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EXECUTIVE SUMMARY

This document is the quadrennial report of the Contraception and Reproductive Health Branch (CRHB) to the National Advisory Child Health and Human Development (NACHHD) Council. The CRHB is a Branch within the Center for Population Research (CPR) at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The CRHB provides the NICHD with a focus for research and research training in contraception and other selected areas of reproductive health.

Between 2004 and 2007, the Branch supported activities in five program areas:

- Contraceptive Research and Development
- Contraceptive and Reproductive Evaluation
- Prevention of HIV/AIDS and Other Sexually Transmitted Diseases (STDs)
- Selected Reproductive and Other Gynecologic Health Issues
- Research Training

In the area of Contraceptive Research and Development, the Branch supports research through both grant and contract mechanisms. It maintains an investigator-initiated grant portfolio primarily focused on contraceptive research. In addition, the Branch provides support for four sites under the U54 Contraceptive Development Research Center Program (CDRCP) and eight sites under the U01 Male Contraceptive Development Program. Three support contracts, including a biological testing facility, a chemical synthesis facility, and a peptide synthesis facility are also supported through the Branch. In addition, the CRHB supports a center for synthesis and testing of non-steroidal and non-hormonal male contraceptive agents. The Branch's largest contract program is the Contraceptive Clinical Trials Network (CCTN), which includes 12 sites for female contraceptive research, two sites for male contraceptive research, and a data coordinating center.

In the area of Contraceptive and Reproductive Evaluation, the Branch previously supported a number of large epidemiologic studies, including the Cancer and Steroid Hormone Study, the Collaborative Review of Sterilization, and the Women's Contraceptive and Reproductive Experiences study. The CRHB currently supports a Cochrane Collaboration Center for Fertility Regulation and the World Health Organization (WHO) project to develop Global Guidance for Family Planning Based on the Best Available Science.

In the area of Prevention of HIV and other STDs, the Branch has had an active program in evaluating the contraceptive activity of candidate spermicides/microbicides in the preclinical phase and in Phase I/II/III clinical trials. The Branch supports a contract with Family Health International to study the relationship of hormonal contraception and HIV acquisition and progression in Zimbabwe and Uganda. Another contract supports the evaluation of the correlation of vaginal/cervical lesions associated with microbicide preparations, identified through colposcopy, to alterations in susceptibility to STD transmission in experimental animals. In addition to these activities, prior to the end of 2006, the CRHB also supported a large microbicide grant portfolio, which included both basic research and support contracts to track the progress of the many compounds under development, and a microbicide quality-assurance

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contract to assist in standardizing and validating the various assays used in preclinical microbicide development. Also prior to the end of 2006, the Branch supported the Women's HIV Interdisciplinary Network, which studies immunology, HIV and associated co-factors, and the molecular biology of HIV in women.

In the area of Selected Reproductive and Other Gynecologic Health Issues, the CRHB supports the Pelvic Floor Disorders Network (PFDN), a highly productive clinical trials network, which has addressed a variety of research topics in the field of urogynecology. With the National Institute on Aging, the Branch also provides support for clinical trials related to the treatment of menopausal symptoms.

In the area of Research Training, the CRHB supports two T32 sites for training in epidemiology and clinical trial methodology, a small number of K23 and K24 awards, as well as a few international fellowship awards through the Fogarty International Center.

As part of the NICHD's continued efforts to improve strategic planning for its components, the CRHB sought advice and feedback on its possible future directions from an expert panel, which included those with expertise in male and female contraception, reproductive endocrinology, drug development, clinical trials, epidemiology, and pelvic floor disorders. The group included two members of the NACHHD Council as well as two representatives from advocacy groups. (See [Appendix C](#) for a list of panel members.) The panel provided extensive review and analysis of current research efforts supported by the Branch, as well as trends in funding and training. The results of the panel's analysis are included in the [Future Directions for the Branch](#) section of this report.

INTRODUCTION TO THE BRANCH

The mission of the Contraception and Reproductive Health Branch (CRHB), part of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), is to support research on the discovery, development, efficacy, safety, and mechanisms of action of various methods of contraception. The Branch also supports research on other areas of reproductive health, including pelvic floor disorders and the interaction of Sexually Transmitted Diseases (STDs), including HIV, and contraception.

The current Branch was formed in 1997 with the merger of the Contraceptive Development Branch and the Contraceptive and Reproductive Evaluation Branch (CARE). During the ensuing 10 years, the Branch has undertaken and discontinued research in several areas. For instance, in the past, the CARE Branch maintained a large portfolio of contracts for observational studies of contraception. The final portion of funding for these studies ended in December 2006.

From 1998 through 2006, the CRHB maintained a large portfolio of grants and contracts in the areas of microbicides and HIV infection in women and girls. Based on internal review and analyses of priorities, the Branch decided to divest itself of the majority of these projects,

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particularly those not directly related to spermicidal microbicides. At the same time, the Branch has provided increased support to the field of pelvic floor disorders research.

The Branch recently underwent significant changes in personnel with the loss of six staff during the past two years, three of whom retired or resigned in December 2007. With the recent hiring of a new medical officer, the Branch now consists of six members. The hiring of additional personnel is planned for the near future.

During the last two years, there has been an important change in the support of contraceptive research by large pharmaceutical firms both in the United States and Western Europe. All of the firms in the United States and many of the firms in Europe have abandoned their contraceptive research programs. In addition, both the United States Agency for International Development and the World Health Organization (WHO) have experienced a significant decrease in the funding allocated to contraceptive research. Given these changes, the National Institutes of Health (NIH) has become an increasingly important source of funding for contraceptive research. At the same time, funding for all research at NIH has remained constant over the past several years. Given these circumstances, it becomes particularly important for the CRHB to make wise choices about the allocation of its limited resources.

The Branch is now the largest source of support for research on contraception within the federal government. Through a combination of grants, contracts, interagency agreements, and centers programs (see [Figure 1](#) and [Figure 2](#)), the CRHB's budget was nearly \$35 million for fiscal year 2007 (see [Figure 3](#) and [Table 1](#)).

To get feedback on which to base its decisions, the CRHB sought advice on possible future directions from an expert panel. This panel conducted a thorough review of the Branch's portfolio, activities, and history, while considering three overarching questions related to the Branch's mission. The results of the panel's discussions as well as a description of possible research directions for the CRHB are included in the [Future Directions for the Branch](#) section of this report.

The following sections of the report describe the Branch's activities within its five main program areas.

PROGRAM AREAS

CONTRACEPTIVE RESEARCH AND DEVELOPMENT

Within this program area, the goal of the CRHB is to promote contraceptive research and development for preventing unintended pregnancies by:

- Conducting Phase I, II, or III clinical trials to evaluate the safety and efficacy of new contraceptive methods for women and men;

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- Stimulating research to develop methods for male contraception, including hormonal and non-hormonal control of sperm production and/or sperm function;
- Supporting basic and translational contraceptive research and development that may lead to new hormonal or non-hormonal methods for inhibiting ovulation or fertilization; and
- Conducting experimental studies in animals to determine safety and efficacy of novel potential contraceptive agents.

The federal government has supported contraceptive research and development activities since 1968, when the Assistant Secretary for Health and Scientific Affairs of the then Department of Health, Education, and Welfare established the Center for Population Research (CPR) at the NICHD, with the goal of developing new contraceptives. In 1970, congress passed Public Law 91-572, adding Title X to the Public Health Service Act to authorize grants and contracts for research and research training in family planning and population sciences. Additional support came in 1993, when congress passed legislation (Public Law 103-43) directing the NICHD to establish extramural centers devoted to contraceptive research and development. This goal was re-emphasized in the 1996 amendment to the Public Health Service Act.

Although a range of contraceptive methods for women is currently available, the proportion of unintended pregnancies in the United States still approximates 50 percent. Some of these unintended pregnancies can result from failure to use available contraception methods because of an individual's dissatisfaction with those methods, illustrating the critical need for methods that enhance use by meeting the diverse needs of women throughout their reproductive lives. Moreover, many women who require highly effective contraception have medical contraindications to the use of hormonal methods and prefer not to use an intrauterine device (IUD), meaning they must rely on their partners for contraception; however, current methods for male contraception are limited to condoms or vasectomy. Thus, a need exists for a wider variety of contraceptive methods that recognize and meet the needs of individuals with different ethnicities, cultures, and religious values, but that adapt as the needs of individuals change over time. It is toward this optimal situation that the Branch strives.

In 2004, the Institute of Medicine (IOM) issued a publication titled *New Frontiers in Contraceptive Research: A Blueprint for Action*, which summarized the deliberations from an international committee of experts in the field of contraception. The committee was forceful in its recommendations to:

- Identify and validate novel contraceptive targets;
- Enhance contraceptive drug discovery, development, and clinical testing; and
- Facilitate and coordinate future implementation of contraceptive research and development.

The CRHB is directing its resources to carry out these recommendations.

The Branch uses a variety of funding mechanisms to promote contraceptive research and development (see [Figure 1](#)). New ideas are generated by the Contraceptive Development Research Centers Program (CDRCP), by the Male Contraceptive Development Program, by CRHB staff, and through conferences, careful reading of the literature, and investigator-initiated grants. Selected new contraceptive leads move forward with assistance from one of the Branch's support contractors. For instance, the Chemical Synthesis Facility and Peptide Synthesis Facility

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prepare compounds for the Branch and for other extramural scientists involved in contraceptive research. The Biological Testing Facility studies biological activity, pharmacology, and toxicology of compounds of interest. The Contraceptive Clinical Trials Network (CCTN) conducts Phase I through Phase III trials of promising contraceptives developed from Branch-sponsored projects and from other investigators.

The Branch continues its efforts to develop new hormonal and non-hormonal contraceptive methods for women. In addition, when the NICHD established strategic goals for *Reproductive Health in the 21st Century* in 2000, researchers concluded that a successful reproductive health agenda must include development of effective, safe, and acceptable contraceptive methods for men beyond those presently available (e.g., periodic abstinence, withdrawal, condoms, or vasectomy). Effective new methods for male fertility regulation would not only benefit men, but would also be a major contribution to women's health. In order to implement this strategic goal, the CRHB, in collaboration with the other two components of the CPR, initiated and restructured research programs to encourage development of male contraceptives using a combination of basic, applied, clinical, and behavioral research.

Male contraceptives must have no effect on libido or sexual function for them to be widely used. Historically, development of male contraceptive drugs has lagged substantially behind development of female contraceptives due, in part, to the complexity of the male reproductive system. Further lags are related to social/behavioral aspects of sexual activity based on the suppositions that, due to the availability of safe and effective female contraceptives, male methods are unnecessary; men are unwilling to take contraceptive pills or injections; and men will not adhere to contraceptive drug regimens as carefully as do women. These suppositions are in contrast to acceptability studies conducted with more than 9,000 men in nine countries on four continents. In these acceptability studies, men of all nationalities and religions indicated a willingness to use a male contraceptive if a safe, effective product were available. Notwithstanding those surveys, the three large pharmaceutical companies that were previously involved in male contraceptive development have abandoned their activities in this area. Recent mergers of two of these companies with other entities have resulted in decisions that focus on therapeutic areas considered to be more lucrative.

CONTRACEPTIVE AND REPRODUCTIVE EVALUATION

With the Branch's loss of two of the three staff members who had training in epidemiology, this program area has been de-emphasized during the past four years. Past Branch reports have included descriptions of support for and activity in a number of large epidemiologic studies, including the Collaborative Review of Sterilization (CREST) study, the Cancer and Steroid Hormones (CASH) study, and the Women's Contraceptive and Reproductive Experiences (CARE) study.

Current Branch activities in this area include grant support for a small number of investigator-initiated epidemiologic studies, as well as support of The Cochrane Collaboration. In addition, this program area supports the continuous updating of a series of WHO documents that addresses evidence-based provision of contraceptives.

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PREVENTION OF HIV/AIDS AND OTHER STDs

Since late 2006, the Branch has markedly reduced its involvement in this program area, except for development and evaluation of spermicidal microbicides and continued support for contracts to investigate the impact of hormonal contraception on HIV acquisition and disease progression. Prior to the end of 2006, the Branch had an active program addressing the following issues:

- Increasing understanding of the transmission, acquisition, and prevention of HIV/AIDS and STDs in the female genital tract;
- Reviewing current models and developing new models for investigating heterosexual HIV-infection mechanisms and prevention of HIV transmission;
- Evaluating hormonal and barrier contraceptive methods for their effects in preventing or enhancing heterosexual HIV and STD transmission;
- Evaluating the safety and efficacy of contraceptives and infertility treatments in HIV-positive women; and
- Evaluating the effect of sex on HIV/AIDS.

Most of the CRHB grant and contract portfolio that addressed the issues above was transferred to either the Division of AIDS at the National Institute of Allergy and Infectious Diseases (NIAID), or the NICHD's Pediatric, Adolescent, and Maternal AIDS (PAMA) Branch.

SELECTED REPRODUCTIVE AND OTHER GYNECOLOGIC HEALTH ISSUES

Within this program area, the goal of the CRHB is to advance research on these issues by:

- Sponsoring research efforts on reproductive health topics that have been either overlooked or underfunded; and
- Focusing research efforts on topics that are considered important to women's health, minority health, and aging because these topics relate to reproductive health within the purview of the CRHB.

The IOM noted a need for additional NIH research attention to obstetrics/gynecology (OB/GYN) topics as early as 1992 in its report, *Strengthening Research in Academic OB/GYN Departments*. Further recommendations from congress, professional societies, and women affected by reproductive/gynecological disorders during the last decade have also led the NICHD to increase its research in this area.

Although the NICHD has been among the major funding sources for a broad range of research in OB/GYN, the CRHB recognizes that research on some gynecologic topics is still underfunded. For example, during their lifetimes as many as 11 percent of women in the United States will undergo a major surgical procedure to correct urinary incontinence or pelvic organ prolapse. As the U.S. population ages, the need for treatments for these disorders will also increase.

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In response to these needs, the NICHD has expanded its funding for research on female pelvic floor disorders, including pelvic organ prolapse, urinary and fecal incontinence, and other sensory and emptying abnormalities of the lower urinary and gastrointestinal tracts. Beginning in 1999, the CRHB's activities to support and initiate research in pelvic floor disorders has included: two Requests for Applications (RFAs), including the initiation of a clinical trials network; one Program Announcement (PA); three workshops; and two NIH State-of-the-Science conferences. Although budgetary restrictions have precluded new initiatives in recent years, the infusion of funds from 1999 to 2001 has created a new generation of NIH-funded researchers in pelvic floor disorders.

RESEARCH TRAINING

Within this program area, the goal of the CRHB is to promote training in areas of contraception and reproductive health research that attracts new investigators to the field by:

- Supporting training of obstetricians and gynecologists in epidemiology and clinical research to ensure future cadres of investigators in contraception and reproductive health research; and
- Providing training for pharmacologists, biologists, and epidemiologists to promote future research in this field.

The 1992 IOM report, *Strengthening Research in Academic OB/GYN Departments*, noted that few academic obstetricians and gynecologists received formal research training; it called this situation, "an important obstacle to successful applications for research funding." The IOM went on to recommend that the NICHD and other research funding entities target training support to expand the number of research training opportunities for physicians in OB/GYN.

In its 1994 report, *Careers in Clinical Research: Obstacles and Opportunities*, the IOM recommended that academic centers develop interdisciplinary programs to award advanced degrees in evaluative sciences related to clinical research. The CRHB has supported one such program, training obstetricians and gynecologists in epidemiology and clinical research, since 1996. From 2001 to 2005, the Branch supported four additional programs; two of the four programs successfully recompleted in 2005. Additional support for trainees is provided through the Loan Repayment for Contraception and Infertility Researchers program.

The next section highlights some of the research activities and accomplishments within each of the Branch's five program areas.

HIGHLIGHTS FROM CRHB-FUNDED RESEARCH IN CONTRACEPTIVE RESEARCH AND DEVELOPMENT

U54 CONTRACEPTIVE DEVELOPMENT RESEARCH CENTER PROGRAM (CDRCP)

In 1993, congress passed Public Law 103-43 directing the NICHD to fund contraceptive research centers and to focus the efforts of these centers on research that may lead to new contraceptive products. Because the complexity of contraceptive research and development could severely limit progress achieved by individual investigators working alone, the Institute funds the CDRCP through a specialized cooperative research center award mechanism (U54), in which NIH scientific and programmatic staff are substantially involved with the awardees during performance of the activity.

Under this mechanism, the NICHD supports outstanding centers, composed of researchers and technical service core facilities, that are interactively organized to conduct research for discovering and/or developing promising new leads for regulation of fertility, as well as additional relevant projects. The focus of individual projects includes basic, preclinical, or clinical research, or a combination of these areas. The CDRCP also serves as a national resource for supporting the career development of young scientists who elect to pursue research in fertility regulation. The previous funding round for the CDRCP ended in 2007, and a new round has begun. Individual Centers funded from 2002 through 2007 are listed below. (See [Figure 4](#) for site locations.)

- Population Council—Principal Investigator (PI): Regine Sitruk-Ware
 - o Subproject 1 (PI: Y.Y. Tsong) conducted studies to develop a vaginal ring that delivers a progesterone receptor modulator for contraception.
 - o Subproject 2 (PI: R. Sitruk-Ware) examined the effectiveness of a Carraguard®-levonorgestrel combination for providing dual-use protection against STDs and pregnancy.
 - o Subproject 3 (PI: C.Y. Cheng) investigated the possibility of developing contraceptive agents to affect cell-junction dynamics specific to the testes.
- University of Washington—PI: William Bremner
 - o Subproject 1 (PI: W. Bremner) conducted a clinical trial of a new contraceptive agent, acyline, in men.
 - o Subproject 2 (PI: R. Braun) was a basic research project designed to conduct genetic studies on the control of spermatogenesis in mice.
 - o Subproject 3 (PI: J. Beavo) investigated the roles of phosphodiesterases and their inhibitors in the testes.
 - o Subproject 4 (PI: M. Griswold) examined the cell-specific patterns of gene expression and their control in the testes.
 - o An important additional goal of this center is to attract new fellows and support new investigators in male contraception research.

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- University of California, Davis—PI: Paul Primakoff
 - Subproject 1 (PI: P. Primakoff) was designed to screen for contraceptive targets that could be used to block sperm function in fertilization.
 - Subproject 2 (PI: D. Myles) explored gamete-surface metalloproteases as contraceptive targets.
 - Subproject 3 (PI: H. Florman) investigated ion-channel-based anti-fertility agents on sperm.

Two additional, non-U54 grants were also funded from the RFA for the CDRCP. The PIs for these two grants served as members of the Program's Steering Committee, and their research efforts were integrated into the overall Program.

- Jackson Laboratories—PI: John J. Eppig—The *Trapping Cumulus Products for Contraceptive Targeting* project explored the interactions of cumulus cells, which produce paracrine regulators that promote oocyte development.
- University of Virginia—PI: Kenneth Tung—The *Autoimmune Oophoritis: Consequences of Gamete Vaccines* project, conducted in animals, examined the factors that control development of autoimmune ovarian disease following immunization with certain gamete-specific antigens.

In the new cycle of support, which began in 2007, The Population Council and the University of Washington successfully recompeted. In addition, the Branch is funding two new centers at the University of Kansas (focus on translational research aimed at product identification and optimization for male contraception) and the Oregon Health Sciences University (investigation of non-hormonal methods of ovulation inhibition for contraception). The current centers and their component projects are described within the [Male Contraception](#) and [Female Contraception](#) sections of this report.

MALE CONTRACEPTION

The CRHB has supported research on and development of pharmacological approaches to male contraception, including hormonal and non-hormonal agents, to inhibit sperm production or sperm function. The productivity of investigators in the area of male contraceptive development has been impressive, resulting in many publications, patents, and clinical trials. In recent years, the Branch has expanded research in this area. The current ongoing efforts utilize a number of funding mechanisms supported by CRHB, including:

- U54 CDRCP (nine projects in three centers);
- U01 Male Contraceptive Development Program (eight projects);
- Two sites within the CCTN (Phase I and II, and potentially Phase III safety and contraceptive efficacy trials in men);
- A research and development contract to identify, synthesize, and conduct preclinical development of new agents for male contraception; and
- International meetings—*The Future of Male Contraception*—that bring together investigators from academia and industry to present the latest basic and clinical research in male contraceptive development.

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Each of these areas of research is summarized below.

U54 CDRCP Projects on Male Contraception

As explained earlier in this report, the CDRCP was recently recompeted, and several of the resulting projects focus on male contraception.

One of the projects at The Population Council is exploring the clinical development of MENT™ (7 α -methyl-19-nortestosterone), which has progressed from preclinical to clinical phase research. This synthetic androgen is more potent than testosterone in its effects on muscles and the pituitary gland, even though its stimulatory effect on the prostate is less than that of other testosterone derivatives. Another Population Council project focuses on a potential non-hormonal target for male contraception—specifically, tight junctions, which are required for appropriate Sertoli-cell–germ-cell interactions during spermatogenesis. Several lead candidates for regulating this target are derivatives of lonidamine. One such candidate, AF-2364 [1-(2,4-dichlorobenzyl)-1H-indazole-3-carbohydrazide], specifically targets Sertoli cells by crosslinking with a modified follicle-stimulating hormone (FSH) molecule; the complex then binds to the FSH receptor on Sertoli cells, but does not elicit a response. Using this agent, reversible contraception has been demonstrated in rats.

CDRCP research at the University of Washington focuses entirely on male contraceptive development. During the last funding cycle, these investigators conducted groundbreaking clinical trials in men using an injectable formulation of acyline, a potent gonadotropin-releasing hormone (GnRH) antagonist, to assess safety and suppression of spermatogenesis. Building on these studies, the CRHB collaborated with a small pharmaceutical firm, Merrion Pharmaceuticals, that developed an oral formulation of acyline; the clinical research team at the University of Washington has completed Phase I studies, which indicate promising results. Acyline is expected to have clinical utility in a hormonal male contraception regimen, as well as in treatment of prostate and gynecologic cancers. Additional projects at the University of Washington Center focus on discovering and characterizing new contraceptive targets in the spermatogonial stem cells, as well as in enzymes required for sperm motility. This important work has been published in numerous journals and this publishing will continue during the current funding cycle.

As explained earlier, the Branch has been supporting two new centers since 2007. One of these new centers—at the University of Kansas—will focus on product identification and medicinal chemistry for the optimization for male contraception. Under a separate research and development contract with the CRHB, the University has developed a lead candidate, which is a derivative of lonidamine, called gamendazole. Testing of this agent in male rats demonstrated the potential for reversible contraception. Projects within the center are directed at continuing the characterization of gamendazole, as well as at developing new agents for male contraception.

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U01 Male Contraceptive Development Program

In response to a 2003 RFA to develop novel methods for regulating male fertility, the CRHB began funding eight grants, which together comprise the Male Contraceptive Development Program. The funded projects include research on approaches to inhibit sperm-specific calcium channels (CatSpers), agents that interfere with tight junctions between germ cells and Sertoli cells (adjudin), and agents that inhibit glycosylation (miglustat). Other projects studied identification of new potential targets for male contraception. The investigators and projects in this Program (see [Figure 5](#) for site locations) include the following:

- The Population Council—PI: C.Y. Cheng—Junction dynamics and male fertility regulation
- Children’s Hospital Boston—PI: D. Clapham—Male contraception/CatSper 1,2 sperm-specific ion channels
- University of Virginia—PI: B. Hinton—C-Ros pathways as targets for contraceptive development
- University of California, Irvine—PI: G. MacGregor—A novel gene required for Sertoli-spermatids adhesion
- University of North Carolina, Chapel Hill—PI: D. O’Brien—Novel sperm glycolytic enzymes as contraceptive targets
- University of Oxford (United Kingdom)—PI: F. Platt—Glycosphingolipids as targets for male contraception
- University of Pennsylvania—PI: P.J. Wang—Regulation of spermiogenesis in mice
- Northwestern University—PI: E. Xu—Functional genomic approach to male contraception

The Branch issued an RFA for a second round of funding opportunities for research on new methods for male contraception in 2008.

Male Contraceptive Clinical Trials Network (CCTN)

In 2004, the NICHD established a male contraceptive component of its CCTN that includes two of the leading male contraceptive research sites in the United States and a coordinating center:

- Los Angeles Biomedical Research Institute, at Harbor-UCLA Medical Center, Los Angeles, California—PIs: Ronald Swerdloff and Christina Wang
- University of Washington, Seattle, Washington—PI: William Bremner
- Health Decisions, Chapel Hill, North Carolina (Coordinating Center)—PI: James Higgins

The Male CCTN (see [Figure 6](#) for site locations) is currently evaluating a hormonal regimen consisting of two gels (Nestorone®, a new progestin, and Testim®, a marketed transdermal testosterone formulation) that are self-administered daily. Preliminary results indicate that the preparations will successfully reduce gonadotropin levels. Further studies are planned to evaluate whether the regimen can fully inhibit spermatogenesis.

Research and Development Contract: Synthesis and Testing of Non-Steroidal and Non-Hormonal Male Contraceptive Agents

In addition to the CDRCP and the CCTN projects on male contraceptive development, the Branch also supports a contract with the University of Kansas to investigate the use of medicinal chemistry and high-throughput screening (HTS) to develop novel agents for male contraception.

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HTS assays have been developed to find inhibitors of male contraceptive target enzymes, including testes-specific soluble adenylyl cyclase, cdk2/cyclin A1, alpha-4-Na-ATPase, GAPDS, and phosphodiesterase III and IV. The research has identified promising compounds for inhibition of the cdk2/Cyclin A. Future efforts will be directed at using x-ray crystallography and molecular modeling to optimize inhibitory activity in an effort to develop an effective anti-spermatogenic agent.

Male Contraceptive Products under Development

ORALLY ACTIVE ANDROGENS

Dimethandrolone (DMA) and Dimethandrolone Undecanoate (DMAU)

DMA and its longer-acting ester, DMAU, are androgenic compounds developed by members of the developed by the RTI International, Inc., in collaboration with members of the CRHB. In rabbits, oral dosing with DMAU produces complete azoospermia, which is fully reversible when dosing is discontinued. Preclinical safety studies in monkeys and rats are planned to permit later Phase I clinical trials in men.

In the search for new androgenic steroids with melting points high enough to permit formulation as aqueous microcrystalline suspensions, the CRHB synthesized and evaluated the biological properties of several esters of DMA resulting in domestic and foreign patent applications. Not only do some of these esters exhibit prolonged androgenic activity following parenteral administration in aqueous suspensions, but they also possess potent oral activity.

In castrated rat models, single subcutaneous, aqueous suspension injections of 1.2 mg DMAU induced and maintained increases in size of sex accessory structures, considered the classical measure of androgenic activity, for 14 weeks. The initial elevations in serum levels of free alcohol dropped during the first four to five weeks and then remained steady until the end of the 14-week study. Effects of the compound in orchidectomized rhesus monkeys induced small elevations in prostate-specific antigen, indicating that these compounds are also active in primates.

Several DMA esters showed oral androgenic activity greater than that of methyltestosterone, the only orally active androgen currently available in the United States. Methyltestosterone, like other orally active 17-alkylated steroids, induces hepatotoxicity, which limits chronic administration.

DMAU is also being developed for use as the add-back androgen necessary in hormonal methods of male contraception. Bulk quantities of DMAU are available for preclinical drug safety studies and for studies up to and including Phase II clinical trials.

CDB-4754 (11 β -methyl-19-nortestosterone 17 β -dodecylcarbonate)

CDB-4754 is a potent, orally active, androgenic compound anticipated to have markedly reduced or no hepatotoxicity. Synthesis of the compound was scaled-up at the Branch-supported Chemical Synthesis Facility (described later in this section) to produce sufficient quantities of Good Manufacturing Practice (GMP) material for toxicology and Phase I and II clinical trials.

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NON-HORMONAL ANTI-SPERMATOGENIC AGENTS

Indenopyridines (Nitrogen Heterocycles)

CRHB-supported research continues to study the anti-spermatogenic activity of a series of indenopyridines. One lead candidate is CDB-4022, which has been evaluated in animal studies for activity. The target cell for CDB-4022 appears to be the Sertoli cell, and Leydig cell function does not seem to be impaired; thus, no supplemental androgen therapy is required. Oral dosing in monkeys for seven days caused reversible suppression of sperm production, but showed no effect on serum testosterone levels. Monkeys dosed with CDB-4022 had suppression of sperm to fewer than 1 million per milliliter after two weeks; this suppression lasted for six weeks with full recovery observed by 16 weeks. In addition to the reduction in sperm production, motility of the few remaining sperm was absent. No overt side effects, other than mild sedation, were noted in the monkeys. The Branch is planning additional preclinical safety and efficacy studies for CDB-4022.

Bioisosteres of Lonidamine

In vitro binding assays of testes-specific adenylate cyclase and CDK2/Cyclin A1 have identified a class of novel spermatogenesis inhibitors derived from lonidamine. This discovery could be critical in the development of new male contraceptives. Research supported by the CRHB found that the newly synthesized lonidamine analog, 7-azaindazolecarboxylic acid, had anti-spermatogenic activity after oral administration in the rat and was devoid of mutagenic activity in the Ames test. Another orally active indazole carboxylic acid analog, gamendazole, has been shown to cause reversible contraception in rats. Additional studies of these and other lonidamine derivatives are ongoing.

SpermCheck

Researchers identified a sperm-specific antigen as a potential target for the development of a contraceptive vaccine, but proof-of-efficacy studies in animals were not successful. However, this highly specific antigen formed the basis of a different product, which measures sperm concentration in semen. The product recently launched commercially and will be a useful adjunct in determining efficacy of hormonal, non-hormonal, or surgical contraception in men.

NEW COMPOUNDS FOR CONTRACEPTION AND REPRODUCTIVE HEALTH

In addition to the investigator-initiated research supported by the CRHB, the Branch has synthesized and characterized promising agents for male contraception via its research and development support contracts. The CRHB has developed several promising hormonal and non-hormonal agents for male contraception. These agents are described below.

Levonorgestrel Butanoate (LB)

A collaborative effort between the NICHD and the Special Programme of Research, Development, and Research Training in Human Reproduction at the WHO resulted in the discovery of LB, an ester of levonorgestrel, which is a synthetic progestational agent widely employed in progestin-only and combination (with estrogen) oral contraceptives. LB was tested at the Biological Testing Facility, where its potent long-term progestational activity was

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discovered. This drug has been extensively studied in rodents and primates in efforts that include completion of a one-year toxicology study, and a pharmacokinetic study to support Phase I/II clinical investigation of the drug as a long-acting injectable contraceptive for women. A Phase I dose-ranging study was performed by the WHO, but problems were experienced with the formulation.

In addition, the free alcohol moiety, levonorgestrel, has been successfully employed in oral form in combination with a supplemental androgen, by intramuscular injection with testosterone enanthate, in experimental studies to induce azoospermia or oligospermia in normal men. Thus, the foundation existed for the use of LB in aqueous microcrystalline suspension as a sustained source of active steroid. Formulation studies to develop a stable and clinically acceptable aqueous suspension have been completed.

Acyline

Acyline is one of the most potent and promising GnRH antagonists for reproductive and contraceptive use in humans. This peptide was originally synthesized and patented by the Salk Institute for Biological Studies with NICHD funding. Structural modifications of GnRH, made by substituting natural amino acids with unnatural amino acids (e.g., D-amino acids with unnatural L-amino acids), enhanced potency and reduced concomitant histamine release to a minimum. Early clinical studies in men found that acyline, given as a single subcutaneous dose of 300 ug/kg, suppressed testosterone levels for two weeks without discernible side effects. Currently, the University of Washington and Massachusetts General Hospital are undertaking additional clinical trials of acyline in healthy volunteers. To minimize the frequency of injections, a long-acting and/or slow-release formulation of acyline is necessary for broad clinical use. For instance, one modification puts a polyethylene glycol moiety at positions 5 and 6 in the formulation of acyline. Investigation of a slow-release formulation that uses polylactide-coglycolide beads is also being tested by Newport Scientific, Inc.

Under a Material Transfer Agreement, the NICHD provided to a small company, Merrion Pharmaceuticals, a quantity of GMP-produced acyline to develop an oral formulation. Phase I clinical trials of the material, conducted at the University of Washington, indicated enhanced absorption of the formulated material.

International Meetings: The Future of Male Contraception

Research results from each of programs described in this section as well as those from other domestic and international programs have been described in a forum called *The Future of Male Contraception*. The first such meeting was held in September 2004, and the second was held in September 2007. The meetings were jointly sponsored by the NICHD and CONRAD, with some support from the WHO, the University of Washington, Schering A.G., and Organon.

The meetings were intended to bring together basic and clinical investigators, as well as pharmaceutical scientists, to focus on male contraception. Participants had the opportunity to present their latest work at these meetings. Attendees report that multiple collaborations have developed as a result of these meetings.

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The Web site <http://www.futureofmalecontraception.com> provides abstracts of the presentations and serves as a resource for investigators interested in this topic.

FEMALE CONTRACEPTION

Contraceptive Clinical Trials Network (CCTN)

The CCTN includes 12 field centers devoted to research on female contraception, and a Statistical and Clinical Coordinating Center. (See [Figure 6](#) for site locations.) The CCTN also makes use of a CRHB Scientific Advisory Committee, which is composed of outside experts in the fields of clinical contraceptive research, pharmacology, and epidemiology.

The clinical field centers were selected on the basis of their capacity to carry out Phase I, II, and III trials of oral, injectable, implantable, or topical contraceptive drugs and contraceptive devices. Each site has, at a minimum, a qualified senior clinical investigator, study coordinator, data/research manager, and access to clinical facilities capable of recruiting adequate numbers of subjects for the various clinical trials.

In the female contraceptive development area, the CCTN has conducted several large-scale clinical trials, including those described below.

PHASE II COMPARATIVE STUDY EVALUATING THE SAFETY AND EFFICACY OF CDB-2914 VERSUS LEVONORGESTREL FOR EMERGENCY CONTRACEPTION

This randomized controlled trial of the new chemical entity, a progesterone receptor modulator called CDB-2914, aimed to determine its effectiveness for women seeking emergency contraception within 72 hours of unprotected intercourse. Levonorgestrel was used as the control product. At the start of the trial, levonorgestrel had not been approved by the U.S. Food and Drug Administration (FDA) for emergency contraception, but approval was granted within one year of the start of enrollment. Because the directions for use of levonorgestrel required taking two doses, 12 hours apart, CDB-2914 was packaged with a placebo second dose to ensure similarity. A total of 1,672 women participated in the study.

Results included the following:

- In the evaluable population, there were seven pregnancies (0.9%) in the CDB-2914 arm and 13 pregnancies (1.7%) in the levonorgestrel arm. This difference was not statistically significant.
- Based on the expected date of ovulation, 85 percent and 69 percent of anticipated pregnancies were averted by CDB-2914 and levonorgestrel, respectively.
- Side effects were similar, but the CDB-2914 group reported slightly more nausea.
- As the time between unprotected intercourse and product dosing increased, efficacy for CDB-2914 remained high, but efficacy for levonorgestrel began to decrease.

Based on these findings, the licensee is currently conducting additional clinical trials to determine if the efficacy of CDB-2914 remains high up to 120 hours after unprotected intercourse.

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DOSE-FINDING STUDY TO DETERMINE THE MINIMAL EFFECTIVE DOSE OF CDB-2914 FOR EMERGENCY CONTRACEPTION

The dose used in the original trial was 50 mg of CDB-2914 in unmiconized crystalline form. Pharmacokinetic studies in monkeys indicated that bioavailability of CDB-2914 would increase about two-fold with micronization. Preliminary results indicated that 10 mg unmiconized dose was ineffective. The researchers compared the original formulation (50 mg unmiconized CDB-2914) with 10 mg micronized CDB-2914 for contraceptive efficacy and side effects.

Results included the following:

- The lower dose was slightly less effective than the original dose of drug.
- The side effects profile was not significantly affected.

Based on the efficacy data, the licensee has selected a single dose of 30 mg micronized CDB-2914 in a tablet formulation for further Phase III studies of emergency contraceptive efficacy.

PHASE III COMPARISON TRIAL OF A SPERMICIDE, BUFFERGEL®, USED WITH A DIAPHRAGM VERSUS NONOXYNOL-9 USED WITH A DIAPHRAGM

BufferGel® was developed as a potential dual-function agent that would be both spermicidal as well as microbicidal. The CCTN conducted a Phase III trial in 1,055 women; the study design was a randomized (2:1), controlled, double-masked, non-inferiority trial in women who agreed to use the method as their primary birth control for a period of six months. A subset of women was enrolled for an additional six months of product use. The modified intent-to-treat population was defined as the population who used the product, and for whom pregnancy follow-up was available.

Results included the following:

- In this population, the six-month pregnancy rate per hundred women was 10.1 percent for BufferGel® and 12.3 percent for nonoxynol-9.
- The 12-month rates were 16.7 percent and 17.0 percent, respectively.
- In addition, there was a category of “correct and consistent use” which resulted in pregnancy rates of 4.7 percent for BufferGel® and 6.1 percent for nonoxynol-9 at six months.
- The pregnancy rate of BufferGel® was not inferior to that of nonoxynol-9.
- The two products had similar acceptability ratings: 68 percent of BufferGel® users and 70 percent of nonoxynol-9 users liked their respective products and said that they would use it if it were available.
- More than half the women in both groups said that they preferred the method (diaphragm plus gel product) to condom usage.
- There were no differences in the types or rates of adverse events.
- Very few women (< 4 percent) discontinued due to an adverse event; however, more than 50 percent of the women discontinued from the trial before completion of six months.

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In terms of secondary outcomes, there seemed to be a significantly lower incidence of symptomatic urinary tract infections and less frequent observance of *Ureaplasma urealyticum* with BufferGel®, but no apparent difference in the incidence of bacterial vaginosis, symptomatic yeast infections, or changes in other vaginal microflora.

OPEN-LABEL CONTRACEPTIVE EFFICACY TRIAL OF BUFFERGEL® USED WITH A DIAPHRAGM

FDA guidelines call for two pivotal Phase III trials in order to register a product for approval. One of the trials must be comparative, and the other may be open label. The CRHB conducted an open-label contraceptive efficacy trial of BufferGel® used with a diaphragm. The trial enrolled 221 women who agreed to use the method as their primary birth control for a period of six months. The six-month cumulative pregnancy rate was 9.8 percent.

Note: BufferGel® (without a diaphragm) is currently also under evaluation as a microbicide. The contraceptive efficacy of the gel in the absence of a diaphragm is unknown. If the results of the microbicide trial indicate any benefit, the CRHB may conduct a trial to evaluate BufferGel® for contraceptive efficacy in the absence of a diaphragm.

PHASE III COMPARISON TRIAL OF A SPERMICIDE, C31G, VERSUS CONCEPTROL® FOR CONTRACEPTIVE EFFICACY

C31G (also known as SAVVY) is an amphoteric surfactant composed of two chemical agents, myristamine oxide and cetyl betaine, formulated at a 1-percent concentration as a clear vaginal gel. *In vitro* and *in vivo* studies have shown both spermicidal and microbicidal properties for the gel. The CRHB is conducting a contraceptive efficacy study of C31G gel compared with a marketed product, Conceptrol®, which contains nonoxynol-9. The study design is a randomized (3:2), controlled, double-masked, non-inferiority trial in women who agreed to use the product as their primary method of birth control for a period of six months. A subset of women was enrolled for an additional six months of product use. To date, 1,578 women have been enrolled in the study, and enrollment ended in January 2008. Follow-up will likely be completed in July 2008.

Note: C31G has been tested in two large clinical trials for preventing HIV transmission. Although there were challenges posed by the study population in terms of estimating compliance and other factors, data from the study do not indicate protective activity for the C31G gel compared with that of a vehicle-control gel consisting of hydroxyethylcellulose. The incidence of seroconversion in both arms of the trials was lower than anticipated, but this finding could be attributed to increased condom usage or other reductions in high-risk behavior as a result of aggressive counseling of the participants. The pregnancy rate in the population assigned to the C31G gel was equal to the control arm, but was markedly higher than the pregnancy rate observed in the CRHB contraceptive efficacy trial, suggesting either lack of use or inconsistent use of the product. However, in view of the results of these studies, it is not possible to claim dual-protection benefit for the C31G gel.

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PHASE III TRIAL OF A CONTRACEPTIVE VAGINAL RING CONTAINING ETHINYL ESTRADIOL AND NESTORONE®, A NEW PROGESTIN

A contraceptive vaginal ring releasing 15 ug ethinyl estradiol and 150 ug Nestorone®, a new progestin, is proposed for 13 cycles (one year) of contraceptive use. Nestorone®, developed by The Population Council, is a derivative of 19 norprogesterone that is inactive orally and has been used successfully for contraception in lactating women. The early developmental work on the contraceptive vaginal rings was supported, in part, through the U54 CDRCP. Now the product is in the final stage of clinical testing in preparation for a New Drug Application for the ring. The FDA requested two Phase III studies that evaluate contraceptive efficacy in 400 women for one year (13 cycles) as well as 20,000 cycles of safety data. In addition, the FDA requested substudies (100 subjects in each) to identify vaginal microbiology changes that occur during ring use, clotting factor and hepatic enzyme measurements at baseline, six, and 12 months of product use, and endometrial biopsies at baseline, six, and 12 months of product use. The Population Council is conducting a study in 1,000 women in parallel to the CCTN study, which will include approximately 1,200 women. To date, 1,024 women have been enrolled in the CCTN trial, and a similar number have been enrolled in The Population Council trial.

CDB-2914 for Contraception and Fibroid Treatment

The success of the comparison trial of CDB-2914 for emergency contraception led to the negotiation of a Collaborative Research and Development Agreement (CRADA) with a small company, HRA Pharma, which is located in France and holds the license for CDB-2914. The company is currently conducting two Phase III trials on CDB-2914 in preparation for obtaining FDA approval for use of the compound for emergency contraception up to 120 hours after unprotected intercourse. Currently marketed emergency contraceptive agents are less effective after 72 hours.

In collaboration with The Population Council and HRA Pharma, the CRHB has supported the development of vaginal rings, which can deliver a continuous low dose of CDB-2914. As a site in the CDRCP, The Population Council is conducting Phase II clinical trials to determine the dose needed for inhibition of ovulation resulting in effective contraception.

The CRADA has also been used to support a collaboration between HRA Pharma, the CRHB, and the Section on Reproductive Medicine within the Program in Reproductive and Adult Endocrinology, NICHD Division of Intramural Research, to investigate the efficacy of three months of daily oral CDB-2914 for reduction of size and symptoms of uterine fibroids in women who are scheduled for hysterectomy due to fibroids. The preliminary results of this study have demonstrated effective reduction of fibroid size and symptoms.

The protocol was expanded to allow women to choose to continue treatment with CDB-2914 for an additional three months, rather than having the hysterectomy. A study is now planned to investigate whether, after the initial reduction of fibroid size and symptoms by oral CDB-2914, maintenance of size and lack of symptoms can be maintained with use of the vaginal ring that releases continuous low-dose CDB-2914.

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CDB-4124 for Treatment of Fibroids and Endometriosis

CDB-4124 is another selective progesterone receptor modulator developed by the CRHB. It is currently licensed to Repros Therapeutics, Inc., and is in use in clinical trials for the treatment of fibroids and endometriosis. Currently, Phase III trials are underway for the treatment of bleeding associated with uterine fibroids; similarly, a trial using the compound for the long-term treatment of fibroids is ongoing. There is also a Phase II trial underway for the treatment of endometriosis.

New Estrogens

One facet of oral contraceptive technology that has received little attention over the last three decades is the development of new, orally active estrogens with better pharmacologic profiles than existing products. Specifically, research seeks estrogens that have fewer side effects— notably, nausea, vomiting, alterations in liver function and histopathology, and clotting disorders—than those associated with the currently available estrogens, such as ethynylestradiol and mestranol. Some clinicians have suggested that the presence of the 17-ethynyl moiety, which protects the steroids from rapid metabolism by the liver (the so-called “first-pass” effect) and, thus, confers oral activity, is also responsible for many of the side effects observed with these drugs.

In an effort to develop non-ethynylated estrogens, researchers synthesized a series of estradiol nitrate esters, many of which exhibit estrogenic activity in rats and rhesus monkeys in both oral and/or subcutaneous administration. Measuring increases in the uterine weight of immature rats as an endpoint, the research found that the most potent compound of this series, 7 alpha-methyl estradiol, 11 beta-nitrate ester (CDB-1357), was more than 14 times as potent as ethynylestradiol; it was 40 times as potent in the rat postcoital test when administered orally.

However, following oral administration in ovariectomized rhesus monkeys, this compound was found to be less than half as active as ethynylestradiol in inducing estrogen withdrawal bleeding. Blood levels of CDB-1357 were also lower than anticipated when compared with levels for estradiol. Because the compound was highly active in inducing estrogen withdrawal bleeding after subcutaneous administration in monkeys, researchers speculate that either rapid metabolism due to the “first-pass” effect and/or poor absorption were responsible for the reduced activity seen after oral administration in primates. Indeed, all of the nitrate esters of estradiol that seemed more potent than ethynylestradiol after oral administration in the rat were less active when given to monkeys. This reduction in potency could be more than offset by an increase in dose, if the nitrate esters induced fewer side effects; however, the potential for reduction in side effects has not yet been demonstrated in animal studies.

Notwithstanding the findings summarized above, studies have identified several other good candidates in this series of estradiol nitrate esters, in particular, 11 beta-hydroxy estradiol-11,17 dinitrate-3-acetate (CDB-3701). However, establishing their superiority to ethynylestradiol or its methyl ester as the estrogenic component of oral contraceptive tablets will depend upon clinical and histopathological findings from toxicity studies in animals, and/or in clinical trials.

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RESEARCH AND DEVELOPMENT CONTRACTS FOR CONTRACEPTIVE DEVELOPMENT

The Branch currently supports three contracts to further research on identification and development of both male and female contraceptive agents. These contracts are described below.

Biological Testing Facility

This support contract, with Bioqual, Inc., has the capability to conduct more than 150 different screens and assays for classic endocrine activity and drug-induced alterations in reproductive performance in both male and female animals. The testing facility performs dose-finding and pharmacokinetic studies in-house, but also undertakes safety studies through subcontracting mechanisms. These studies have required the development of a broad spectrum of radio- and enzyme-based assays and their validation for several animal species.

Assays involve *in vivo* animal studies in mice, rats, rabbits, and rhesus monkeys. The work includes classic endocrine screens and assays, pharmacokinetic studies, and complex anti-fertility investigations (to explore the mode of action of new chemical entities aimed at identifying the precise level of interference in the reproductive process) at all levels of reproductive performance. This work provides information on the biological activity of new compositions of matter and, depending on the chemical class being investigated, allows the development of new synthetic approaches to experimental compounds. In addition, dose-finding studies are conducted as a prerequisite for toxicology studies and help in the design of safety studies, which Bioqual, Inc., subcontracts out to facilities known for their expertise in this area and for their familiarity with FDA regulations.

In addition to animal studies, the facility conducts *in vitro* assays using a broad range of cell cultures transfected or co-transfected with appropriate plasmids. This operation also includes a large number of radio- and immunometric assays for endogenous substances, and for circulating experimental drug levels. This facility conducts a number of molecular biology investigations to discover both genomic and non-genomic bases for drug action.

Chemical Synthesis Facility

This support contract, with Southwest Foundation for Biomedical Research (SFBR), synthesizes novel steroids—an important component of CRHB product development—identified as promising agents for male or female contraception and reproductive health. In many cases, SFBR is required to develop a new synthetic pathway to optimize yield and reduce cost of production. SFBR has the capability to synthesize steroids under Current GMP (cGMP) for use in clinical trials conducted in the CCTN and elsewhere.

Previously, novel progesterone receptor modulators, including CDB-2914 and CDB-4124, were synthesized under earlier funding cycles for this contract. These compounds were licensed to small companies, which are currently developing them for contraception and for treatment of fibroids. A promising new estrogen, CDB-3701 (11 β , 17 β -dinitratoestradiol 3-acetate), has also been synthesized and is scheduled for toxicology studies pursuant to Phase I clinical trials.

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Additional compounds synthesized under this contract include novel orally active androgens, such as DMA, its longer-acting ester, DMAU, and CDB-4754 (11 β -methyl-19-nortestosterone-17 β -dodecylcarbonate). In the rabbit model, analogs of 11 β -methyl-19-nortestosterone were found to be devoid of hepatotoxicity, which would be an important advance in the development of oral androgens. Since the new contract was awarded in 2007, the Chemical Synthesis Facility has synthesized compounds for toxicology studies to be followed by Phase I clinical trials.

Peptide Synthesis Facility

The Peptide Synthesis Facility support contract, with Multiple Peptide Systems, provides peptides required for research and development of new agents for male and female contraception, as well as for other reproductive health applications. Importantly, the facility synthesizes peptides that cannot be obtained from commercial sources.

One recent example includes cGMP-produced acyline (CDB-3833) for use in clinical trials. This material has been used for the Branch-supported male contraceptive studies at the University of Washington; it is also in use in investigations on polycystic ovary syndrome at Massachusetts General Hospital. Supplies of acyline are maintained as a resource for basic and clinical research in the scientific community. A portion of this material was provided to Merrion Pharmaceuticals for development of an oral formulation of acyline. Additionally, drug delivery systems for acyline have been prepared and are currently undergoing anti-ovulatory testing at the Branch's Biological Testing Facility.

Another product synthesized under the contract was cGMP-produced metastatin, which was provided for a translational research project approved by the NIH Rapid Access to Interventional Development program. Additional peptides have been requested by other investigators for projects within the U54 CDRCP.

HIGHLIGHTS FROM CRHB-FUNDED RESEARCH IN CONTRACEPTIVE AND REPRODUCTIVE EVALUATION

THE COCHRANE COLLABORATION

The CRHB makes use of an international network of medical and scientific organizations that performs ongoing, systematic reviews of randomized, controlled clinical trials on specific medical interventions. Known as The Cochrane Collaboration, this network provides clinicians with up-to-date and valid information for decision making, thus, reducing the lag time in transferring scientific knowledge from individual randomized trials to clinical practice. Most of the major areas of medicine are included in one of the 50 review groups; the review reports are made widely accessible through the Cochrane Library (<http://www.cochrane.org>).

Funding from the CRHB allows Family Health International (FHI) to contribute to the Cochrane Fertility Regulation Review Group, which is based in Leiden, the Netherlands. The Fertility

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Regulation Review Group coordinates worldwide efforts to identify, analyze, and disseminate easily understood formats of information based on scientific evidence about effective family planning. The support allows FHI to produce approximately three to four reviews annually. These reviews can markedly enhance decision making by practitioners in the field. In addition, this information assists the CRHB and the contraceptive research community in identifying gaps in knowledge and contributes to suggesting possible future research topics for the Branch and other researchers.

During the past four years, the CRHB has provided support for the following published reviews:

- Combined oral contraceptive pills for acne;
- Fertility awareness-based methods for contraception;
- Continuous or extended-cycle versus cyclic use of combined oral contraceptives;
- Spermicide alone used for contraception;
- Biphasic versus monophasic oral contraceptives for contraception;
- Steroid hormones for contraception in women with sickle-cell disease;
- Strategies to improve compliance and acceptability of hormonal contraception methods;
- Vasectomy occlusion techniques for male sterilization;
- Triphasic versus monophasic oral contraceptives for contraception;
- The effect of steroidal contraceptives on carbohydrate metabolism in women without Diabetes Mellitus;
- The effect of steroidal contraceptives on bone fractures in women;
- Steroid hormones for contraception in men;
- Scalpel versus no-scalpel incision for vasectomy;
- Oral contraceptives for functional ovarian cysts;
- Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with IUD use;
- 20 mcg versus >20 mcg estrogen-combined oral contraceptives for contraception;
- Advance provision of emergency contraception for pregnancy prevention; and
- Combination injectable contraceptives.

GLOBAL GUIDANCE FOR FAMILY PLANNING BASED ON THE BEST AVAILABLE SCIENCE

In 2002, with input from the NICHD, the WHO Department of Reproductive Health and Research produced the *WHO Selected Practice Recommendations for Contraceptive Use*, which serves as a companion to the second edition of the *WHO Medical Eligibility Criteria for Contraceptive Use (2001)*, a volume also produced with input from the NICHD that defines safe and effective use criteria for various contraceptive methods.

The two documents were subsequently updated with support from the CRHB. A third edition of *Eligibility Criteria for Contraceptive Use* was published in 2004 and a second edition of *Selected Practice Recommendations* was released in 2005. From these evidence-based documents, two tools for improving the global quality of family-planning care were developed: the *Decision-Making Tool for Family-Planning Clients and Providers* published in 2005, and *Family Planning: A Global Handbook of Providers*, published in 2007.

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In addition, in fiscal year 2003, a partnership of organizations, with NICHD support, developed and pilot tested a system to provide global family-planning guidance. The system assures continuous and comprehensive identification, critical appraisal, and synthesis of new research results as they become available. It is a collaborative effort between the Department of Reproductive Health and Research at the WHO, the Johns Hopkins University Bloomberg School of Public Health Center for Communication Programs (JHU/CCP), and the Centers for Disease Control and Prevention (CDC)/WHO Collaborating Center for Reproductive Health (CDC/WHOCC).

The first step, undertaken by the JHU/CCP, consisted of conducting ongoing, comprehensive bibliographic surveillance to identify studies relevant to the guidance topic by screening POPLINE® database input (averaging 850 records per month); posting bibliographic information to a database; and categorizing the bibliographic data according to the research issue it addressed.

The next step, undertaken by the CDC/WHOCC, consisted of determining which new pieces of evidence were relevant; critically appraising relevant new evidence; getting peer reviews and, subsequently, creating final appraisals; and conducting systematic reviews. The CDC will also assist the WHO in determining whether the new evidence necessitates revision of existing recommendations.

The third step, conducted by the WHO, was to determine whether an update to the guidance was warranted, pending the next expert working group meeting to establish the medical eligibility criteria for contraceptive use and the selected practice recommendations for contraceptive use. Updates will be provided electronically pending the next printing of the guidance document.

HIGHLIGHTS OF CRHB-FUNDED RESEARCH IN PREVENTION OF HIV/AIDS AND OTHER STDS

MICROBICIDE DEVELOPMENT

Microbicides are an important component of the NICHD's efforts in HIV prevention. The CRHB has focused on development of dual-use products, e.g., those that have both a contraceptive effect and an anti-microbial action.

In October 2001, the CRHB commenced a Phase II/III randomized, controlled, and double-masked clinical trial of the contraceptive efficacy of BufferGel® within the CCTN (see the [Female Contraception](#) section for details on this trial and its outcomes). In addition to the endpoint of pregnancy, the trial collected data on secondary microbiologic endpoints, including incidence of bacterial vaginosis, *E. coli* colonization, and urinary tract infections. A subset of women underwent colposcopic examination, performed at the first visit and repeated at each of the three or five subsequent visits. A separate open-label trial of BufferGel® with 221 subjects enrolled was also performed. The trials demonstrated that the safety, efficacy, and rate of

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adverse events with BufferGel® was comparable to that of the nonoxynol-9 comparator. The efficacy of BufferGel® as a microbicide to prevent HIV transmission is currently being tested in the NIAID-sponsored HPTN035 trial. The results of that trial will be available in early 2009.

The CRHB also supported the preclinical development and Phase I clinical testing of the microbicial spermicide C31G, or SAVVY; the contraceptive aspects of this trial are described in the [Female Contraception](#) section of this report. *In vitro* tests and animal studies indicated high potency against sperm and pathogens, with acceptable results in a rabbit vaginal irritation assay. Unfortunately, the clinical trial of HIV prevention with C31G was terminated early because of a very low overall HIV seroconversion rate in both the C31G and control arms.

Prior to the end of 2006, the CRHB maintained a microbicide grant portfolio that included projects on the following topics:

- Vaginal physiology and vaginal immunology as they influence STDs and HIV infection;
- Interrelationship among hormones, coitus, and intravaginal products, and their effects on systemic and local immune systems in HIV infection and disease; and
- Cervical and vaginal factors that heavily influence transmission of HIV from female to male, male to female, and mother to newborn.

The CRHB also maintained two microbicide support contracts. One contract supported the creation of a portfolio management system to help the NICHD and the NIAID track the progress of the many compounds under development. The second was a microbicide quality-assurance contract that assisted in standardizing and validating the various assays used in preclinical microbicide development. These contracts were transferred to the NIAID.

HIV IN WOMEN AND GIRLS

Until late 2006, the CRHB supported the Women's HIV Interdisciplinary Network (WHIN). Projects under the WHIN umbrella covered immunology, HIV and associated co-factors, and the molecular biology of HIV in women. All these projects used explant tissue models to study various aspects of HIV in women. The WHIN is still ongoing, but is now supported by the NIAID.

The CRHB also provided support to the Centers for AIDS Research (CFAR). The CFARs are currently co-sponsored by seven NIH Institutes and are directed by a steering committee composed of members representing each Institute. The CFARs are generally located at institutions that support more than \$20 million in AIDS research and are charged with the task of coordinating AIDS research at a local level. The CRHB funded supplemental grants to the CFARs to support microbicide studies and research on issues related to women and girls. The Branch was also the primary funder of the CFAR at the University of North Carolina, which had a strong interest in genital HIV and microbicide/STD prevention research, as well as in behavioral research.

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With the decision that, relative to HIV/AIDS prevention, the CRHB should focus primarily on the spermicidal aspects of microbicides, all of the grants and contracts related to HIV/AIDS, excluding the microbicide clinical trials, were transferred to the NICHD's PAMA Branch or to the NIAID's Division of AIDS prior to the end of fiscal year 2007.

Hormonal Contraceptives and Risk of HIV Acquisition (HC-HIV) Study

It is not known whether hormonal contraceptives have any effect on susceptibility to HIV infection in women. To address this question, in fiscal year 1997, the NICHD began a prospective observational study of 6,400 women at high risk for HIV in three countries: Thailand, Uganda, and Zimbabwe. This effort was called the HC-HIV Study. After enrolling equal numbers of HIV-seronegative women who were using oral contraceptives, depot medroxyprogesterone acetate, or no steroidal method of contraception, researchers followed the participants for seroconversion over a time period of 15 months to 35 months. The first phase of the study was completed in 2005, and primary outcome data were published in 2007. The investigators did not find any association between hormonal contraceptive use and HIV acquisition overall. However, hormonal contraceptive users who were HSV-2 seronegative had an increased risk of HIV acquisition, a finding which requires further research. [Appendix B](#) lists publications that resulted from the HC-HIV Study.

The study participants who became HIV-seropositive in the HC-HIV Study were offered enrollment in the Genital Shedding (GS) Study, which evaluates the effect of hormonal contraception on HIV genital shedding and disease progression among women with primary HIV-1 infection. Objectives of the GS Study are to:

- Examine the effect of hormonal contraceptive use on HIV-1 disease progression;
- Evaluate the time from infection to AIDS, or the need for antiretroviral therapy among a general population of African women; and
- Evaluate the safety and efficacy of hormonal contraceptives when used concomitantly with antiretroviral therapy and other common medications, such as anti-tuberculosis drugs.

This second-phase study includes research on HIV subtype fitness and host-immune response during both the acute and chronic phases of HIV infection, allowing the examination of possible hormonal contraceptive effects on the progression of HIV disease. The study cohort is unique in that it is the only primary infection cohort composed of African women from the general population (i.e., not sex workers or from other high-risk groups). The follow-up rate is high; 85 percent of scheduled visits have been completed despite political and economic upheaval. Findings from this second phase will help inform the development of guidelines for the use of contraception in HIV-infected women.

Evaluation of Colposcopy for Use in Vaginal Product Development

Because of concerns about the validity of colposcopy for evaluating cervico-vaginal lesions in microbicide trials, the CRHB published a Request for Proposals (RFP) to evaluate the correlation of colposcopically identified vaginal/cervical lesions to alterations in the susceptibility of vaginal epithelial tissue to STDs. The goals of this effort included description of both naturally occurring and exogenously produced lesions of the vaginal/cervical epithelium,

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establishment of the natural history of such lesions, performance of STD-challenge testing, and infection measurement. The recipient of the contract was required to have established capability in models of STDs via the vaginal/cervical epithelium, as well as demonstrated experience with performing colposcopic exams consistent with the WHO/CONRAD *Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products*.

A single bidder was identified—University of Texas Medical Branch, Galveston—and was awarded the contract. Researchers at this site proposed using a mouse model to correlate colposcopically visible lesions with increased susceptibility to genital HSV-2 infection. They also indicated that they would compare optical coherence tomography (OCT) with colposcopy, with the expectation that OCT would prove to be more sensitive in detecting epithelial changes.

In the initial trials using nonoxynol-9, the researchers were unable to demonstrate increased susceptibility to infection. However, they are moving forward with studies of benzalkonium chloride and, with the assistance of the CRHB, are acquiring a number of other microbicides currently used in human clinical trials. They are also extending the evaluation of OCT to include histologic correlation.

HIGHLIGHTS FROM CRHB-SUPPORTED RESEARCH ON SELECTED REPRODUCTIVE AND OTHER GYNECOLOGIC HEALTH ISSUES

PELVIC FLOOR DISORDERS

As many as one-third of adult women in the United States may suffer from one or more female pelvic floor disorders, such as pelvic organ prolapse, urinary or fecal incontinence, or other sensory and emptying abnormality of the lower urinary and gastrointestinal tracts. An estimated 11 percent of women will undergo a major surgical procedure to correct urinary incontinence or pelvic organ prolapse in their lifetimes. The aging population in the United States will markedly increase the need for treatment of these disorders; as a result, there is an urgent need for research into their etiology, diagnosis, treatment, and prevention.

In response to this ongoing need, as identified in professional communities and with congressional direction, the Branch, in collaboration with the American Urogynecologic Society, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the NIH Office of Research on Women's Health (ORWH), and the Reproductive Sciences Branch and the Division of Epidemiology, Statistics, and Prevention Research within NICHD, has undertaken a number of activities in the area of pelvic floor disorders research.

Epidemiologic Research on Pelvic Floor Disorders

In response to an RFA (HD-00-012) issued by the NICHD, the NIH issued 10 awards to support epidemiologic research on pelvic floor disorders. Eight awards were funded through the NICHD; one was funded by the NICHD and the ORWH through a Research Enhancement

Awards Program (REAP) award; and one was funded through the NIDDK. The NICHD-supported recipient institutions and their projects are described below.

- University of California, San Francisco—PI: Jeanette S. Brown
 - o Title: *Reproductive Risk Factors for Pelvic Organ Prolapse*
 - o Description: Dr. Brown and her research team are estimating prevalence of and associated risk factors for pelvic organ prolapse in 1,100 randomly selected participants of the NIDDK-funded Reproductive Risk Factors for Urinary Incontinence at Kaiser Study (RRISK). Because the time interval between childbirth and the clinical presentation of pelvic floor disorders is typically years or even decades, the very large dataset now available for this retrospective cohort analysis is an efficient means of assessing the longitudinal development of pelvic floor disorders within an ethnically diverse population.
- Mayo Clinic—PI: Adil E. Bharucha
 - o Title: *Epidemiology and Mechanisms of Fecal Incontinence*
 - o Description: Dr. Bharucha and his research team are describing the epidemiology of fecal incontinence in women in three steps:
 1. Follow-up of a 1994 survey of 1,000 women to study the natural history and incidence of fecal incontinence, and to survey a new sample of 5,000 women to estimate prevalence and identify subjects with frequent fecal incontinence for further study;
 2. Analyze risk factors in a case-control design of 200 women with fecal incontinence and 200 age-matched controls; and
 3. Test for specific pelvic abnormalities using magnetic resonance imaging in 100 women with fecal incontinence, compared to 100 controls.
- University of Utah—PI: Peggy A. Norton
 - o Title: *Genetic Determinants of Pelvic Floor Disorders*
 - o Description: Dr. Norton and her research team are studying the genetic determinants of pelvic floor disorders in 150 affected sister pairs to identify phenotypes for pelvic floor disorders that are most likely to have a genetic component, and to test likely candidate genes using genetic linkage analysis of the affected sister pairs.
- University of Michigan—PI: John DeLancey
 - o Title: *Race Differences in Female Urinary Incontinence: Epidemiology and Biology*
 - o Description: Dr. DeLancey and his research team are studying racial differences in women with urinary incontinence in two phases:
 1. A population-based questionnaire survey to estimate the prevalence of urinary incontinence by race; and
 2. Nested case-control studies with clinical testing in groups of Caucasian and African American women who have stress or urge incontinence versus controls who do not have incontinence.
- Oregon Health Sciences University—PI: Jeanne-Marie Guise
 - o Title: *The Epidemiology of Fecal Incontinence After Childbirth*
 - o Description: Dr. Guise and her research team are studying the epidemiology of fecal incontinence after childbirth in three steps:
 1. A population-based study to estimate the incidence of postpartum fecal incontinence;

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2. A nested case-control study to compare risk factors between women with and without fecal incontinence; and
 3. A population-based prospective cohort study of 1,200 women with postpartum fecal incontinence to identify prognostic factors, describe natural history, and correlate physical findings with symptoms.
- University of Iowa—PI: Ingrid E. Nygaard
 - o Title: *Natural History of Pelvic Organ Prolapse: A Prospective Cohort Study*
 - o Description: Dr. Nygaard and her research team are studying the natural history of pelvic organ prolapse using a prospective cohort study design of women who are already enrolled in the Women’s Health Initiative at the University of Iowa. Women complete a symptom survey and receive a physical examination for prolapse staging on four occasions at yearly intervals. This effort should provide data on the prevalence and risk factors for prolapse, onset or progression of prolapse, and correlation between signs and symptoms of prolapse.
 - University of Louisville—PI: Michael H. Heit
 - o Title: *Model for Differences in Incontinence Care Seeking*
 - o Description: Dr. Heit and his research team are studying care-seeking behavior in women with urinary incontinence. By developing and validating a specific questionnaire, this project aims to further understand the motivation and expectations women have for treatment of pelvic floor disorders.
 - University of Maryland—PI: Kristen Kjerulff
 - o Title: *Epidemiology of Female Pelvic Floor Disorders*
 - o Description: Dr. Kjerulff and her research team are describing the epidemiology of pelvic floor disorders through a systematic analysis of several national databases, including the National Ambulatory Medical Care Survey, National Hospital Ambulatory Medical Care Survey, National Hospital Discharge Survey, Nationwide Inpatient Sample, and National Survey of Ambulatory Surgery. These data provide important information on the nationwide scope and public health burden of care sought for pelvic floor disorders.
 - University of Rochester (co-funded by ORWH through a REAP award) —PI: Gunhilde Buchsbaum
 - o Title: *Urine Loss and Prolapse in Nuns and Their Parous Sisters*
 - o Description: Dr. Buchsbaum and her research team are studying the prevalence of urinary incontinence and pelvic organ prolapse in elderly nulliparous nuns, compared to their biological sisters who are parous, to provide information about the heritability versus life impact, particularly childbirth, on the occurrence of pelvic floor disorders.

Pelvic Floor Disorders Network (PFDN)

The PFDN originally funded eight applications in July 2001. That effort included seven clinical sites (Loyola University, Chicago; University of Alabama; University of North Carolina; University of Iowa; University of Pittsburgh; Johns Hopkins University; and Baylor University) and a data coordinating center (University of Michigan).

The PFDN now supports seven clinical sites and a data coordinating center, but with a substantially different composition than that of the 2001 PFDN. (See [Figure 7](#) for current site locations.) The current PFDN includes:

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- Three new clinical sites:
 - o Cleveland Clinic (PI: Matthew Barber)
 - o University of California, San Diego (PI: Charles Nager)
 - o University of Texas Southwestern (PI: Joseph Schaffer)
- Two previous PFDN PIs at new institutions:
 - o PI: Ingrid Nygaard now at the University of Utah
 - o PI: Anthony Visco now at Duke University
- Three new PIs at institutions in the previous PFDN:
 - o PI: Linda Brubaker at Loyola University, Chicago
 - o PI: Holly Richter at the University of Alabama at Birmingham
 - o PI: Morton Brown at the University of Michigan, Data Coordinating Center

PFDN OUTPUT

The PFDN had a remarkably rapid start-up; the researchers developed a full protocol to begin enrollment in their first trial, a randomized surgical trial, within the first year of the Network's initiation. Through the tremendous effort of investigators and research staff, the PFDN has been extremely productive, summarized below. (Please visit [Appendix D](#) for a complete listing of PFDN studies, a timeline for these studies, and a listing of Network presentations and journals that have published Network-related articles.)

- 11 studies completed
 - o Four index studies, including two randomized surgical trials and two cohort studies
 - o Six adjunct studies
 - o One supplementary study
- Five ongoing studies
 - o Three index studies, all randomized trials (two surgical, one non-surgical)
 - o One adjunct study
 - o One supplementary study

Through 2007, PFDN investigators had presented 46 abstracts at national and international scientific meetings, representing 15 different professional organizations (see [Appendix D](#)), and published 28 peer-reviewed manuscripts in 15 different well-respected journals. The widespread distribution of the Network's output represents success in meeting its goal of conducting multidisciplinary research relevant to clinicians in several medical specialties who care for women with pelvic floor disorders.

For 2008, five abstracts have already been submitted for presentation; one manuscript is in press, three are in revision, and three are under journal review. Several other manuscripts are in active preparation (see [Figure 8](#)).

THE FUTURE OF THE PFDN

The CRHB will maintain the cooperative agreement mechanism to fund the PFDN in performing further studies on the diagnosis, treatment, and prevention of pelvic floor disorders. Pending the availability of funds, plans for the Network include adding clinical sites to the current seven sites. In addition, investing more funds in salary support for investigators will enhance the Network's ability to maximize multidisciplinary aspects of study development and implementation. By expanding the clinical base and size of available study populations,

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investigators in the PFDN will be able to enroll subjects more quickly and perform clinical trials more efficiently. Provided that the PFDN remains productive for the remainder of the second five-year cycle (ending in 2011), the next recompetition for PFDN clinical sites and data coordinating center is scheduled to occur in 2010, meaning the third five-year cycle of support would begin in July 2011.

National Health and Nutrition Examination and Survey (NHANES) and the PFDN

To estimate the prevalence of pelvic organ prolapse, urinary incontinence, and fecal incontinence in a population-based sample of American adults (with over-sampling for minority populations), and to describe clinical and demographic factors associated with those pelvic floor disorders, PFDN investigators worked with NHANES staff to incorporate several new questions into the Survey about childbirth history and symptoms associated with pelvic organ prolapse (for women), and on fecal incontinence and urinary incontinence (for men and women). Data collection is planned for two cycles of NHANES: 2005 to 2006, and 2007 to 2008.

Some data from the 2005-2006 cycle are currently available; PFDN investigators used some of these data for abstract and manuscript submissions, as well as for presentations (as appropriate) at the December 2007 NIH State-of-the-Science Conference, [*Preventing Fecal and Urinary Incontinence*](#). Further work is planned for when data from two cycles, representing a larger sample, will be available in approximately two years (at the end of 2009).

The National Children's Study Adjunct Study: Pelvic Floor Disorders in Women After Childbirth

The National Children's Study is a long-term longitudinal study of environmental exposures and childhood illnesses. The Study also presents a perfect opportunity to perform a parallel long-term study of mothers, their childbirth experiences, and the subsequent development of pelvic floor disorders.

PFDN investigators are developing a proposal that will be submitted as an adjunct study to the National Children's Study (although in preliminary discussions with Study staff, interest was so high that the proposal may be combined into the core protocol). Specific aims in studying mothers of children in the Study include:

- Describing the natural history (e.g., incidence, remission, progression, and regression) of pelvic floor disorders over time;
- Estimating the prevalence of symptomatic pelvic floor disorders during pregnancy, after delivery, and long-term up to 20 years after the index delivery; and
- Estimating the attributable risk of pregnancy and delivery (index and subsequent) for the development of pelvic floor disorders.

Support for Pelvic Floor Disorders Research

The Branch issued the PA, *Mid-Career Researchers in Female Pelvic Floor Disorders* (PAR-01-085), to stimulate applications from mid-career investigators studying pelvic floor disorders who wanted protected time to devote to patient-oriented research, and who would serve as mentors to junior investigators. With participation from the NIDDK, the PA was released without set-aside

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funds on April 27, 2001, and expired in April 2004. Six investigators were funded through this mechanism.

A 1999 meeting convened by the CRHB aimed to standardize terminology on female pelvic floor disorders; this meeting has impacted researchers, both nationally and internationally. It would be possible to further estimate the impact of the meeting by examining a series of publications in pelvic floor disorders to see how well outcome measures conform to the recommendations made at the 1999 meeting. In preparation for this follow-up meeting, research results published since 1999 could be synthesized on standardization of terminology and outcomes measurements into a summary document for discussion and consensus building. Proceedings from such a follow-up meeting could then be published and could be widely distributed to researchers and clinicians through professional medical societies and research organizations.

Publication of proceedings from the 2002 meeting, *Basic Science and Translational Research in Female Pelvic Floor Disorders*, will also be instrumental in guiding the development of Branch initiatives in translational research. For example, the Branch may emphasize the establishment of collaborative relationships between fields not typically involved in pelvic floor disorders, such as neurology, muscle physiology, vascular biology, biomechanics, and engineering. In addition, an RFA specifically devoted to stimulating applications in basic science and translational research on pelvic floor disorders is in production for funding in fiscal year 2010. The number of investigator-initiated applications on pelvic floor disorders research has increased since 1999. However, the number is not yet high enough to maintain a self-sustaining community of researchers in this field; stimulation of new applications is still necessary to support and encourage research in this early phase of maturation of the research community.

OTHER ACTIVITIES

In 2000, the NIDDK initiated the Urinary Incontinence Treatment Network (UITN), which consists of nine clinical sites and a biostatistical coordinating center. In 2006, the UITN went through non-competitive renewal with continuation of all sites and the coordinating center into the second cycle. The NICHD fully funds one clinical site and partially funds two other sites in the UITN. (See [Table 2](#) for a listing of UITN studies.)

Currently, five clinical sites are common to both UITN and PFDN:

- Loyola University, Chicago
- University of Alabama at Birmingham
- University of California, San Diego
- University of Texas Southwestern
- University of Utah

Investigators in both Networks are working together to develop a research protocol that could potentially be performed at all 11 sites in the UITN and the PFDN.

RESEARCH TRAINING

REPRODUCTIVE EPIDEMIOLOGY TRAINING

In 1996, the NICHD funded the establishment of a two- to three-year formal postgraduate training program in reproductive epidemiology at the University of Pennsylvania that included the following components:

- A core curriculum in clinical epidemiology, research methods, and biostatistics;
- Elective courses in reproductive biology and basic science;
- Research symposia; and
- Independent research in basic and clinical epidemiology.

To date, 16 fellows have completed the program, and five are currently in training.

In response to the needs for obstetricians/gynecologists (as outlined in the two IOM publications mentioned earlier), the CRHB issued the *Training in Epidemiology and Clinical Trials for Obstetricians and Gynecologists* RFA and awarded grants to four institutions in 2001. These T32 Programs—for two or three years—were jointly based in departments of OB/GYN and epidemiology in medical schools or schools of public health. Fellows received training in biostatistics and in the design and execution of clinical research; they were also required to participate actively in clinical research at their institutions. Between 2001 and 2005, a total of 19 fellows were trained at the four institutions. Two of the four programs recompeted for funding in 2005, but only one was successful.

OTHER BRANCH TRAINING PROGRAMS

The CRHB, in collaboration with the Fogarty International Center at the NIH, co-funds contraceptive research training programs for foreign scientists. In addition, the CRHB currently supports three K23 awards and two K24 awards.

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FUTURE DIRECTIONS FOR THE BRANCH

In 2005, the NICHD implemented a modified strategic planning process for the development of its Branch reports to include external scientific and public input. In accordance with this process, the CRHB convened an expert panel of 12 individuals to provide advice on which it could base its decisions about future research directions. This panel included experts in male and female contraception, reproductive endocrinology, drug development, clinical trials, epidemiology, and pelvic floor disorders. The group included two members of the NACHHD Council as well as two representatives of advocacy groups. (See [Appendix C](#) for a list of panel members.)

The group received comprehensive information about the Branch in advance including detailed information about budgets, individual grants and contracts, and the 2004 IOM report, *New Frontiers in Contraceptive Research: A Blueprint for Action*. As with the expert panels convened to review the activities of other NICHD Branches, the CRHB panel was charged with addressing three overarching questions:

- Given its mission, what are the most important *scientific opportunities* that the Branch should try to pursue in the next four years?
- Given its mission, what are the most important *public health issues* that need to be addressed by the Branch in the next four years?
- Which areas of the Branch's portfolio have progressed to a point where less emphasis is needed?

The following section summarizes the panel's discussions.

PANEL DISCUSSION

Contraceptive Research and Development

There was a consensus that, given the relative lack of interest in contraceptive research on the part of the pharmaceutical industry, the CRHB plays a very important role in moving contraceptive research forward. There was considerable discussion about taking advantage of the new biotechnology areas, such as genomics, proteomics, and bioinformatics and general support from the panel for the Branch to move toward these technology modes. However, the panel clarified the fact that such a move would require a considerable commitment of resources and additional expertise not currently within the Branch. The panel suggested coordinating such efforts with academia and other NIH Institutes and Centers as an aspect critical to the success of these endeavors. The panel also suggested that the Branch de-emphasize the concept of the CRHB as a "virtual pharmaceutical firm," but that it emphasize its role as an organization that could enable contraceptive development through its connections with a number of other entities.

Panel members noted that interaction with industry, academia, and other research organizations, both within and outside of NIH, would be important for the Branch's continued success. Such interaction should include collaboration with other funding organizations, such as the Bill and Melinda Gates Foundation, as well as trans-NIH efforts to help ensure that NIH resources are

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used effectively and duplication of effort is avoided. For the CRHB, interaction with the pharmaceutical industry is critical, even though the industry is not currently pursuing development of new contraceptives. The Branch must still depend upon industry to license, produce, and distribute the new contraceptives it develops. Members emphasized that involving pharmaceutical firms in the design of late discovery and clinical trials performed by the CRHB may encourage the firms to take on new products resulting from this research; new mechanisms may be required to aid in building collaborations with some parts of industry. The panel also indicated that advancing innovative preclinical and clinical research should take precedence over commercial concerns, such as product acceptability and pricing, because an innovative product may create its own new market.

MALE CONTRACEPTION

Panel members discussed the fact that the specifics of the market for male contraceptives are unclear, and some expressed skepticism about the likelihood of widespread use. Although research to identify male contraceptive targets is ongoing, it is clear that non-hormonal male contraceptives are early in development, meaning it is most likely that the first marketed male contraceptive regimen will be hormonal. It will be much easier to assess real-world acceptability of male contraception when a marketed product is available. Several panel members emphasized that clear criteria and specific goals need to be set for male contraceptive development both within the CRHB and in the larger research community. There was consensus that it was appropriate to move forward with the oral androgens research the Branch currently has in preclinical trials.

FEMALE CONTRACEPTION

The panel agreed that the most critical issues for female hormonal contraception are those related to safety and ineffectiveness due to inconsistent use or to discontinuation of use because of dissatisfaction with a method's side effects. One hormonal approach that may avoid the estrogenic and progestational side effects would be the use of a selective progesterone receptor modulator. The CRHB currently has a CRADA with a pharmaceutical firm with such an agent, CDB-2914, for development as an emergency contraceptive; the Branch is also in early clinical development of a vaginal ring with CDB-2914. The panel encouraged the Branch to continue its development of these products. There was also a discussion about the underuse of IUDs in the United States, and the role that the CRHB might play in increasing acceptability of this method. The panel also discussed the possibility of an IUD that contained CDB-2914.

Panel members expressed less enthusiasm for identifying new targets for female contraception than it did for male contraception. Nonetheless, this area was seen as an appropriate research avenue for the Branch to pursue. The panel was supportive of the development of LB for both female and male contraception. Although not a contraceptive per se, a biomarker to predict ovulation would allow one-time monthly use of a contraceptive that blocks ovulation. The panel also expressed enthusiasm about this type of research.

Contraceptive and Reproductive Evaluation

The panel was enthusiastic about the CRHB's support of The Cochrane Collaboration and of the WHO Project for Global Guidance for Family Planning Based on the Best Available Science.

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The panel noted that these processes produce evidence-based information that helps to define the research agenda for contraception worldwide.

Although the Branch has supported a number of large epidemiologic studies in the past, this activity was seen as a lower priority than many of the other areas discussed by the panel. The one exception was the topic of safety concerns for contraceptives. In particular, the panel discussed the ongoing concerns about both efficacy and safety of hormonal contraceptives among obese women, particularly in reference to venous thromboembolism. Panel members added that the Branch was the only entity that could support research on these issues using epidemiologic studies.

Prevention of HIV/AIDS and Other STDs

Overall, the panel placed this research area as a low priority, with the exception of the possibility of performing a contraceptive trial with BufferGel® alone, should the results from the NIAID-supported HPTN035 microbicide trial prove favorable. The panel understood that the majority of the activities CRHB previously conducted in this area were transferred to other units in the NICHD and NIAID.

Selected Reproductive and Other Gynecologic Health Issues

The panel was very supportive of the Branch's ongoing activities, specifically for the PFDN, and felt that continued support, including an expansion of activities into basic and translational research, was appropriate. Branch staff explained that the upcoming publication of RFAs related to translational research in pelvic floor disorders would help meet the need for expanded funding in this area, as noted by the panel. The panel also suggested collaboration with other NIH Institutes, specifically the National Institute of Arthritis, Musculoskeletal, and Skin Diseases, could potentially broaden the scope of the research and the resources available in this area.

The panel discussed—at length—the topic of menopause research supported by the CRHB. The consensus was that collaboration with other NIH Institutes on various topics within menopause research was appropriate for the Branch. However, because several other Institutes actively support and conduct research in this area, the panel indicated no need for the CRHB to make this area a priority.

Prioritization of Research Areas

The panel provided its opinions on the prioritization of the Branch research areas discussed. From top priority to lowest priority, the panel suggested the following:

- New biotechnology (e.g., genomics, proteomics, bioinformatics) to identify and characterize male and female reproductive targets and identify lead agents for preclinical testing
- Female contraceptive development (hormonal)
- Male contraceptive development (hormonal)
- Pelvic floor disorders research
- Epidemiologic studies
- Spermicide/microbicide studies
- Menopause research

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FUTURE RESEARCH DIRECTIONS FOR THE BRANCH

Contraceptive Research and Development

Based on the recommendations of the expert panel, the Branch will consider the following activities:

- Develop a consortium program to support the development of new, non-hormonal contraceptives targeted to unique reproductive tract targets as its highest priority in this area. The focus would be on both male and female targets, although with a likely greater emphasis on male targets.
- Issue an RFP for a group of support contracts to provide services, such as target characterization with structural analysis of binding sites, target validation with transgenic animals, target specificity with sensitive expression assays, identification of lead compounds with high throughput screening, and lead optimization with molecular modeling.
 - o These services would be available for projects currently supported by the CRHB, as well as for collaborative academic and commercial organizations seeking to develop new contraceptives.
 - o These services could also interact with the Branch's other support contracts, which provide biological testing and chemical synthesis.
- Convene a panel of drug development experts to provide specific recommendations on the optimal approach to structuring this research program.
- Expand available expertise in the areas described above to run the new program.
 - o The CRHB will have to expand its staff with scientists who have this type of background.
 - o The Branch will also identify existing assets at other NIH Institutes and Centers, as well as facilities that may exist at currently funded academic and commercial organizations.
 - o The CRHB will use this process as part of a global effort to energize contraceptive development.
- Continue to focus on developing hormonal contraceptives for women that have improved safety and side-effect profiles and enhanced acceptability.
 - o In particular, the Branch will consider testing products that have a potentially better safety profile for obese women.
 - o The development and testing of new estrogens may also be a priority.
 - o The Branch plans to support the development of a vaginal ring containing CDB-2914 and may also develop an IUD containing the same product.
 - o Branch may also pursue research to identify biomarkers for ovulation prediction.
- Continue development of dual-use contraceptives, such as spermicide/microbicides, diaphragms, and female condoms, that provide protection from HIV and other STDs.
- Pursue research on contraceptive delivery systems, including needle-free, long-acting microspheres and intranasal administration with long-acting nano contraceptive preparations, in conjunction with the development of new contraceptives.
- Complete the full range of studies of new orally active androgens for male hormonal contraception:
 - o Once the toxicology testing of these agents is completed, the Branch will move rapidly into clinical testing, with the goal of developing a highly effective and well-tolerated combination oral androgen/progestin preparation.

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- o Acceptability studies will be an important component of all future clinical research on new male contraceptives.

Contraceptive and Reproductive Evaluation

Based on the recommendations of the expert panel, the Branch will consider the following activities:

- Estimate the mean age at menopause among American women and assess trends in the mean age at menopause overall and among various race/ethnicity subgroups. Pending approval of funding, the Branch will commence this activity using data from NHANES.
- Identify factors associated with age at menopause (using the same NHANES dataset). In particular, this analysis will examine the possible association between contraceptive hormones usage and age at menopause.
- Given that obesity is an increasing problem within the U.S. population, and in light of the fact that the NIH has identified obesity as a research priority, the CRHB will consider partnering with other Institutes, Centers, or agencies to develop epidemiologic studies of the safety and efficacy of hormonal contraception in overweight and obese women.

Prevention of HIV/AIDS and Other STDs

Most Branch activities in this area, excluding development of spermicide/microbicides and other barrier methods of contraception, are either nearing completion or were transferred out of the Branch; efforts within this topic area will continue to be much reduced. Depending upon the results of the NIAID HPTN035 study, the Branch may pursue a Phase III trial of BufferGel® with funding assistance from other entities, such as the NIH Office of AIDS Research.

Selected Reproductive and Other Gynecologic Health Issues

Based on the recommendations of the expert panel, the Branch will consider the following activities:

- Issue funding opportunity announcements to solicit both R01 and R03 applications for translational research in pelvic floor disorders.
 - o This program will encourage collaboration between basic and clinical scientists in the field, with the hope that knowledge gained by the basic scientists can inform the development of clinical interventions for pelvic floor disorders.
 - o Collaboration with other Institutes (in addition to NIDDK) that might have an interest in the basic science aspects of this research will also be pursued.
- Continue support for the PFDN.
 - o The OPTIMAL trial (see [Appendix D](#)) will start within the next year.
 - o The RUBI-2 study, examining the efficacy and impact of botulinum toxin A versus anticholinergic therapy for the treatment of urge urinary incontinence, will also begin within the next year.

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FIGURES AND TABLES

FIGURE 1: BRANCH FUNDS BY SUPPORT MECHANISM, FISCAL YEAR 2003 THROUGH FISCAL YEAR 2007

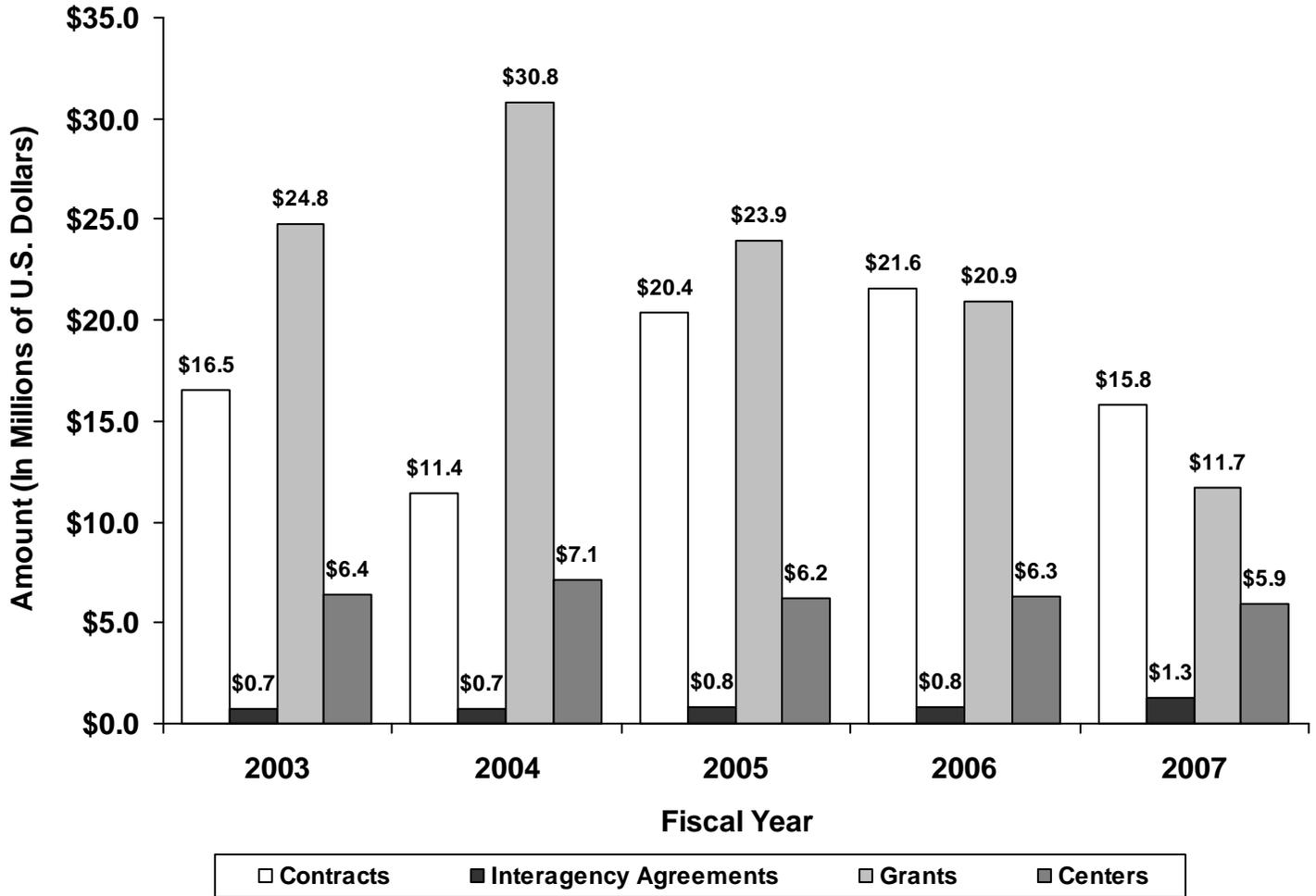
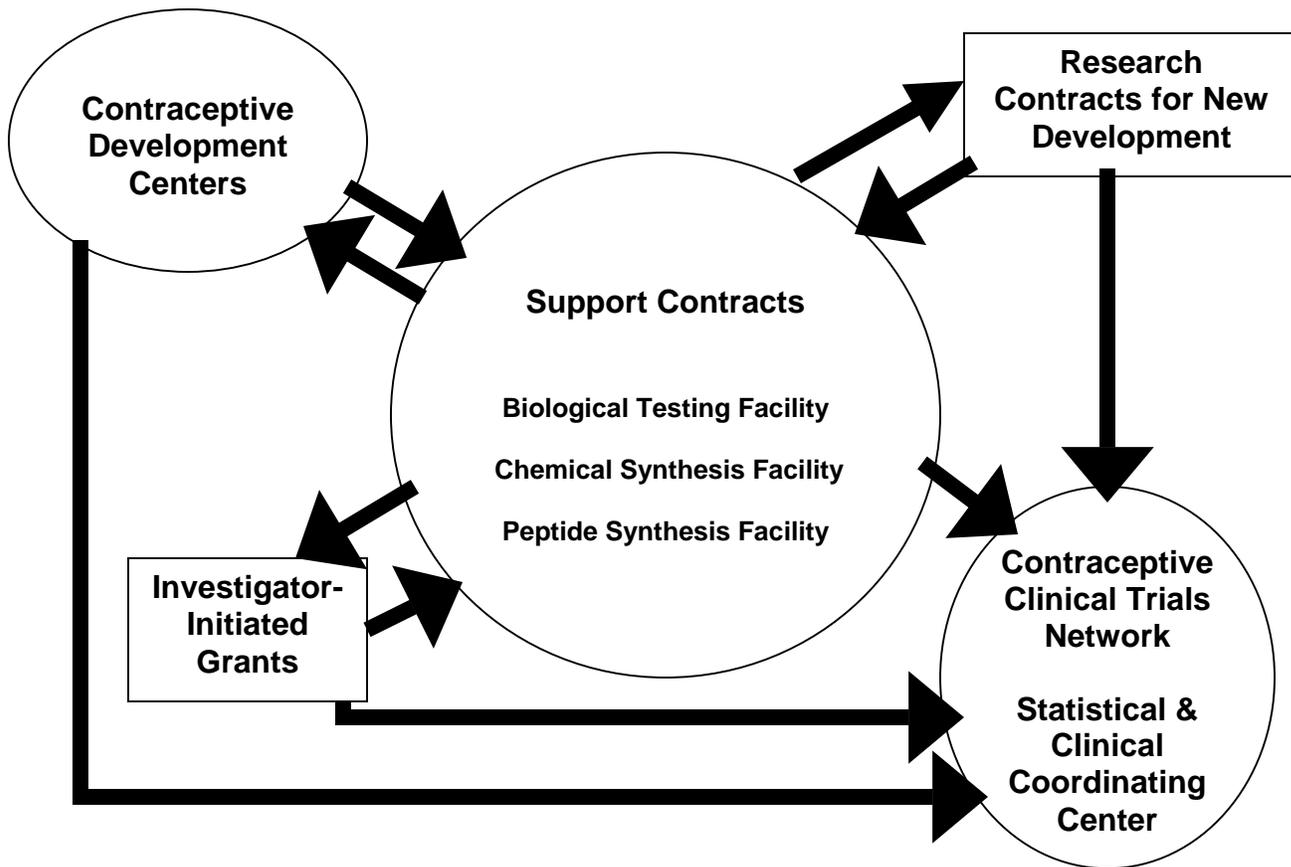
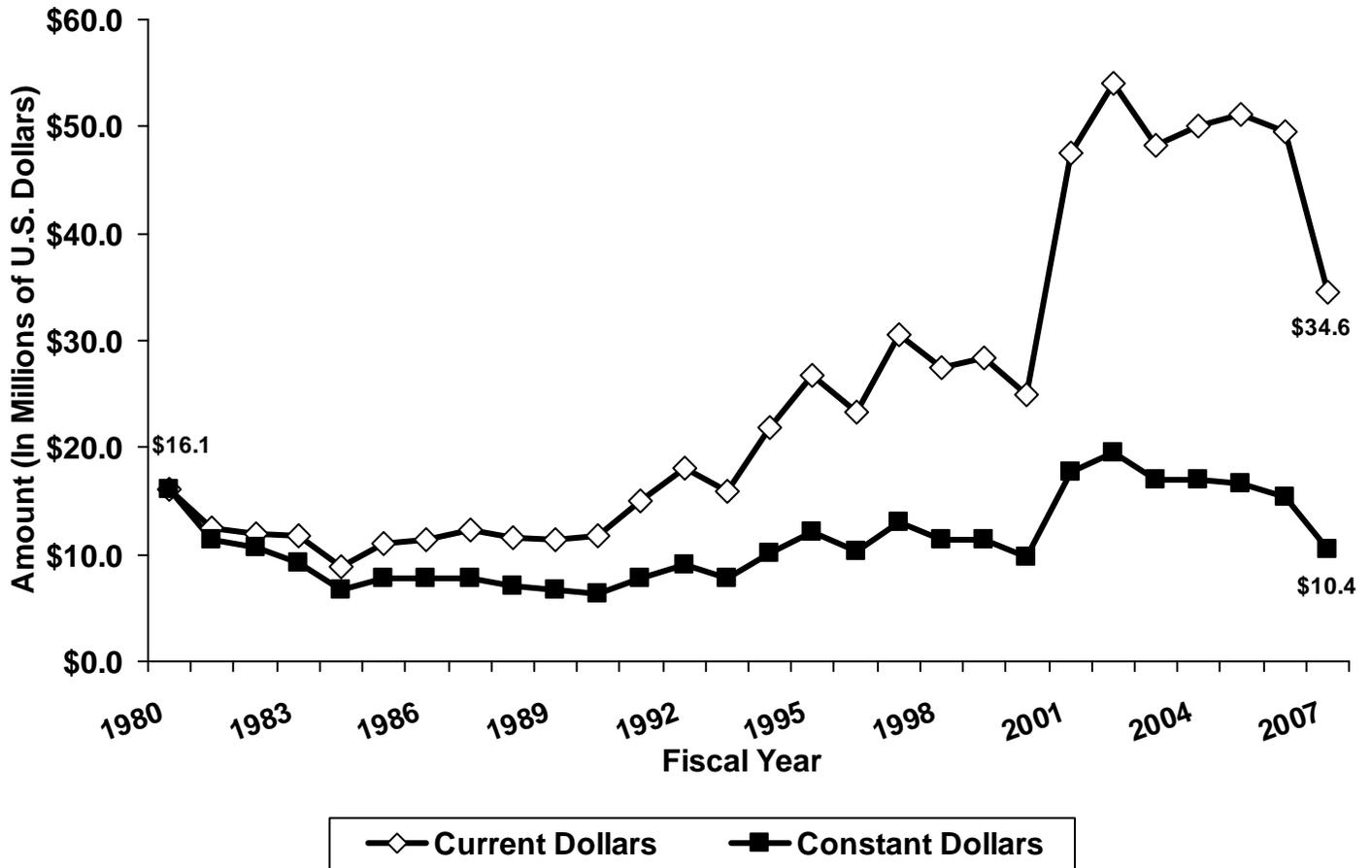


FIGURE 2: BRANCH MECHANISMS FOR CONTRACEPTIVE DEVELOPMENT



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FIGURE 3: BRANCH FUNDS IN CURRENT AND CONSTANT DOLLARS, FISCAL YEAR 1980 THROUGH FISCAL YEAR 2007



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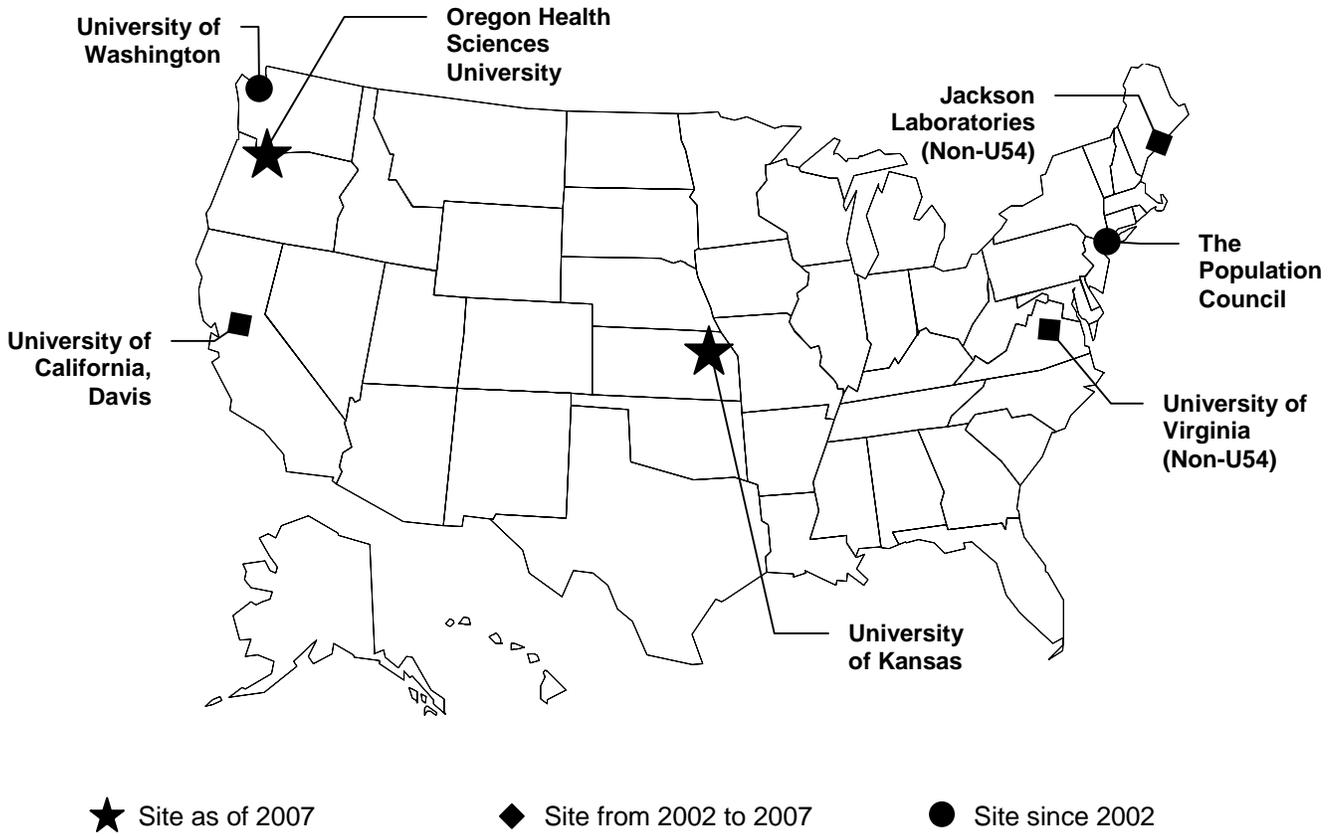
TABLE 1: BRANCH PROJECTS BY PROGRAM AREA, FISCAL YEAR 2007

Program Area	No. of Grants	Amount*
Contraceptive Research and Development		
Contraceptive Research	21	\$5,722,776
Preclinical Contraceptive Development	6	\$3,157,775
Contraceptive Clinical Studies	18	\$12,309,808
Research and Development Support Facilities	3	\$2,239,440
Subtotal	48	\$23,429,799
Contraceptive and Reproductive Evaluation		
Contraceptive Epidemiology	3	\$966,920
Subtotal	3	\$966,920
Prevention of HIV and Other STDs		
Preclinical Product Development	5	\$1,602,454
HIV/STD Pathogenesis	2	\$887,111
Clinical Studies	2	\$1,150,802
Subtotal	9	\$3,640,367
Selected Reproductive and Other Gynecologic Health Topics		
Epidemiology	3	\$1,138,525
Clinical Studies	9	\$3,861,558
Subtotal	12	\$5,000,083
Research Training		
Training Grants/Career Development	11	\$1,604,148
Subtotal	11	\$1,604,148
Total	83	\$34,641,317

* All amounts in millions of U.S. dollars.

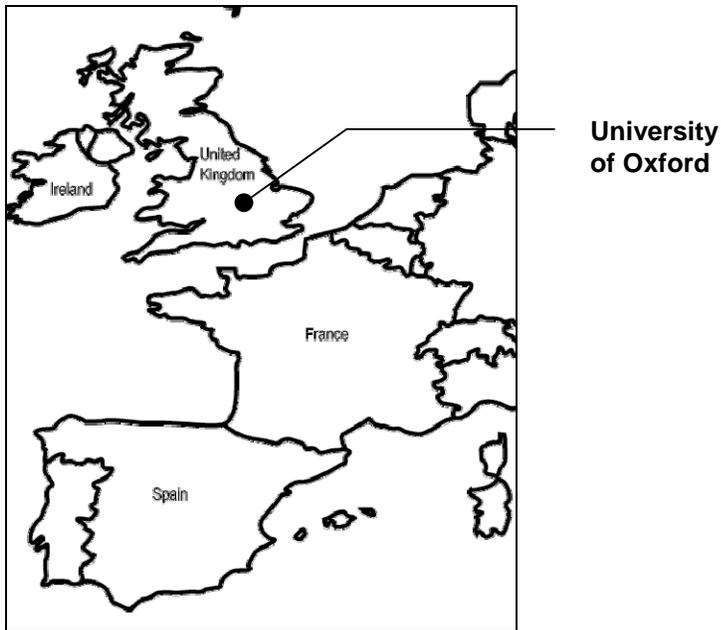
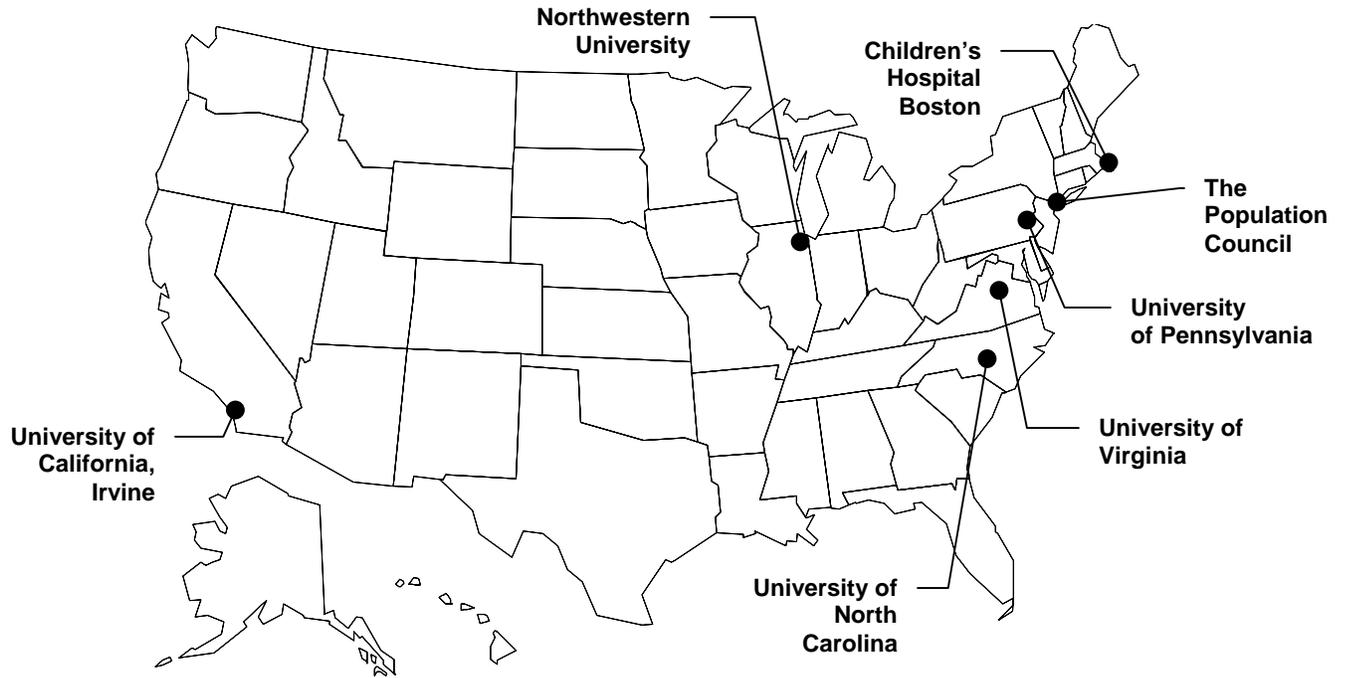
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FIGURE 4: CONTRACEPTIVE DEVELOPMENT RESEARCH CENTERS PROGRAM (CDRCP) SITES



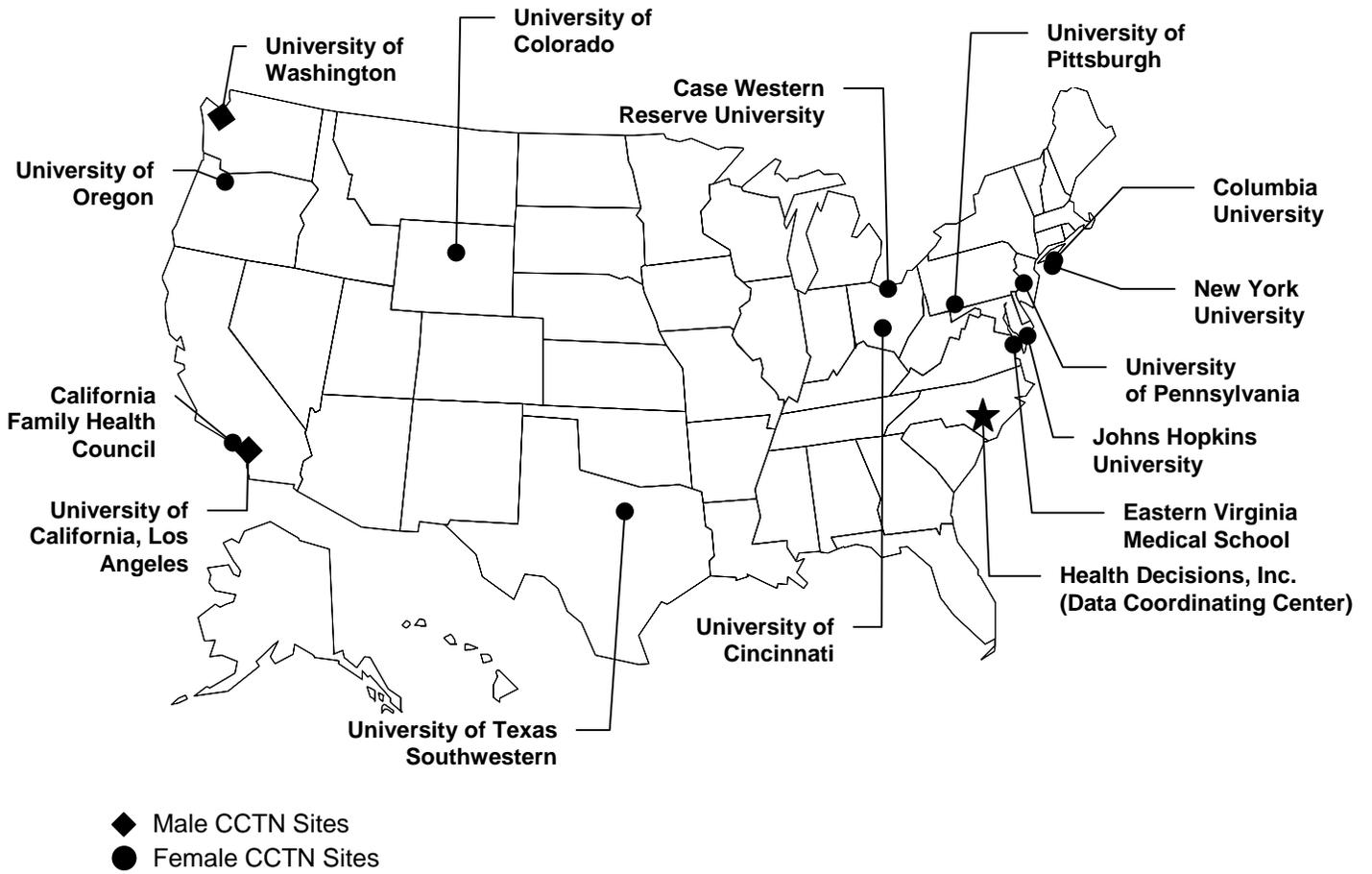
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FIGURE 5: MALE CONTRACEPTION DEVELOPMENT PROGRAM SITES



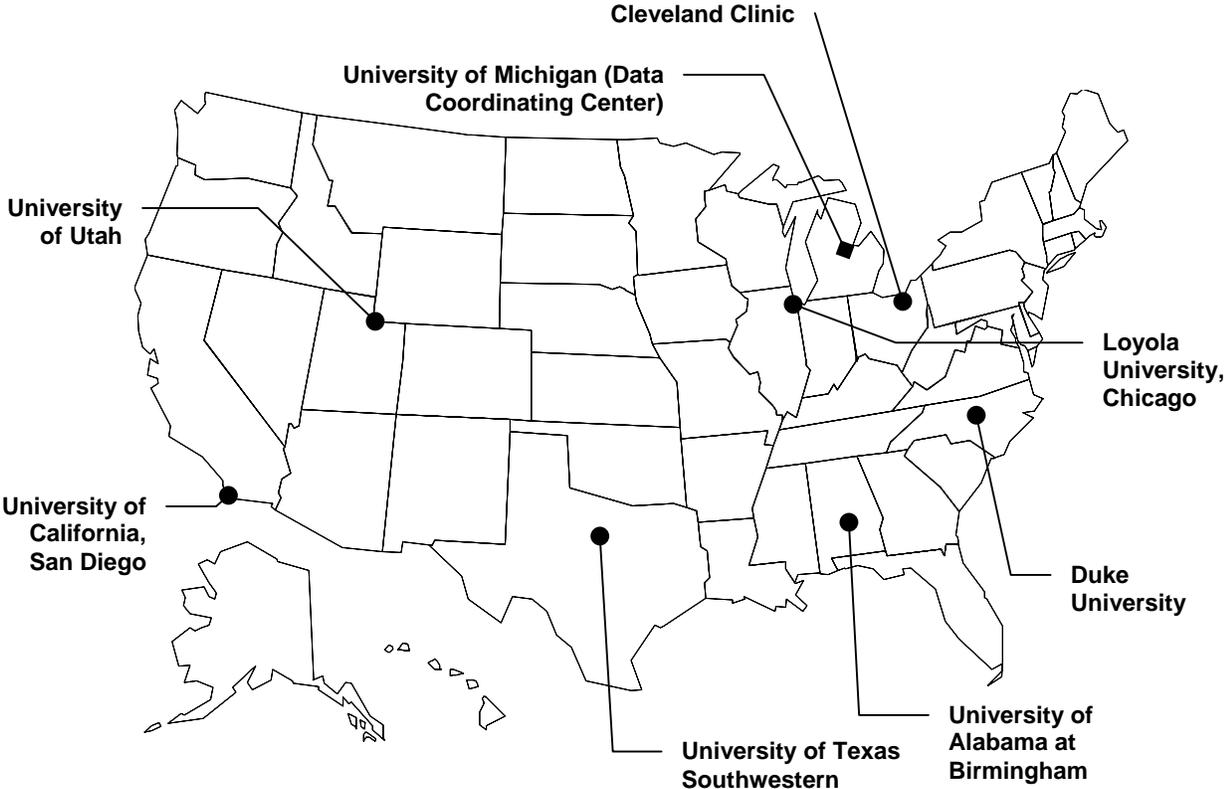
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FIGURE 6: CONTRACEPTIVE CLINICAL TRIALS NETWORK (CCTN) SITES



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FIGURE 7: PELVIC FLOOR DISORDERS NETWORK (PFDN) SITES



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FIGURE 8: PFDN OUTPUT (THROUGH FISCAL YEAR 2007)

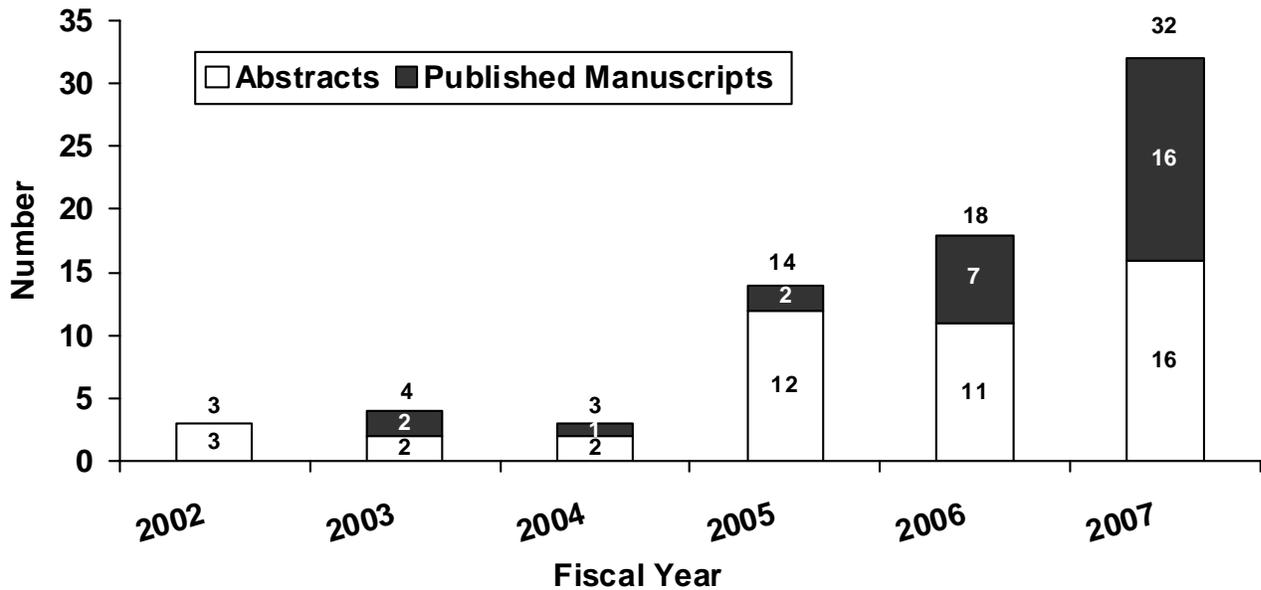


TABLE 2: URINARY INCONTINENCE TRIALS NETWORK (UITN) STUDIES, ACTIVE AND COMPLETED

Title	Sample Size	Study Population	Intervention	Analysis
Trial of Mid-Urethral Slings (TOMUS)	594	Planned mid-urethral sling surgery for stress incontinence.	Retropubic versus transobturator mid-urethral sling.	Enrollment ongoing.
Behavioral Therapy Enhances Drug Reduction for Incontinence Trial (BE-DRI)	307	Urge or mixed (predominantly urge) incontinence.	Drug (tolterodine) versus drug + behavioral therapy and pelvic muscle exercises.	Follow-up ongoing; 1 manuscript published.
Stress Incontinence Surgical Treatment Efficacy Trial (SISTER)	655	Planned surgery for stress incontinence.	Autologous rectus fascial sling versus Burch colposuspension	12 manuscripts published.

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APPENDIX A: BIOSKETCHES OF CURRENT BRANCH STAFF

H. Trent MacKay, M.D., M.P.H., joined the CRHB in 1998. He became acting Branch chief in January 2006 and Branch chief in July 2006. He has represented the Branch in the areas of contraceptive clinical trials and clinical and epidemiologic aspects of obstetrics and gynecology (OB/GYN). Dr. MacKay received his undergraduate degree from Stanford University, his M.D. and postgraduate medical training from the University of California, San Francisco (UCSF), and his M.P.H. in maternal and child health from the University of California, Berkeley. Dr. MacKay has been actively involved in family planning and contraceptive research for the past 35 years, starting with research on an inflatable intrauterine device (IUD) and quinacrine sterilization while he was an OB/GYN resident at UCSF. After seven years of private practice, he served as an Epidemic Intelligence Service officer in the Division of Reproductive Health at the Centers for Disease Control and Prevention (CDC) from 1983 to 1985. He was a full-time faculty member at the University of California, Davis, from 1985 to 1992. Prior to coming to NIH, Dr. MacKay was a medical epidemiologist in the Division of Sexually Transmitted Disease (STD) Prevention at the CDC from 1992 to 1998, where he was the acting Branch chief of the Training and Health Communications Branch. At NIH, he has been the project officer for the Contraceptive Clinical Trials Network (CCTN) as well as for the Statistical and Clinical Coordinating Center for the CCTN. He published and awarded four grants for a Request for Application entitled *Epidemiologic and Clinical Trials Training for Obstetricians and Gynecologists* and published an RFA for research on progestin contraception and endometrial bleeding. Dr. MacKay has been a reviewer for *Contraception*, the *American Journal of Obstetrics and Gynecology*, *Obstetrics and Gynecology*, the *Journal of the American Medical Association*, and others. In addition to his NIH duties, from April 2001 through November 2006, Dr. MacKay was the department head of obstetrics and gynecology and subsequently associate director for Women's Health Services at the National Naval Medical Center, Bethesda, Maryland. He is a professor of OB/GYN at the Uniformed Services University of the Health Sciences. Since coming to NIH, Dr. MacKay has served two years as the chairperson of the Board of the Association of Reproductive Health Professionals.

Diana Blithe, Ph.D., received her bachelor of arts from Douglass College of Rutgers University, majoring in chemistry. She received her Ph.D. from the Department of Biochemistry and Biophysics and the Wistar Institute at the University of Pennsylvania in Philadelphia. Dr. Blithe did her postdoctoral training in the Laboratory of Molecular Biology at the National Cancer Institute as a National Research Service Award Fellow. She has expertise in biochemistry, endocrinology, and glycobiology. Following her postdoctoral training, she joined the Developmental Endocrinology Branch of the NICHD, where she conducted studies on the structure and function of glycoprotein hormones. She has published numerous papers in the fields of endocrinology and glycobiology. In 1996, Dr. Blithe joined the NICHD's Contraceptive Development Branch, which was a predecessor to the present CRHB. Her current responsibilities include serving as the program director for the Contraceptive Development Research Centers Program (CDRCP) and the Male Contraceptive Development Program of the NICHD. In addition, she serves as the project officer of the CCTN, which conducts clinical trials on new contraceptives for both women and men. Dr. Blithe also is a principal investigator on a collaborative research and development agreement with HRA Pharma to develop

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CDB-2914 as a progesterone receptor modulator for contraceptive and therapeutic applications. Her additional responsibilities in the Branch include reviewing technology transfer arrangements with commercial partners. She has organized several international meetings, including two *Future of Male Contraception* meetings and a recent landmark meeting, *Progesterone Receptor Modulators and the Endometrium*. Dr. Blithe has served on the editorial boards of the *Journal of Biological Chemistry* and the *Archives of Biochemistry and Biophysics*. She is a member of The Endocrine Society and currently serves on the editorial board of *Endocrine* and as an *ad hoc* reviewer for other journals.

Steven C. Kaufman, M.D., M.S., came to the NICHD as a medical officer in the Contraception and Reproductive Evaluation Branch in 1992. He received his B.A. in biology from the University of Rochester, his M.D. from Albany Medical College, and an M.S. in statistics from the University of Wisconsin, Madison. He also completed a U.S. Public Health Service Epidemiology Training Program Fellowship, following which he served as a senior staff fellow in the Biometry and Epidemiology Program at the National Eye Institute (NEI), and then as a medical officer in the U.S. Food and Drug Administration (FDA) Office of Epidemiology and Biostatistics. He currently focuses on coordinating the CRHB grant portfolio, a position that involves serving as health scientist administrator for almost all of the Branch's investigator-initiated grants, providing guidance to grant applicants and CRHB staff about funding opportunities and the grant application process, and advising Branch members about funding opportunity announcements. He recently became the NICHD Loan Repayment Program (LRP) liaison and represents the NICHD on the NIH LRP Policy and Oversight Committee. He has also served as project officer for the Branch's contracts dealing with male condoms, vasectomy, tubal sterilization, infertility, and peri/postmenopausal gonadotropin levels, and was medical officer for a joint NICHD/NIAID cooperative agreement dealing with microbicide development. Dr. Kaufman has made presentations at national scientific meetings on such topics as pre-doctoral training and extramural epidemiology research funding opportunities at the NICHD, and has represented the NICHD on the Surgeon General's Deep Vein Thrombosis Workshop Interagency Planning Committee and at the 2001 and 2003 Expert Consultation on Vasectomy Effectiveness. His publications since joining the NICHD have dealt with vasectomy, tubal sterilization, infertility, episiotomy and peri/postmenopausal gonadotropin levels. He also initiated the CRHB Web site and has served on the Advisory Board for the NIH Web Site on Health Disparities.

June Lee, M.D., Ph.D., joined the CRHB in 1999, from the NEI at the NIH. Her recent duties include: oversight of screening novel compounds for anti-fertility and/or therapies; oversight of developing a CRHB database and oversight of synthesizing and testing of compounds for a broad spectrum of new drugs at the Biological Testing Facility and Chemical Synthesis Facility. She is also the project officer for the Biological Testing Facility and Chemical Synthesis Facility. Dr. Lee is the chair of the National Emerging Drug Screening Program, the Drug Delivery and Therapeutics Committee, and the NIH Advanced Pharmaceutical Screening Interest Group. She is actively involved in the National Emerging Technologies Committee, the NIH Rapid Access to Intervention Development program, the Expert Committee of Obesity Evaluation and Treatment, the NIH Drug Discovery Interest Group, and the NIH Clinical Pharmacology Interest Group. Dr. Lee is a member of the editorial board of *Modern Drug Discovery* and has served as a reviewer for *Clinical Pharmacology* and the *Journal of Drug Delivery & Therapeutics*.

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Susan Meikle, M.D., M.S.P.H., trained at the University of Colorado Health Sciences Center in both OB/GYN and preventive medicine and subsequently practiced in local Denver county clinics and at the county hospital, while also serving as a physician-researcher in the Colorado Kaiser Permanente Medical Group. In 1997, Dr. Meikle entered government employment at the CDC, where she worked on projects, such as the study of the natural history HIV in women, and acted as director of the Assisted Reproductive Technology Surveillance Program. While at the CDC, Dr. Meikle initiated a refugee reproductive health research program to use evidence-based, on-site information to inform reproductive health care in refugee settings. Dr. Meikle moved to NICHD in 1999, where she was program officer for the Maternal-Fetal Medicine Units Network, until she was appointed program officer of the Global Network for Women's and Children's Health Research, a network of cooperative agreements studying interventions in women's and children's health in developing countries, co-funded by the Bill and Melinda Gates Foundation. Dr. Meikle went on to become the first in-house obstetrician-gynecologist at the Agency for Healthcare Research and Quality, serving as a resource for the Agency's evidence-based medicine materials, including the development of systematic reviews in the field of women's health, while also carrying out independent intramural research. In March 2007, Dr. Meikle returned to the CRHB at the NICHD to work on clinical trials in contraception and to serve as the project scientist for the pelvic floors disorders research program.

Joseph M. Kaczmarczyk, D.O., M.P.H., joined the CRHB as a medical officer in March 2008 and immediately assumed the duties of the medical officer for the CCTN and of the program official for the Pelvic Floor Disorders Network (PFDN). Prior to joining the NICHD, Dr. Kaczmarczyk was the medical officer in the FDA Office of Women's Health for more than four years, where he was the project officer for the FDA Office of Women's Health extramural research program and was a member of the FDA's Institutional Review Board. Dr. Kaczmarczyk began his U.S. Public Health Service career in 1987 as an obstetrician-gynecologist with the Indian Health Service. During a more than a decade with the Health Resources and Services Administration's Bureau of Primary Health Care, he held a variety of positions, including senior advisor on integrative medicine and alternative health practices, which involved directing an initiative to integrate complementary medicine and alternative health practices with conventional primary care with a focus on women, as well as ethnically, racially, and culturally diverse populations. During 2000 to 2002, he was the senior medical advisor on the staff of the White House Commission on Complementary and Alternative Medicine Policy. Dr. Kaczmarczyk received his B.A. from Lycoming College, his M.S. in physiology and biophysics from West Virginia University, his D.O. from the Philadelphia College of Osteopathic Medicine, and his M.P.H. in health services administration from the Uniformed Services University of the Health Sciences. He completed his internship at Sun Coast Hospital, Florida, his OB/GYN residency at the Hospital of the Philadelphia College of Osteopathic Medicine, and an occupational medicine residency at the Uniformed Services University of the Health Sciences. Dr. Kaczmarczyk is board-certified in three specialties: OB/GYN, occupational medicine, and holistic medicine. He is a commissioned officer in the U.S. Public Health Service, holds the rank of Captain, and has more than 20 years of active duty. Dr. Kaczmarczyk is an associate professor of OB/GYN at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, where he also has a secondary appointment as adjunct associate professor of preventive medicine and biometrics. He was the president of the

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American College of Osteopathic Obstetricians and Gynecologists (ACOOG) from 2002 to 2003. Currently, Dr. Kaczmarczyk is the ACOOG representative to the Association of Professors of Gynecology and Obstetrics Undergraduate Medical Education Committee.

OTHER BRANCH STAFF, 2004 TO 2007

- Robert Spirtas, Dr.P.H., epidemiologist, Branch chief (retired December 2005)
- Joanne Luoto, M.D., M.P.H., medical officer (died June 2006)
- Patricia Reichelderfer, Ph.D., microbiologist (transferred November 2006)
- Hyun K. Kim, Ph.D., medicinal chemist (retired December 2007)
- Richard Blye, Ph.D., pharmacologist (retired December 2007)
- Anne Weber, M.D., M.S., medical officer (resigned December 2007)

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APPENDIX B: PUBLICATIONS FROM THE HORMONAL CONTRACEPTIVES AND RISK OF HIV TRANSMISSION (HC-HIV) STUDY

- Brown, Wald, Hubbard, Bakka, Rungruenthanakit, Moncada, Chipato, Rugpao, Mmiro, Celentano, Salata, Morrison, Richardson, & Padian. (2007). Incident and prevalent Herpes Simplex Virus Type 2 infection increases risk of HIV acquisition among women In Uganda and Zimbabwe. *AIDS, July 31;21(12)*, 1515-1523.
- Steiner, Kwok, Dominik, Byamugisha Chipato, Magwali, Mmiro, Rugpao, Sriplienchan, & Morrison. (2007). Pregnancy risk among oral contraceptive pill, injectable, and condom users in Uganda, Zimbabwe, and Thailand. *Obstetrics and Gynecology, 110(5)*, 1003-1009.
- Turner, Morrison, Padian, Kaufman, Salata, Chipato, Mmiro, Mugerwa, Behets, & Miller. (2007). Men's circumcision status and women's risk of HIV acquisition in Zimbabwe and Uganda. *AIDS, Aug 20;21(13)*, 1779-1789.
- Morrison, Wang, Van Der Pol, Padian, Salata, & Richardson. (2007). Pregnancy and the risk of HIV-1 acquisition among women in Uganda and Zimbabwe. *AIDS, May 11;21(8)*, 1027-1034.
- Morrison, Richardson, Mmiro, Chipato, Celentano, Luoto, Mugerwa, Padian, Rugpao, Brown, Cornelisse, & Salata. (2007). Hormonal contraception and the risk of HIV acquisition. *AIDS, Jan 2;21(1)*, 85-95.
- Minnis, Muchini, Shiboski, Mwale, Morrison, Chipato, & Padian. (2007). Audio computer-assisted self-interviewing in HIV prevention research: Reliability assessment among women in Harare, Zimbabwe. *Contraception, 75*, 59-65.
- Williamson, Liku, McLoughlin, Nyamongo, & Nakayima. (2006). A qualitative study of condom use among married couples in Kampala, Uganda. *Reproductive Health Matters, 14(28)*, 89-98.
- van de Wijgert, Morrison, Salata, & Padian. (2006). Vaginal washing associated with increased risk of HIV acquisition? (letter). *AIDS, Jun 12;20(9)*, 1347-1348.
- Pettifor, van der Straten, Dunbar, Shiboski, & Padian. (2004). Early age of first sex: A risk factor for HIV infection among women in Zimbabwe. *AIDS, Jul 2;18(10)*, 1435-1442.

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APPENDIX C: EXPERT PANEL MEMBERS

Kurt T. Barnhart, M.D., M.S.C.E.
Associate Professor of OB/GYN
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania

Sandra Carson, M.D.*
Professor of OB/GYN
Warren Alpert Medical School, Brown
University
Director, Division of Reproductive
Medicine and Infertility, Women and Infants
Hospital of Rhode Island
Providence, Rhode Island

Daniel Davis, M.D.
Medical Officer
Division of Reproductive and Urologic
Products, Center for Drug Evaluation and
Research
U.S. Food and Drug Administration
Silver Spring, Maryland

Gordon Duncan, Ph.D.
Consultant
CG Therapeutics, Inc.
Seattle, Washington

Victoria Handa, M.D.
Associate Professor of OB/GYN
Director, Advanced Training Program in
Female Pelvic Medicine and Reconstructive
Surgery
Johns Hopkins Bayview Medical Center
Baltimore, Maryland

Daniel Johnston, Ph.D.
Wyeth Research
Collegeville, Pennsylvania

Vivian Lewis, M.D.*
Professor of OB/GYN
Director, Division of Reproductive
Endocrinology
University of Rochester Medical Center
Rochester, New York

Kirsten Moore, M.P.A.
President
Reproductive Health Technologies Project
Washington, DC

Herbert Peterson, M.D.
Professor and Chair
Department of Maternal and Child Health
School of Public Health
University of North Carolina
Chapel Hill, North Carolina

Ronald S. Swerdloff, M.D.
Chief
Division of Endocrinology
Harbor-UCLA Medical Center
Los Angeles, California

Kirsten Thompson
Director
Male Contraception Coalition

Andre Ullman, M.D., Ph.D.
Laboratoire HRA Pharma
Paris, France

* Member of the NACHHD Council

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APPENDIX D: PELVIC FLOOR DISORDERS NETWORK (PFDN)

ACTIVE AND COMPLETED STUDIES

Title/Type of Study	Sample Size	Population Characteristics I	Intervention	Analysis
17P01 OPTIMAL Trial: <u>O</u> perations and <u>P</u> elvic Muscle <u>T</u> raining in the <u>M</u> anagement of <u>A</u> pical Support <u>L</u> oss Randomized Controlled Trial (RCT)	400	Apical prolapse and stress incontinence	Factorial 2x2 design with double randomization: <ul style="list-style-type: none"> • Uterosacral ligament versus sacrospinous ligament suspension for apical prolapse; • Perioperative pelvic muscle therapy versus usual care 	Pending
16P01 OPUS Trial: <u>O</u> utcomes following vaginal <u>P</u> rolapse repair and mid- <u>U</u> rethral <u>S</u> ling RCT and parallel Patient Preference Trial (PPT)	RCT = 350 PPT = 200	Vaginal prolapse in stress-continent women	Tension-free Vaginal Tape (TVT) versus no TVT at vaginal prolapse surgery, to test prophylactic TVT versus delayed TVT for post-operative stress incontinence within first year after index surgery	Pending
13P01 ATLAS Trial: <u>A</u> mbulatory <u>T</u> reatment for <u>L</u> eakage <u>A</u> ssociated with <u>S</u> tress RCT	450	Stress or mixed (stress and urge) incontinence	Three randomized groups: <ul style="list-style-type: none"> • Pelvic muscle exercises • Continence pessary • Both pelvic muscle exercises and continence pessary 	Pending
1S02 E-CARE Study: <u>E</u> xtended <u>C</u> ontraceptive and <u>R</u> eproductive <u>E</u> xperiences (CARE) Cohort extension of RCT	215	Follow-up after CARE trial enrollment	No intervention	Pending
1J06 Adaptation to Pelvic Floor Disorders in Women Focus Groups & Clinical Validation	240+	Populations from ATLAS, OPUS, OPTIMAL, and fecal incontinence studies	No intervention	Focus groups: Published: <ul style="list-style-type: none"> • 1 abstract • 1 manuscript Clinical validation: Pending.

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Title/Type of Study	Sample Size	Population Characteristics I	Intervention	Analysis
12P01 RUBI Trial: <u>R</u> efractory <u>U</u> rge Incontinence and <u>B</u> otulinum Toxin A <u>I</u> njection RCT	43 (of 210, <i>halted early</i>)	Refractory detrusor overactivity incontinence	Botulinum toxin A (Botox®) versus placebo (saline) via cystoscopic detrusor injection	Published: 2 abstracts Submitted: 1 manuscript
1P01 CARE Trial: <u>C</u> olpopexy <u>A</u> nd urinary <u>R</u> eduction <u>E</u> fforts RCT	322 (of 480, <i>halted early</i>)	Planned abdominal sacrocolpopexy in stress-continent women	Burch colposuspension versus no Burch, to prevent postoperative stress incontinence	Published: <ul style="list-style-type: none"> • 19 abstracts • 12 manuscripts • 1 manuscript in press, • 1 manuscript in revision Submitted: 2 manuscripts In preparation: 6 manuscripts
2P01 CAPS Study: <u>C</u> hildbirth <u>A</u> nd <u>P</u> elvic <u>S</u> ymptoms Cohort Study	922	Three groups: <ul style="list-style-type: none"> • Vaginal delivery with anal sphincter tear • Vaginal delivery controls • Cesarean delivery controls 	No intervention	Published: <ul style="list-style-type: none"> • 9 abstracts • 6 manuscripts • 1 manuscript in revision In preparation: 1 manuscript
2S02 CAPS MRI-Ultrasound Supplementary Study	235	Pelvic MRI and endoanal ultrasound on subset of three groups in Childbirth and Pelvic Symptoms (CAPS) study	No intervention	Published: <ul style="list-style-type: none"> • 4 abstracts • 2 manuscripts • 1 manuscript in revision Submitted: 1 manuscript In preparation: 5 manuscripts
7P01 Colpocleisis Study: Pelvic Symptoms and Patient Satisfaction After Colpocleisis Cohort Study	153	Planned colpocleisis	No intervention	Published: <ul style="list-style-type: none"> • 1 abstract • 1 manuscript In preparation: 2 manuscripts

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Title/Type of Study	Sample Size	Population Characteristics I	Intervention	Analysis
1J01 Reliability of Questionnaires for Condition-Specific Health-Related Quality of Life	88	Previous surgery for prolapse within the past year	No intervention	Published: <ul style="list-style-type: none"> • 1 abstract • 1 manuscript
1J03 Effects of Examination Technique Modifications on Pelvic Organ Prolapse Quantification (POP-Q) Results	133	Outpatient POP-Q examination for prolapse	No intervention	Published: <ul style="list-style-type: none"> • 2 abstracts • 1 manuscript
1J05 Correlation of Microtip Transducers and Water Perfusion Catheters	210	Planned urodynamic testing	No intervention	Published: <ul style="list-style-type: none"> • 1 abstract • 1 manuscript
1J10 Voiding Function in Women with Pelvic Organ Prolapse	160	Prolapse and stress incontinence	No intervention	Published: <ul style="list-style-type: none"> • 3 abstracts • 2 manuscripts Submitted: 1 manuscript
2J01 Modified Manchester Questionnaire	39	Fecal incontinence	No intervention	Published: <ul style="list-style-type: none"> • 1 abstract • 1 manuscript
2J03 Spanish Language Translation of Pelvic Floor Disorders Instruments	50	Prolapse, urinary incontinence, or fecal incontinence	No intervention	Published: 1 manuscript

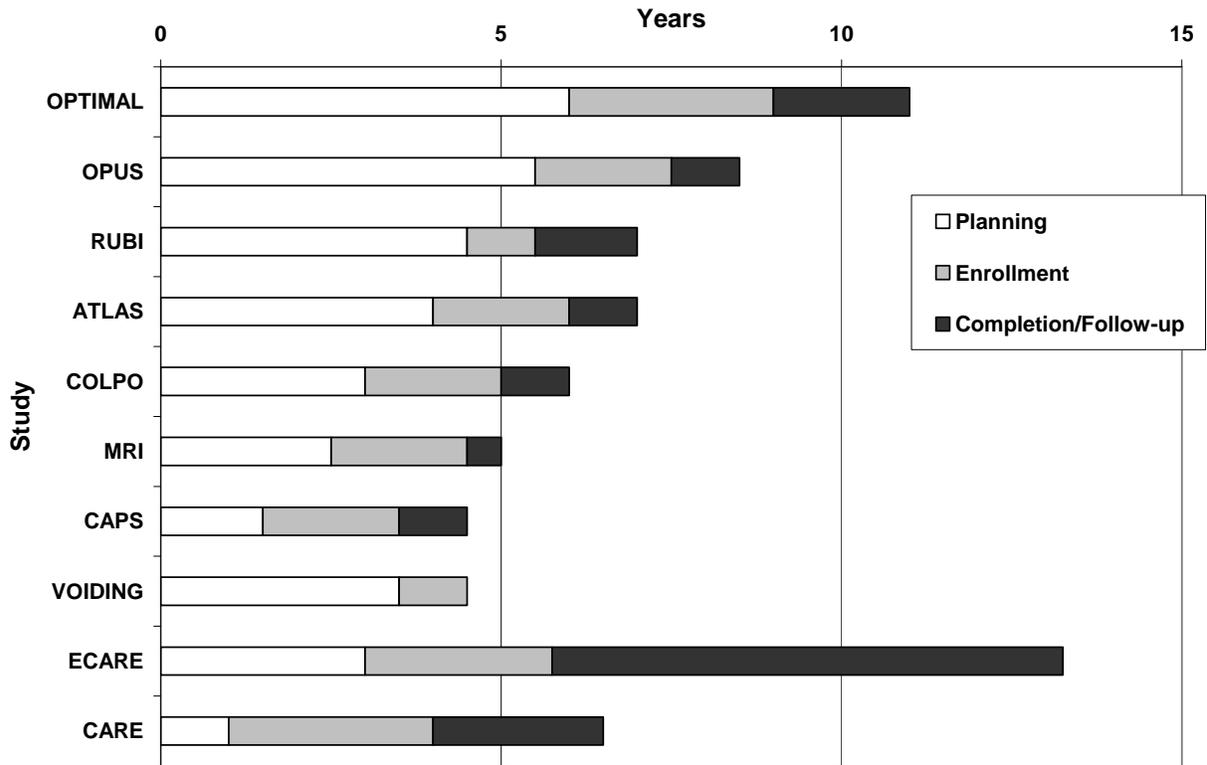
TIMELINE OF PFDN STUDIES

Study	Enrollment Opened	Enrollment Closed	End (Follow-Up Completed*)
1P01 CARE	April 2002	February 2005	March 2007
1S02 ECARE	May 2004	March 2007	April 2012
1J10 VOIDING	October 2004	September 2005	--
2P01 CAPS	September 2002	September 2004	April 2005
2S02 CAPS MRI-US	September 2003	March 2005	May 2005
7P01 COLPO	July 2004	March 2006	April 2007
13P01 ATLAS	July 2005	September 2007	October 2008
12P01 RUBI	April 2006	December 2006	December 2007
16P01 OPUS	May 2007	December 2008	December 2009
17P01 OPTIMAL	November 2007	May 2010	May 2012

* Does not include data analysis or dissemination of results

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GRAPHIC TIMELINE OF PFDN STUDIES



In above graph, the horizontal axis represents time in years since PFDN initiation, with zero time being July 2001; therefore, 5 years represents the completion of the first cycle (June 2006) and 10 years, the completion of the second cycle (June 2011). The duration of time shown in gray represents time to complete enrollment; the duration of time shown in black represents time to study completion (end of follow-up). Time devoted to data analysis and dissemination of results is not shown in this graph.

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PFDN PRESENTATIONS AND PUBLICATIONS

Scientific Meetings

- American College of Obstetricians and Gynecologists
- American Geriatric Society
- American Motility Society
- American Public Health Association
- American Urological Association
- American Urogynecologic Society
- Central Association of Obstetricians and Gynecologists
- International Continence Society
- International Urogynecologic Association
- Radiological Society of North America
- Society of Gynecologic Investigation
- Society of Gynecologic Surgeons
- Society of Maternal-Fetal Medicine
- Society of Pelvic Surgeons
- Society of Urodynamics and Female Urology

Journals

- *American Journal of Gastroenterology*
- *American Journal of Obstetrics and Gynecology*
- *Applied Research in Quality of Life*
- *Controlled Clinical Trials; Clinical Trials*
- *Diseases of the Colon & Rectum*
- *International Journal of Gynecology & Obstetrics*
- *International Urogynecology Journal*
- *Journal of the American College of Surgeons*
- *Journal of the American Geriatric Society*
- *Journal of Applied Research*
- *Journal of Urology*
- *Neurourology & Urodynamics*
- *New England Journal of Medicine*
- *Obstetrics & Gynecology*
- *Physical Therapy*