CREST Scholar Orientation: Resources and Opportunities at NICHD

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OUTLINE

• NICHD Mission, Vision, Strategic Plan
• High Program Priority Areas
• Reproductive Medicine Clinical Trials Program at NICHD
  • RMN
  • New Reproductive Medicine clinical trial program (ConFIRM)
• Resources for clinical research at NICHD
  • Data and Specimen Hub (DASH)
  • RMN repository/ies
  • Funding opportunities for clinical research
• Clinical Reproductive Scientist Training (CREST) and you
  • Making the most of your CREST experience
  • Continuing your involvement in clinical research
NICHD Mission and Vision

- To lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all.
- Healthy pregnancies, healthy children, healthy and optimal lives.
NICHD Organization

- **Office of the Director**
- **Division of Extramural Research (DER)**
- **Division of Intramural Population Health Research (DIPHR)**
- **Division of Intramural Research (DIR)**
- **National Center for Medical Rehabilitation Research (NCMRR)**
NICHD Strategic Plan 2020: Themes

• Understanding the Molecular, Cellular and Structural Basis of Development
• Promoting Gynecologic, Andrologic and Reproductive Health
• Setting the Foundation for Healthy Pregnancies and Lifelong Wellness
• Improving Child and Adolescent Health and the Transition from to Adulthood
• Ensuring Safe and Effective Therapeutics and Devices
• Cross-cutting Topics
  • Health disparities
  • Disease Prevention
  • Infectious Disease
  • Nutrition
  • Global Health
Extramural Scientific Branches (12)

- Contraception Research Branch (CRB)
- Fertility and Infertility Branch (FIB)
- Gynecologic Health and Disease Branch (GHDB)
- Maternal and Pediatric Infectious Disease Branch (MPIDB)
- Pediatric Growth and Nutrition Branch (PGNB)
- Population Dynamics Branch (PDB)
- Pregnancy and Perinatology Branch (PPB)
Fertility and Infertility Branch (FIB) Mission

- FIB’s mission is to encourage, enable, and support research aimed at alleviating human infertility, uncovering new possible pathways to control fertility, and expanding fundamental knowledge of processes that underlie human reproduction.
FIB High Program Priority Areas

- Early Pregnancy Loss and Predictors of Pregnancy Outcome
- Fertility and Overall Health
- ‘Omic Approaches to Investigate Infertility Pathogenesis
- Nutrition, Metabolism, Circadian Rhythms, and Reproduction
- Early Reproductive Transitions

In addition, applications for FIB that propose technical innovations or that address health disparities or involve diverse populations (race, ethnicity, disability, or patients with diseases not previously recognized to have a fertility/infertility component) will have higher priority, even if they do not address one of the science areas listed in the following priorities.

- https://www.nichd.nih.gov/about/org/der/branches/fib
FIB Examples of HPP topics

• Gamete quality and pre-placental processes as they relate to the etiology of early pregnancy loss
• Transgenerational epigenetic inheritance
• The relationship of fertility status to overall health and disease
• Genetic basis of idiopathic male and female fertility
• Impact of nutrition and metabolism on fertility
• Identification of biomarkers to study reproductive transitions
• Development of innovative technologies and model systems that can advance progress in reproductive biology and medicine
Translation Continuum

- Bench
- Bedside
- Clinic
- Community
- Population & Policy
RMN/ConFIRM and CREST

• Interaction between CREST scholar and clinical trial PIs
• CREST scholars have participated in RMN studies as co-Investigators at CREST ‘ancillary’ sites
• RMN PIs and coordinators provided guidance for navigating IRB, grants offices, recruiting participants and conducting trials
• CREST may use RMN or other data to investigate new questions of clinical importance
• Increase knowledge through publications and presentations
Continuum of Clinical Research Mapped on Translational Blocks

"1st Translational Block"

Basic Research → Human Studies → Clinical Trials → Implementation

Centers ↔ RMN ↔ CREST

"2nd Translational Block"

Sung, N, Crowley, W.F. et al JAMA, 2003
Reproductive Medicine Network

• Funded by NICHD from 1989-2019
  • Cooperative multi-center clinical trial network
• To carry out large clinical trials in the area of male and female infertility and reproductive diseases and disorders.
• Goal: Trials that have immediate impact on clinical practice
• New Model is a multi-investigator linked R01 program
  • Reproductive Medicine Clinical Trial Program/CONFIRMsortia for Infertility and Reproductive Medicine (CONFIRM)
Reproductive Medicine Network: 2013-2018+1

- Multicenter Clinical Trial Network (www.c2s2.yale.edu/rmn)
  - 6 Main Sites + 1 DCC (Data Coordinating Center)
  - 6 Ancillary Sites (modeled on CREST Collaboration)
  - Steering Committee Chair appointed by FI Branch/NICHD

- Goal
  - To develop novel and more effective strategies for diagnosis, treatment, and prevention of infertility and underlying causes
  - To evaluate new interventions for treatment of infertility
  - To more rapidly bring scientific discoveries to the bedside

- Studies/clinical trials on female infertility, male infertility incl comparative effectiveness of IVF standard treatments

- Geographic Diversity and Inclusion

- Data and Specimen Repository
  - data for completed trials in DASH
  - Specimen repositories at PI Institutions

- Resource for CREST Scholars for mentorship and secondary analyses
RMN Protocols Completed in Last Cycle

- **ACTorNOT** -- Optimal Treatment for Women with a Persisting Pregnancy of Unknown Location: Active Treatment versus No Treatment
  The “ACTorNOT” Trial (Barnhart-PI)

- **FIT-PLESE** -- Improving Reproductive Fitness with Pretreatment with Lifestyle Modification in Obese Women with Unexplained Infertility: FIT-PLESE (Legro-PI)

- **MOXI** -- Males, Antioxidants, and Infertility--RCT of the effect of antioxidants on semen parameters and male fertility (Steiner-PI)
Optimal Treatment of Persisting Pregnancy of Unknown Location: RCT of Women at Risk for an Ectopic Pregnancy
Active Treatment vs. Expectant Management (No Treatment):
The “ACTorNOT TRIAL-Barnhart(PI)

- Pragmatic randomized clinical trial evaluating optimal management for women with a pregnancy of unknown location
  - expectant management
  - empiric methotrexate
  - uterine evacuation
- 1:1:1:1 randomization
- Outcome is change of plan from initial strategy
- Secondary outcome -- efficacy and cost analysis
- Sample size goal - 275
FIT-Plese

Overview

Obese Women (BMI $\geq$30 and Age $\leq$ 40y) with Unexplained Infertility (N = 380)

**Phase I**

Lifestyle: 16 weeks

Intensive Lifestyle Modification:
- Weight Loss AND Increased Physical Activity (N = 190)

Standard Lifestyle Modification:
- Increased Physical Activity (N = 190)

**Phase II:**

Infertility Treatment

3 cycles of Ovarian Stimulation with Clomiphene /Insemination
(Clamp physical activity and weight during this phase)

**Phase III:**

Pregnancy (3 visits): One per trimester for weight, blood pressure, and glycemic measures

**Primary Outcome:** Good Birth Outcome: Healthy singleton or twin Live Birth ($\geq$ 37 weeks, 2500-4000g, no major anomaly)

**Phase IV:**

Infancy

Infant Follow up
MOXI Overview

• Study Population: 790 Couples with male factor infertility

• Inclusion criteria:
  • Sperm concentration ≤15 Million/ml or, total motility ≤40%, or normal morphology (Kruger) ≤4%, or DNA fragmentation (SCSA) >25%
  • Females (≤38 yo) with tubal patency, regular menstrual cycles, and evidence of ovulation

• Primary Outcome: Live birth

• Secondary:
  • Pregnancy, time-to-pregnancy, miscarriage
  • Subgroup analyses (type of sperm abnormality)

• Internal Pilot
  • 120
  • Changes in semen parameters
Other RMN Protocols

• Recent
  • PrISICE Pilot -- Preimplantation Genetic Screening (PGS) and Deferred Transfer of Cryopreserved Embryos over “Freeze-Only” Deferred Transfer without PGS or Immediate Embryo Transfer during a “Fresh” In Vitro Fertilization Cycle (Cedars, Coutifaris-PIs)
  • ENDOMarker -- Evaluation, Validation and Refinement of Noninvasive Diagnostic Biomarkers for Endometriosis (Barnhart-PI)

• Previous
  • PPCOS I – Pregnancy in Polycystic Ovary Syndrome I (CC vs. Met vs. CC+Met
  • PPCOS II – Pregnancy in Polycystic Ovary Syndrome II (CC vs. Letrozole)
  • AMIGOS – Assessment of Multiples Gestations with Ovarian Stimulation (CC vs. Letrozole vs. Gonadotropins) and IUI
  • PSY-FI – PsychoSocial Family Issues associated with Multiple Gestations
  • PhOx – RCT of Physiologic (3%) vs. Standard Oxygen Tension for IVF
Reproductive Medicine Network: 2013-2018+1

• Multicenter Clinical Trial Network
  • 6 +1 Main Sites
  • 6 Ancillary Sites (modeled on CREST Collaboration)
  • SC Chair appointed by FI Branch/NICHD

• Goal
  • To develop novel and more effective strategies for diagnosis, treatment, and prevention of infertility and underlying causes
  • To evaluate new interventions for treatment of infertility
  • To more rapidly bring scientific discoveries to the bedside

• Studies/clinical trials on female infertility, male infertility including comparative effectiveness of IVF standard treatments-Concept protocols reviewed~delayed onset

• AB and DSMB appointed by NICHD Director

• Geographic Diversity and Inclusion

• Data and Specimen Repository funded through DCC

• Resource for CREST Scholars for mentorship and secondary analyses
ConFIRM—Consortia for Reproductive Medicine and Infertility

- Multi-PI linked R01 Consortia
  - R01 applications with common clinical trial protocol
- DCC included in linked application with same clinical trial protocol. DSMB is constituted in DCC R01.
- PI may identify ancillary affiliated clinical site or subcontract with distant site.
- PI may be a part of more than one (maximally 3) multi-PI linked application.
- Separate maximal site infrastructure costs and protocol capitated costs.
## Reproductive Medicine Collaborative Clinical Trials Program (Collaborative R01)

<table>
<thead>
<tr>
<th>PI/MPI</th>
<th>Institution</th>
<th>Consortium – n/N</th>
<th>Special Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>V. Baker/J. Segars</td>
<td>Johns Hopkins University</td>
<td>RCT of programmed or natural cycle for frozen embryo transfer – NatPro -- 1/3</td>
<td>DCC, sIRB</td>
</tr>
<tr>
<td>K. Hansen</td>
<td>Univ of Oklahoma Hlth Sciences Ctr</td>
<td>RCT of programmed or natural cycle for frozen embryo transfer – NatPro -- 2/3</td>
<td></td>
</tr>
<tr>
<td>R. Lathi/V. Winn</td>
<td>Stanford University</td>
<td>RCT of programmed or natural cycle for frozen embryo transfer – NatPro -- 3/3</td>
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<tr>
<td>H. Taylor/H. Zhang</td>
<td>Yale University</td>
<td>Pre-IVF tx with GnRH antagonist in women with endometriosis – PREGNANT –1/4</td>
<td>DCC, sIRB</td>
</tr>
<tr>
<td>N. Santoro</td>
<td>Univ of Colorado Denver</td>
<td>Pre-IVF tx with GnRH antagonist in women with endometriosis – PREGNANT –2/4</td>
<td></td>
</tr>
<tr>
<td>J. Robins</td>
<td>Northwestern Univ at Chicago</td>
<td>Pre-IVF tx with GnRH antagonist in women with endometriosis – PREGNANT –3/4</td>
<td></td>
</tr>
<tr>
<td>S. Young</td>
<td>Univ North Carolina</td>
<td>Pre-IVF tx with GnRH antagonist in women with endometriosis – PREGNANT –4/4</td>
<td></td>
</tr>
<tr>
<td>J. Segars/V. Baker</td>
<td>Johns Hopkins University</td>
<td>RCT of EGCG to improve fertility in women with uterine fibroids – ¼</td>
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</tr>
<tr>
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<td>Yale University</td>
<td>RCT of EGCG to improve fertility in women with uterine fibroids –</td>
<td>DCC</td>
</tr>
<tr>
<td>F. Gonzalez/A. Al-Hendy</td>
<td>Univ Illinois Chicago</td>
<td>RCT of EGCG to improve fertility in women with uterine fibroids –</td>
<td></td>
</tr>
</tbody>
</table>
RM/I Clinical Trial Program as Multi-PI linked R01s (RMCTP-ConFIRM)
Advantages of Linked R01s

- Sites with low priority scores can be excluded prior to funding. However, this may cause recruitment challenge.
- PIs can be part of more than one clinical trial.
- Each PI has independent grant, equal standing.
- No COI with Project Scientist.
- Independent review and prioritization of protocols by study section rather than by SC and AB
Disadvantages of Linked R01s

• Time to initiate studies is long, with administrative delays
  • Protocols were not fully developed.
  • Single IRB review required agreements between institutions.
  • DSMB was constituted after funding.

• Inefficiencies-Time consuming for Program staff
  • Multiple monthly SC meetings
  • Multiple DSMB meetings

• Less collaborative since there is only 1 lead PI in each consortium. Opportunity to bring consortia together to establish a network is delayed due to COVID and delayed starts of recruitment

• Structure is less conducive to provide opportunities for CREST Scholars to receive mentorship

• Structure less nimble to add timely ancillary studies
## Linked R01s vs. Cooperative Agreements

<table>
<thead>
<tr>
<th></th>
<th><strong>Linked R01s</strong></th>
<th><strong>CAs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PIs</td>
<td>Focused on single trial; less interaction; not as engaged; not true network</td>
<td>Network; focused on several trials, consideration of ancillary questions</td>
</tr>
<tr>
<td>DCC</td>
<td>Multiple DCCs-one for each trial; increased cost</td>
<td>Single DCC-less duplication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More efficient processes</td>
</tr>
<tr>
<td>DSMB</td>
<td>Appointed by DCC; independent of NICHD/sponsor</td>
<td>Appointed by NICHD Director- could be perceived as COI; Single DSMB for all network trials-more efficient</td>
</tr>
<tr>
<td></td>
<td>Multiple DSMB, so extra meetings for PO</td>
<td></td>
</tr>
<tr>
<td>AB</td>
<td>In essence SRG serves this purpose wrt protocols and prioritization of clinical trials</td>
<td>Appointed by NICHD Director; available to advise on other issues throughout grant period</td>
</tr>
<tr>
<td>SC</td>
<td>Lead PI and Study team; no true SC; monthly meetings for each consortium</td>
<td>SC-seat of decision making; monthly and quarterly meetings</td>
</tr>
<tr>
<td>SC Chair</td>
<td>None; Program Officer may interact in similar role</td>
<td>SC Chair—added knowledge and perspective; keeps SC on track</td>
</tr>
<tr>
<td>Rep of NICHD</td>
<td>Program Officer-not involved in all activities. Monthly meetings for each</td>
<td>Project Scientist-involved in all aspects of the network; can</td>
</tr>
</tbody>
</table>
## Linked R01s vs. Cooperative Agreements

<table>
<thead>
<tr>
<th>Study topics</th>
<th>Best protocols selected by SRG—may focus on only one aspect of infertility. Program recs to NACCHD are constrained by priority score</th>
<th>PS has vote to prioritize protocols PO and FI Branch Chief can advise on branch priorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks</td>
<td>Less program influence on productivity</td>
<td>COI</td>
</tr>
<tr>
<td>Time to initiation of studies</td>
<td>Delayed onset: Protocol needed to be developed; sIRB approvals delayed; DSMB needed to be constituted; FDA IND needed; only 1 study has recruited 1 subject to date</td>
<td>Delayed onset: Concept protocols needed to be prioritized, revised, approved by AB and DSMB-similar timeline to start</td>
</tr>
<tr>
<td>Ancillary studies</td>
<td>Studies detailed in grant applications</td>
<td>SC can pivot to study timely topics if urgent</td>
</tr>
<tr>
<td>CREST</td>
<td>Not directly involved. Hope to get consensus approval to collaborate</td>
<td>CREST Scholars involved in recruitment and secondary analyses</td>
</tr>
</tbody>
</table>
NICHD Resources for Clinical Research

- Data and Specimen Hub (DASH)
- RMN Biorepositories
- Training
  - Bioethics course – given annually
  - R25 CREST Program
- Career Development Awards
- Funding for pilot studies and secondary analysis to obtain preliminary data (R03)
Centralized resource for researchers to share de-identified data from studies funded by NICHD. DASH also serves as a portal for requesting biospecimens from selected studies in DASH.

Data sharing launched in August 2015; biospecimen request launched in March 2019

Aims to accelerate scientific findings to ultimately improve human health

Study Topics in DASH

- Adrenal Gland Disorders
- Amenorrhea
- Autism Spectrum Disorders
- Birth Defects
- Breastfeeding & Breast Milk*
- Cerebral Palsy
- Child Health *
- Children’s Bone Health & Calcium
- Delayed Puberty
- Diabetes
- Driving Risk
- Early Learning
- Fertility Problems
- High-Risk Pregnancy
- HIV/AIDS*
- Infant Care & Health *
- Infant Mortality
- Infertility & Fertility
- Labor & Delivery
- Men’s Reproductive Health
- Menkes Disease
- Necrotizing Enterocolitis
- Neuroscience
- Obesity & Overweight
- Obstetrics
- Pediatric Injury
- Pelvic Floor Disorders
- Pharmacology
- Preconception & Prenatal Care
- Preeclampsia & Eclampsia
- Pregnancy *
- Pregnancy Loss
- Preterm Labor & Birth *
- Primary Ovarian Insufficiency
- Puberty & Precocious Puberty
- Rehabilitation Medicine
- Sleep
- Spinal Cord Injury
- Stillbirth
- Stroke
- Sudden Infant Death Syndrome
- Traumatic Brain Injury
- Turner Syndrome
- Women’s Health*

https://dash.nichd.nih.gov
DASH has added a new function: managing requests for NICHD biospecimens.

While not a biorepository itself, DASH serves as a portal for access to biospecimens associated with DASH data collections.

Investigators worldwide can now request both biospecimens and data for secondary analyses; other than the costs of preparing and shipping biospecimens, these specimens are free to investigators.

Studies with biospecimens currently available include:
- Genomic and Proteomic Network for Preterm Birth Research (GPN) – three studies
- NICHD International Site Development Initiative (NISDI) – four studies
- Mothers and Infants Cohort Study (MICS)
- National Children’s Study (NCS)

Currently Available Biospecimens
- Amniotic fluid
- Blood
- Breast Milk
- Buffy Coat
- Cord Blood (Buffy Coat, RBC, Plasma, Serum)
- DNA/RNA/Proteins
- Environmental Samples
- Erythrocytes (RBC)
- Hair
- Lymphocytes
- Meconium
- Nail
- Saliva
- Serum/Plasma
- Tissue samples
- Urine
- Vaginal Fluid

Study Topics Areas of Current Biospecimens
- Breastfeeding and Breast Milk
- Child Health
- HIV/AIDS
- Infant Care and Infant Health
- Pregnancy
- Preterm Labor and Birth
- Women’s Health
Process for CREST Scholars to Access DASH data

What you need to do:

1. **Register** as a user in DASH and confirm your registration through the link in the Registration Confirmation email that you will receive from DASH. ***Note: You must select “University of Colorado Denver” as your institution when you register as a CREST Scholar.

2. Email Dr. S after you register in DASH. She will then log into DASH and add you as an ‘Affiliate’ user and inform you that you have been added.

3. You can access study data through the DASH Workbench. Login to DASH and click on the Workbench icon located on the top menu bar of NICHD DASH.

4. The study data will be available in your Inbox on the Workbench, where you may select individual items and Download selected items from your Inbox to your computer.
Mentorship Matters

• Teaching mentee the “rules of the game”
• Providing resources
  • References to others, secretarial support
• Gain access to closed academic circles
• Advocating for mentee
• Providing networking opportunities
• Helping the mentee to promote themselves

Mentorship Matters
Making the Most of CREST

• Find a research topic you’re passionate about!
• Clinical research is TEAM Science-find ways to collaborate
• Chart a path
• Create timeline and be accountable
• Find mentors
• Network and collaborate
• Find sources of funding
  • CTSA, professional societies, foundations, etc.
  • Consider small grant (i.e. R03) opportunities
  • Consider career development (K23) path
THANK YOU!