



Research
Institute

The 2018 ASRM Research Blueprint





“The Charge”

One of the main goals of the ASRM 2014 – 2019 Strategic Plan was to focus on research and called for the development of specific initiatives to enhance the activities and support for ASRM-sponsored Reproductive Research Programs. In particular, the research strategic goal states that this initiative should “Spearhead the agenda for research in reproduction and the development of both the current and future generations of clinical [translational and basic] investigators in the reproductive sciences.” To be specific, the Strategic Research Goals in the ASRM 2014-2019 Strategic Plan called for:

- Continued, but re-evaluated support of research endeavors and programs that
 - Define and prioritize the questions to be addressed,
 - Identify gaps in RCT (randomized controlled trial)-based reproductive practice knowledge for targeting ASRM-sponsored research,
 - Develop clinical research projects designed to answer practice-related questions,
 - Focus on RFA(s) (request for applications) for SPECIFIC topic(s) of interest to the ASRM membership,
 - Consider providing pilot and bridge grants to “junior” investigators,
 - Consider funding projects of longer duration (3-5 years) in key areas of interest,
 - Evaluate research focus and priorities yearly, and
 - Consider implementation of periodic workshops/conferences to identify new reproductive research priorities;
 - Development of a major research endowment;
 - Further development of young investigators through support and mentoring;
 - Consideration for development of ASRM research networks with national and/or global collaborations;
 - Establishment of ASRM research priorities to complement those of other agencies, such as NIH; and,
 - Partner with federal agencies and global organizations to promote, support, and advance research and training in reproductive science and medicine.
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The ASRM Strategic Research Task Force

On January 18 – 20, 2017, a Task Force composed of ASRM leaders in Reproductive Research was assembled at the home offices of ASRM in Birmingham, Alabama. The Task Force included both seasoned and younger investigators with track records of success in basic, translational or clinical investigation and with expertise in male or female reproduction. In addition, representatives of the ASRM affiliated societies were invited to participate. The members of the Task Force were:

Valerie Baker, M.D., Kurt Barnhart, M.D., Karen Berkowitz, Ph.D., Robert Brannigan, M.D., Douglas Carrell, Ph.D., Christos Coutifaris, M.D., Ph.D., Michael Diamond, M.D., Karl Hansen, M.D., Ph.D., Lawrence Layman, M.D., Erica Marsh, M.D., Kyle Orwig, Ph.D., Richard Paulson, M.D., Alex Polotsky, M.D., Catherine Racowsky, Ph.D., Paolo Rinaudo, M.D., Ph.D., Nanette Santoro, M.D., James Segars, M.D., David Seifer, M.D., Carlos Simon, M.D., James Smith, M.D., Amy Sparks, Ph.D., Nathan Treff, Ph.D., Richard Reindollar, M.D. (Ex-Officio), and Sue Gitlin, Ph.D. (Ex-Officio). Three individuals invited, who were unable to attend the meeting, were Linda Giudice, M.D., Ph.D., Dori Lamb, Ph.D., and Richard Legro, M.D.

The two days of the retreat were spent in 4 talks, 3 breakout sessions, followed by a regrouping and prioritization session addressing current and potential future ASRM research focus and support. The goal of the retreat was to develop a comprehensive plan for ASRM to move Reproductive Research forward nationally and internationally by focusing on specific areas of investigation, expansion of investigator initiated research programs and the development of collaborations with other organizations. In addition, a major consideration for the Task Force involved the identification and development of solutions for the training, mentoring and advancement of the next generation of researchers in the Reproductive Sciences. Following the retreat, a Task Force Summary outlined different approaches to address the various research goals and included a list of priority areas of research for the Society to move forward, particularly those not funded by the NIH. This Summary outlined the scope of a possible expansive research plan that would propel ASRM into an exciting new era of Reproductive Research.

The Task Force summary was subsequently presented to the ASRM Executive Committee and Board, reviewed with the leadership of the Fertility and Infertility Branch of NICHD, and also presented for discussion with the NICHD Director, Dr. Diana Bianchi. The purpose of these discussions and meeting were to ensure that the proposed plans were complementary, moved in parallel and, most importantly, were not in conflict with existing federal guidelines. It was felt that such a coordinated and collaborative approach would set the stage for investigators in the reproductive sciences to be engaged in research that will enhance federally restricted research initiatives, such as in human embryo research, and thus provide the opportunity for better translation of research from the bench to the bedside.

The ASRM Strategic Research Steering Committee

On February 13, 2018, a Strategic Research Steering Committee was assembled. It was charged with the development of a focused Blueprint from the previously developed ASRM Research Task Force Summary. The Strategic Research Steering Committee included:

Christos Coutifaris, M.D., Ph.D. (Chair), Valerie Baker, M.D., Linda Giudice, M.D., Ph.D., Karl Hansen, M.D., Ph.D., Lawrence Layman, M.D., Kyle Orwig, Ph.D., Catherine Racowsky, Ph.D., James Smith, M.D., Richard Reindollar, M.D. (Ex-Officio), and Sue Gitlin, Ph.D. (Ex-Officio). Drs. Nanette Santoro and Paolo Rinaudo were unable to attend the meeting.

The 2018 ASRM Research Blueprint

The 2018 ASRM Research Blueprint that resulted from these planning meetings and discussions is presented here and contains:

- I. the foundational concepts for the development of an **ASRM Research Institute** (ARI) with plans to expand its role into the future;
- II. a detailed **prioritization of research areas** to support and fund;
- III. the **support of the current and next generation of researchers**;
- IV. concepts for supporting **collaborative research initiatives** with other organizations including the NIH; and,
- V. a **Roadmap for funding** of current and future research, which includes the development of (1) a large general and unrestricted Reproduction Research Endowment Fund, (2) Named Individual Research Funds and (3) a formula for robust support of ongoing research projects with existing ASRM funds as the Endowment initiatives are developed and grow over the next decade.

I. Development of the “ASRM Research Institute”

The ASRM Research Institute will be created to guide a robust research agenda outlined in this Research Blueprint and to coordinate its evolution as new information and research needs arise. It is critical to engage in a process of “branding” of the Institute and the articulation of its mission, which will involve the support of Basic, Translational and Clinical Investigations relevant to Human Reproduction, Access to Reproductive Care and the Efficacy and Safety of Fertility Treatments and the Assisted Reproductive Technologies. It is envisioned that in Phase I (3-5 years), the primary functions of the Institute will be (1) to set the annual research agenda and develop a budget for supporting that agenda in collaboration with ASRM leadership; (2) to periodically sponsor or co-sponsor workshops/ conferences for exploring areas of potential research support; (3) to oversee the subsequent call for requests for applications (RFAs) for both Institute- and investigator-initiated research; (4) to oversee the evaluation of those applications through a “Study Section” process and selection of grant proposals for funding; and, (5) to follow progress of those awarded grants on an annual basis. This initial stage of responsibilities for the ASRM Research Institute will require the hiring of a Director of Research for ASRM with expertise in reproduction research and a successful track record of extramural funding (likely beginning on a part-time basis) and a research staff assistant. The final administrative structure for the Institute remains to be defined and will depend on both the eventual breadth and depth of the research initiatives to be undertaken and supported (*vide infra*). The administration of the Institute could be housed in either the Birmingham or Washington, DC ASRM facilities.

Once Phase I progresses and the primary goal for enhancing and funding an expanded research agenda is well established, it is proposed that the Institute will enter its Phase II period of development, which will involve an expanded role for developing further the Institute's activities. New functions to be considered include the possibilities of coordinating web-based meetings and support; the provision of biostatistical support of funded research; the formation of a central investigational review board (IRB); the support of data and safety monitoring boards (DSMBs); the development of a central repository for research bio-specimens and database such as SART CORS; and, the provision of support and management for an expanded SART CORS registry platform to include intermediate and long term outcomes of fertility treatment offspring and their parents. No doubt, need for an expanded physical facility and staff may be critical for the success of Phase II development for the Institute and will be considered as needs, functions, and goals are further defined. The details of an expanded ARSM Research Institute, including its optimal location and composition of professional and staff support will likely be an area of focus for the next ASRM Strategic Plan.

II. Prioritization of Research Areas

The Research Steering Committee allocated large portions of its deliberations in developing a detailed prioritization list of the research areas identified and highlighted by the Research Task Force and following discussions with stakeholders. The guiding principles followed by the Committee were that the ASRM Research Institute had to focus its support on those research areas that would have an impact on the practice of Reproductive Medicine. Priority was to be given to areas of research that met the following criteria and were set forth by the Strategic Plan: (1) not fundable by current NIH or other federal or state guidelines, (2) answer timely, basic or clinically relevant questions or, (3) address other ASRM strategic research initiatives important to the field and to the membership. The two overarching themes that encompass this priority are: (1) The effects of the genome, epigenome and the environment on fertility, human development and reproductive health and, (2) Access to Reproductive Care.

These themes fall under the following general areas of research:

- Genetic and epigenetic pre-pregnancy and peri-conceptual considerations involving
 - human gametes
 - human embryos
 - uterus
- Basic and clinical considerations relevant to the Developmental Origins of Health and Disease (DOHaD)
- The environment (in vivo and in vitro) and its effects on reproduction and reproductive health
- Access to Reproductive Care

Priority will be given to the following specific areas of research:

For basic research-

- Human gamete and embryo research
 - Genetic/ epigenetic programming/re-programing and embryo development
 - Human sperm and egg contribution to embryo development
 - Definition of quality of male and female gametes
 - Definition of quality of embryos
- Molecular mechanisms of human implantation and placentation

- Molecular mechanisms involved in female and male reproductive aging
- Role(s) of mitochondria in human gametes, embryos and early development
- Gene-environment interactions
- Investigations into the derivation and differentiation of stem cells
- Consideration should be given in establishing the **Human Trophectoderm Project** in order to define better, at the basic level, the development of human polar and mural trophoblasts and how this may affect the invasive and non-invasive evaluation of human embryos for clinical purposes.

For applied clinical research-

General:

- How to apply precision medicine in clinical reproductive care
- Study the origin of aneuploidy/ meiotic vs. mitotic errors
- Human embryo culture optimization and effects of human embryo manipulation(s) *in vitro*
- “Beyond the Semen Analysis” – Develop additional diagnostics for male factor infertility
- Single cell analytics of gametes for clinical (and research) application(s)
- Study and define the poor-quality oocyte for application to clinical medicine
- Studies on the derivation of human stem cell lineages in females and males
 - In vitro gametogenesis
 - Testicular biopsy of child to identify stem cells for sperm maturation
 - Clinical testing of gametes generated in the laboratory

Access to Care:

- Low cost IVF
 - Vaginal culture
 - IVM for routine IVF (in non PCOS patients)
- Fertility Preservation (male, female, children)
 - Optimization of gamete and reproductive tissue cryopreservation
- Socio-Cultural barriers (geographic, religious, financial, educational, time away from work, etc.)
- Practical IVF (e.g., cost saving studies vs. applications like telemedicine)

Outcomes:

- Short and long-term outcomes of fertility treatments (parents AND offspring)
 - Development of an expanded SART CORS database (and, potentially, with linkage to other databases)
 - Development of iPad/iPhone-type app for direct data input by patient

Other areas of possible interest and importance to the field:

- The microbiome
- Integration of various “-omics” findings
- Gene editing of germline/embryos

It is stressed that the Institute processes should be nimble enough to be in the position of quickly addressing unexpected clinical needs which lead to new opportunities for research (e.g., as happened for Zika).

Note: There are other general and common areas of reproductive research for which current funding already exists, albeit at relatively decreased or low levels. These topics do not meet the criteria listed above for priority areas to fund. The consensus of both the Research Task Force and Steering Committee was to keep these topics for annual review and consideration for placing in a higher priority level based on the current research climate and findings. These areas include research on:

- Endometriosis/Adenomyosis
- Fibroids
- PCOS
- The human placenta (as described in the NICHD Human Placenta Project)

III. Support of the current and next generation of researchers

ASRM has previously supported **the current generation of researchers** primarily through its investigator initiated grants at approximately \$30,000 to \$50,000 per grant for a total of \$200,000 annually. The current NIH funding climate has reduced funding sufficiently to cause a rapid attrition of scientists able and willing to survive these difficult funding times. The Task Force and Steering Committee both felt strongly that the annual research agenda must take into consideration these vital contributors to current discovery through Reproductive Research. RFA-based research funding will be the foundation of the ASRM Research Institute funding and be

determined annually by the areas of research that are prioritized. Bridging grants, a major focus on midlevel career research support and the support of new areas of research for seasoned researchers will be continued, the dollar amount and number being determined annually. For this latter group of grants, it was felt that consideration for several small grants approximating \$50k and several at \$100k or larger should be given annually to drive the success of this area of support by the ASRM Research Institute. Types of grants (such as the R- or K-types by the NIH) can be established with an ASRM prefix to define that these are ASRM awards of similar magnitude and duration as the federal grants (e.g., the existing ASRM-NIH K12 Reproductive Scientist Development Program, *vide infra*).

The health of clinical programs in reproductive medicine and survival of research in the reproductive sciences depend on **the next generation of reproductive scientists**, both basic and clinical. Strong consensus was achieved around the fact that a major role of the ASRM Research Institute should be to assure the survival of Reproductive Research by infusing and supporting a pipeline of young investigators. ASRM has had a long tradition of collaboration with NICHD in supporting the CREST and RSDP scholars programs. In addition, ASRM has been supporting programs involved in the training of MD and PhD fellows such as the Frontiers in Reproduction course, the Gordon Conferences, and the NIH annual conference for fellows going back to the inception of these programs many years ago. The ASRM Research Institute will make supporting the next generation of researchers a major initiative and a priority. This support at the present time will continue to be through the traditional scholars programs such as RSDP. However, it is recommended that strong consideration is given to developing a new mentored research support mechanism by supporting an “ASRM Research Scholar” for a duration of 3-5 years similar to federal individual K mentored awards. This could be funded entirely through the ASRM Research Institute or in collaboration with other organizations such as ABOG, the AUA or AAOGF (named the ASRM-ABOG, the ASRM-AUA or the ASRM-AAOGF scholars). It is recommended that up to \$150k annually will be provided for the support of such a scholar. It should be stressed that success of such programs depends not only on the quality of the scholars and their research project, but also relies heavily on the mentoring plans, institutional environment and networking with investigators and other trainees during this early stage of academic development. This proposed program can only be successful if a critical mass of such budding investigators is developed and encouraged to interact through retreats and other interactive opportunities. It is proposed that until this critical mass of young investigators is developed, coordination of such activities with other, already existing, such programs for RSDP and AAOGF scholars be put in place. The Physician Scientists ASRM SIG group can play an important role in facilitating this important initiative.

IV. Collaborative research initiatives

The Strategic Plan called for “partnership(s) with federal agencies and global organizations to promote, support, and advance research and training in reproductive science and medicine.” Both the Research Task Force and Steering Committee had strong consensus that there are times when Reproductive Research would benefit by such collaborative efforts. For example, the Reproductive Medicine Network may be able to perform a large RCT that answers a critical question that is not possible by other institutions, but only with additional resources provided by the ASRM Research Institute. As such, the ASRM Research Institute is interested in participating in collaborations that will move forward the Reproductive Research agenda and impact care. It can be envisioned that cooperative agreements involving the ASRM Institute and NIH-funded investigators with common research goals can be established to complement what the federal grants cannot fund due to existing restrictions (such as fertilization of human eggs or embryo biopsy). Such collaborative efforts could markedly enhance the impact and hasten clinical application of observations based on federally funded research projects. Such investigations could follow mechanistic studies in laboratory animals or validate basic research on human gamete development by facilitating the performance of fertilization and embryo transfer studies or by complementing observational data involving the manipulation and transfer of human embryos.

V. Roadmap for Funding

This Blueprint outlines an exciting new initiative for ASRM that centralizes and coordinates its Reproductive Research agenda in consideration and coordination with other programs such as the NIH, and moves the ASRM Reproductive Research funding to far higher levels than ever before. It is designed to have the greatest impact possible on our field. In Phase I of the development of the ASRM Research Institute, two aspects of funding are critical and addressed here: first, how funding will be determined on an annual basis; and, second, the sources of such funding.

Annual Funding Decisions

The Strategic Research Steering Committee will meet at least once yearly to oversee the functions of the ASRM Research Institute and to set the Research Agenda for the year. The budget for the ASRM Research Institute and research support will be determined by the Finance Committee and approved by the Executive Committee and the ASRM Board before this meeting. A dollar allocation among the various categories of research endeavors (RFA, investigator initiated,

young investigator training grants, collaborative research endeavors, and other unexpected funding opportunities) will be determined as will the research priorities for the year. Once the total available research budget for the upcoming year is determined and the prioritized topic(s) decisions are made, a call for applications will follow for each of the categories to be funded. Funding decisions will be based on a Study Section model. For multi-year awards, the total dollars for the commitment will be accounted in the first year of the award.

Sources of Funding

During Phase I, the ASRM Research Institute will be funded through the following sources: ASRM funds, Affiliate Society funds, the General Research Endowment Fund, and endowments specific to the Research Institute. Each year, a determination will be made by the Finance Committee the magnitude of ASRM funds available for supporting that year's research applications whether these are one year or multi-year applications. This will be determined by formula from the prior fiscal year performance of the investment portfolio with a target total of \$1-3M based on the current endowment and recent financial performance of the organization. Affiliate Society dollar allocations will be made individually by the affiliate societies and allocations will be made from the General Research Endowment Fund, supported by general fundraising and other donations earmarked for research. It is hoped that named endowments will also provide a portion of the annual funding for selected research project(s) and for the mentored research initiatives of the next generation of investigators in the reproductive sciences. It is anticipated that a major fundraising effort will be initiated in the very near future so that the ASRM Research Institute will be in position to move into Phase II of its development with the goal of expanded infrastructure and expanded, but targeted research initiatives, which will have major impact in the science and practice of reproductive medicine and which no other funding opportunities could support. It is reasonable to estimate that the ultimate 5-year goal should be the availability of \$5-10M per year to be distributed for both the research and the investigator development and support initiatives. Availability of such magnitude of funds will require a corpus of \$100-200M. It is clear and should be understood by all that reproduction-related research and investigator development will only be funded by mechanisms as those described in this Blueprint and that the future of the field of reproduction undeniably depends on it.



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Care Worldwide