND #3
	Dates: 2008/01/01 - present
	Limit: English

Appendix 3: Draft Abstraction Form for Matching Study Variables Between Published Manuscript and CT.Gov

Eligible Study Record*: Author Last name, Publication Date (Month/Year), RefID

CT.gov Identifier: NCT number

CT.Gov Record Field**	Published Manuscript(s)	Agreement
[Primary completion date]	Journal Pub date*	NA
[Last updated data]	NA	NA
[Assigned interventions]	Methods: Number of study arms	M/D/P
[Assigned interventions]	Methods: Intervention 1	M/D/P
[Assigned interventions]	Methods: Intervention 2	M/D/P
[Assigned interventions]	Methods: Comparators	M/D/P
[Study design: allocation]	Methods: randomized	M/D/P
[Primary outcome measure]	Methods: primary outcome measure	M/D/P
[Primary outcome measure]	Results: All planned timepoints reported	M/D/P
[Secondary outcome measure]	Results: secondary outcome-1 reported	M/D/P
[Secondary outcome measure]	Results: secondary outcome-2 reported	M/D/P
[Secondary outcome measure]	Results: secondary outcome-3 reported	M/D/P
[Secondary outcome measure]	Results: secondary outcome-4 reported	M/D/P
[Secondary outcome measure]	Results: secondary outcome-5 reported	M/D/P
[Secondary outcome measure]	Results: secondary outcome-6 reported	M/D/P

*All publications that result from a single trial will be grouped and reviewed together.
**[CT.Gov Field]
Journal publication date: We will use date of first publication (e.g., online publication).
Abbreviations: D=discrepant; M=matching; NA=not applicable; P=possibly discrepant

Appendix 4. Eligibility Criteria

KQ 1:

- **Population:**
  - Women of reproductive age (18-44) with no pregnancy after 12 months of regular intercourse for women under 35, or 6 months for women 35 and older (alternate definitions may be appropriate), and diagnosed PCOS. Subpopulations of interest include groups differing in age; race/ethnicity; obesity/BMI; ovarian reserve; history of prior treatments; primary vs. secondary infertility; *maternal parity*; diagnostic criteria/evaluation (e.*g., WHO categories*); *insurance status (particularly coverage of infertility diagnosis and treatment);* and presence or absence of male factor infertility, other female causes of infertility, or *common comorbidities such as hypertension and diabetes.*
- **Interventions:**
  - Clomiphene citrate, letrozole, diet/exercise/other weight loss strategies, timed intercourse using various technologies in conjunction with oral ovulation induction, metformin, combination oral medications, ovulation induction with gonadotropins with or without intrauterine insemination (IUI), surgery (ovarian drilling), ART (IVF and ICSI) with patient and donor oocytes
- **Comparators:**
  - Any other active intervention (e.g., clomiphene vs. metformin), or timing/sequence of interventions (e.g., ovulation induction/IUI followed by ART if unsuccessful vs. proceeding directly to ART, or timed intercourse with oral medications or injectable gonadotropins).
- **Outcomes:** (Note that these outcomes are ordered in approximate relative importance to patients, based on input from topical experts and Key Informants, rather than temporal occurrence in the clinical pathway.)
  - Live birth (both cumulative and per cycle)
    - Live singleton birth
    - Live multiple birth
  - Pregnancy complications
    - Multiple births (and associated complications)
    - Ectopic pregnancies
    - Miscarriage
  - Neonatal outcomes
    - Death
    - Birthweight (categorized as low birthweight/normal birthweight)

        - Congenital anomalies
    - Time to pregnancy
        - Calendar time (months)
        - Number of cycles
    - Costs
        - Patient
        - Health system
        - Societal
    - Short-term adverse effects of treatments
        - OHSS
        - Surgical complications
    - Long-term outcomes (child)
        - Neurodevelopmental/other issues related to prematurity
        - Specific issues related to infertility treatment (epigenetic changes*, sex chromosomal abnormalities*, etc.)
        - Cancer (all types)
    - Long-term outcomes (maternal)
        - Cancer
        - Subsequent fertility
- **Timing:**
    - Short-term
        - From beginning of treatment through first 12 months of life if live birth occurs
    - Long-term
        - 12 months or more from completion of treatment (no live birth) or from date of live birth
- **Settings:**
    - Subspecialty practice (infertility specialist)
    - General gynecology practice
    - Family practice/general internist/nurse practitioner/other non-gynecologist primary care provider
    - *United States vs non-US*

KQ 2:

- **Population:**
    - Women of reproductive age (18-44) with no pregnancy after 12 months of regular intercourse for women under 35, or 6 months for women 35 and older (alternate definitions may be appropriate), and diagnosed endometriosis. Subpopulations of interest include groups differing in age; race/ethnicity; obesity/BMI; ovarian reserve; history of prior treatments; primary vs. secondary infertility; *maternal parity*; *insurance status;* diagnostic criteria/evaluation; stage of endometriosis; and presence or absence of male factor infertility, other female causes of infertility, or common comorbidities such as hypertension and diabetes.
- **Interventions:**
    - Surgical excision of endometriotic implants, alternative surgical approaches to destruction of lesions (e.g., laser vaporization), gonadotropin-releasing hormone agonists or antagonists, timed intercourse with various technologies, superovulation with gonadotropins with or without IUI, ART (IVF and ICSI) with patient and donor oocytes
- **Comparators:**
    - Either be direct between two alternatives (e.g., surgery vs. gonadotropin-releasing hormone [GnRH] agonists/antagonists), or timing/sequence of interventions (e.g., ovulation induction/IUI followed by ART if unsuccessful vs. proceeding directly to ART).
- **Outcomes:** Same as for KQ 1
- **Timing:** Same as for KQ 1
- **Settings:** Same as for KQ 1

KQ 3:

- **Population:**
    - Women of reproductive age (18-44) with no pregnancy after 12 months of regular intercourse for women under 35, or 6 months for women 35 and older (alternate definitions may be appropriate), and no other diagnosed cause of subfertility/infertility. Subpopulations of interest include groups differing in age; race/ethnicity; obesity/BMI; ovarian reserve; history of prior treatments; primary vs. secondary infertility; *maternal parity*; *insurance status;* diagnostic criteria/evaluation; and presence or absence of common comorbidities such as hypertension and diabetes. Women without male partners (single women or lesbian couples) are also a subgroup of interest, particularly for long-term outcomes.
- **Interventions:**
    - Timed intercourse with various technologies, oral ovulation induction agents (e.g., clomiphene citrate), ovulation induction with gonadotropins with and

without IUI, ART (IVF and ICSI) with patient and donor oocytes, watchful waiting

- **Comparators:**
  - Any other active intervention, or timing/sequencing of timing/sequence of interventions (e.g., ovulation induction/IUI followed by ART if unsuccessful vs. proceeding directly to ART).
- **Outcomes:** Same as for KQ 1
- **Timing:** Same as for KQ 1
- **Settings:** Same as for KQ 1

KQ 4:

- **Population:**
  - Women of reproductive age (18-44) with no pregnancy after 12 months of regular intercourse for women under 35, or 6 months for women 35 and older (alternate definitions may be appropriate), and identified tubal *or peritoneal* disease potentially amenable to surgical interventions (hydrosalpinx, unilateral occlusion, prior tubal sterilization). Subpopulations of interest include groups differing in age, race/ethnicity, obesity/BMI, history of prior treatments, *anatomic* cause of tubal occlusion (e.g., prior sterilization vs. adhesions), *maternal parity, insurance status,* and primary vs. secondary infertility.
- **Interventions:**
  - Surgical repair, ART (IVF and ICSI) with patient and donor oocytes
- **Comparators:**
  - Other active interventions (including combinations of therapy such as surgical removal of hydrosalpinx followed by ART)
- **Outcomes:** Same as for KQ 1
- **Timing:** Same as for KQ 1
- **Settings:** Same as for KQ 1

KQ 5:

- **Population:**
  - Men partnered with women of reproductive age (as defined in other KQs), with no documented female cause of infertility and documented male infertility. Subpopulations of interest include groups differing by cause of male infertility (identified hormonal cause, varicocele, idiopathic), age (male and female), race/ethnicity, obesity/BMI, history of prior treatments, primary vs. secondary infertility, diagnostic criteria used for male infertility, *insurance status,* and presence or absence of common comorbidities such as hypertension and diabetes.

- **Interventions:**
    - ICSI (note that interventions and comparators may vary depending on underlying cause of male factor infertility), testicular sperm extraction, vasectomy reversal, surgical repair of varicocele, IUI, donor insemination, ART, treatment of underlying endocrinopathy
- **Comparators:**
    - Any other active intervention
- **Outcomes:** Same as for KQ 1
- **Timing:** Same as for KQ 1
- **Settings:**
    - Same as for KQ 1, with the addition of male reproductive medicine specialist/urologist.

KQ 6:

- **Population:**
    - Women of reproductive age (18-44) who are potential donors of oocytes for ART, and males donating semen for intrauterine insemination or ART
- **Interventions (women):**
    - Pre-donation testing strategies; ovulation induction with gonadotropins using different induction/retrieval protocols
- **Comparators (women):**
    - Any other active intervention, or women who are NOT undergoing ovulation induction for oocyte donation
- **Comparators (men)**
    - Men who do not donate semen
- **Outcomes (women):**
    - Short-term adverse effects of treatments
        - OHSS
        - Surgical complications
        - Adverse effects of treatments (e.g., GI symptoms for metformin, hot flashes for clomiphene)
    - Long-term outcomes (donor)
        - Downstream fertility
        - Cancer
        - Age at menopause

    - Quality-of-life outcomes
- **Outcomes (men):**
    - Quality-of-life outcomes
- **Timing :**
    - Short term:
        - From time of beginning donation process to 12 months after donation
    - Long-term:
        - 12 months or more from time of first donation
- **Setting:** Subspecialty practice (infertility specialist)