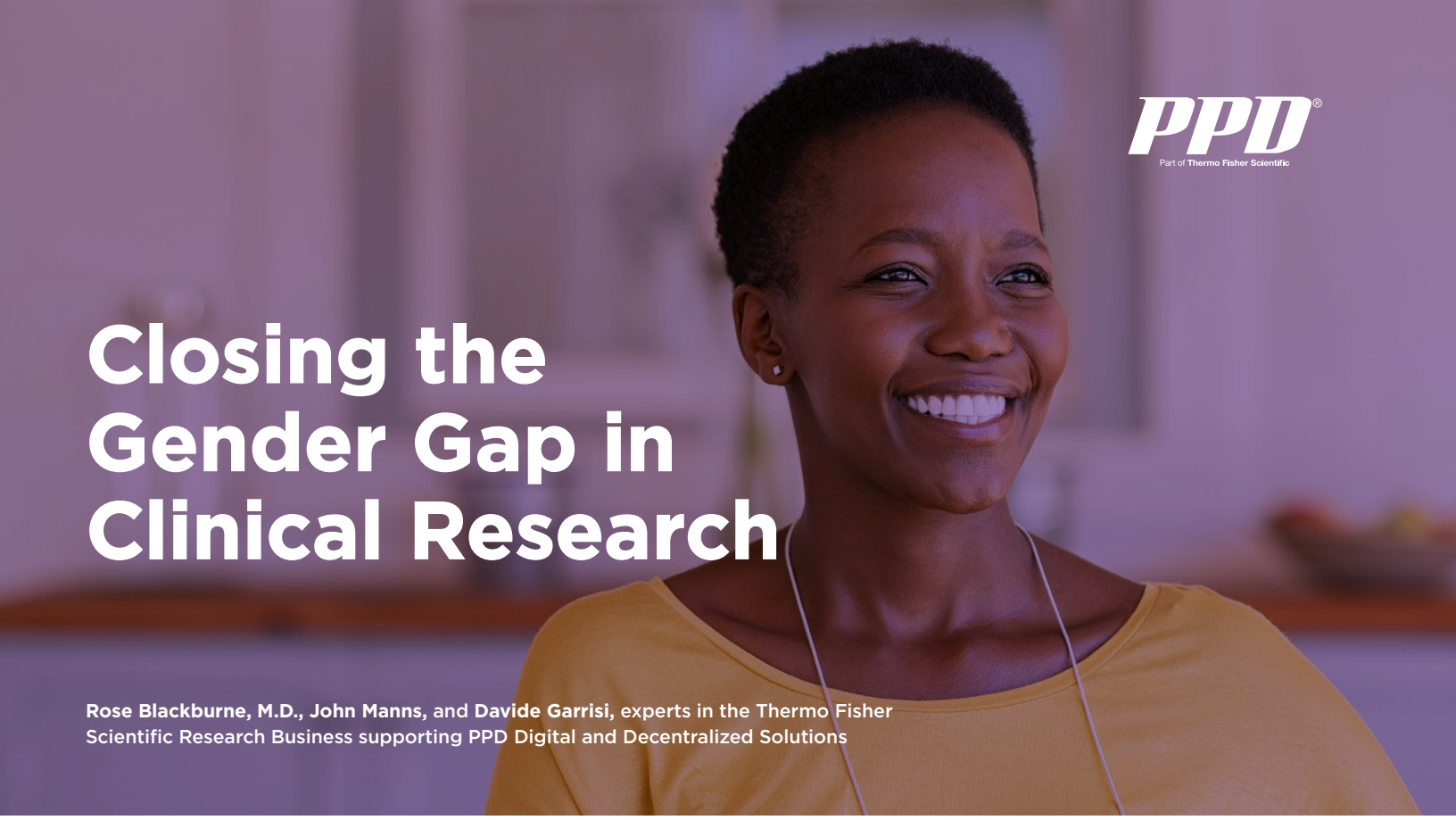

Closing the Gender Gap in Clinical Research

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In previous decades, women, including pregnant and lactating women, were significantly underrepresented in clinical trials, and trials investigating diseases exclusive to women were particularly rare. Even today, investments in non-oncologic conditions that affect women's health account for a smaller portion of total clinical development investments.[1] Recruitment and retention challenges unique to women — and to specific populations of women — are a contributing factor. Targeted recruitment solutions and flexible trial designs and protocols, particularly those that incorporate patients' voices, are critical to facilitate successful clinical studies for a broader range of women's health indications.

A History of Underrepresentation

Historically, women were only included in clinical trials to a limited extent. It was not until a series of regulatory guidance issued around the inclusion of women and minorities in clinical studies beginning in the late 1970s and continuing through the 1980s, 1990s, and 2000s that the issue captured the attention of drug developers and clinical researchers.

Trials including women can be affected by higher dropout rates, particularly for studies that require frequent visits with multiple procedures over an extended time or for drug candidates treating indications for which multiple approved over-the-counter products (OTC) are readily and more easily available. Women of childbearing potential, as well as those who are pregnant and lactating, are often excluded from trials, even for indications for which reproductive-aged women are affected by a specific condition and will be end-users of a given product. Similarly, hormonal contraception products are also

frequently listed as exclusionary medications for a clinical trial. Yet, women are interested in participating in clinical trials,[2] as there are still significant unmet women's health medical needs — and their engagement demonstrates a higher degree of awareness about the impact of their participation for the future.

Real Recruitment Challenges

In addition to the barriers women face due to reproductive health risks, there are myriad reasons why recruiting women into clinical trials can be a challenge. The logistical burden of clinical trial participation can disproportionately preclude women from clinical research. Women often serve as the primary caregiver in single and multi-generational households, holding multiple roles, such as mothers, students, and/or employees. They may have families where they bear responsibility for their children as well as the care of elderly parents, in-laws, or other extended family members. Women interested in a clinical trial for their child's condition also might have to make critical decisions about childcare in order to participate in a trial, such as temporarily taking her other children out of school, hiring a babysitter, or facing the complexities of bringing children with her to study visits.

For women of reproductive age, there are often concerns that an investigational product might impact fertility. Specifically, for pregnant and breastfeeding women, the safety of the fetus or infant is a concern that has traditionally kept women from participating in clinical studies, even those specifically focused on women's health conditions.

Regulatory Considerations

Regulatory agencies have continued to address the impact of exclusion criteria focused on reproductive-age women. Pregnancy and lactation can create barriers to full participation and representation in clinical trials. These agencies are developing and updating guidance to expand and improve opportunities for women to participate in clinical trials, but challenges remain. Women may need to take medication for non-pregnancy-related conditions while pregnant, such as asthma, diabetes, and high blood pressure. And sometimes, medication is taken early in the pregnancy, before a woman knows that she is pregnant.

Another example of regulatory guidance focused on improving opportunities for women in clinical research is the FDA guidance known as the *Pregnancy and Lactation Labeling Rule* (PLLR). It required prescription drugs to remove pregnancy letter categories by June 2020. The PLLR also reorganized information in prescription drug labeling to more clearly describe available data to aid decisions and counseling of patients using prescription drugs specifically for pregnant and lactating women, as well as men and women in reproductive age groups. This guidance also gives recommendations for designing pregnancy exposure registries to monitor pregnancy outcomes in women exposed to approved products during pregnancy. A pregnancy exposure registry collects health information from women who take prescription medicines or vaccines while pregnant. Data are also collected on the newborn baby, and this information is compared with women who have not taken medicine during pregnancy.

Studies may also preclude or require delays in screening due to the need for women of reproductive age to take certain types of hormonal contraceptives, which can be limiting. Perimenopause and postmenopause are additional factors that should be carefully considered when participating in clinical trials. Trials targeting postmenopausal women require proof of menopause for participation. However, this may be challenging. Many women may exhibit symptoms indicative of menopause. Yet, their hormone levels may not meet the requirements of the trial, which is not uncommon in osteoporosis and hormone-replacement studies.

In addition to gender, race, and ethnicity, age is another factor to consider for inclusion: pediatric and adolescent patients up to age 18, elderly patients over 65, and very elderly patients over 75 years are underrepresented in clinical trials. The goal for any clinical trial is to be as representative as possible of the people who ultimately need and use the medicine. Clinical trials should include female patients in all clinically relevant age ranges and ethnic populations worldwide that lack access to comprehensive health care or even contraception.

Regulatory authorities are addressing inclusivity and diverse clinical trials on several fronts. One recent FDA guidance[3] looks at how to broaden participating patient populations. They recommend that new protocols consider changing populations to be more inclusive rather than simply replicating the conventions used for previous trials.

One example of an antiquated protocol measurement that persists is body mass index (BMI). In the United States, people are generally getting bigger in terms of height and weight compared with previous generations.[4] Some of this change is attributable to higher weights, but women are also becoming taller and broader. Using old BMI cutoffs excludes a significant portion of the population. This determination is a real issue for clinical trials in contraceptives, as well as other indications, due to the substantial difference between "real-world" patients and study participants. Compared with the more restricted sample defined by most inclusion and exclusion criteria, there could be reduced real-world effectiveness for women with greater mass. Therefore, it is critical to reevaluate the conventional weight standards and determine how best to tailor them in developing a drug product to better reflect the diversity in the target patient population as final users.

Clinical Investment in Women's Health

Currently, investments in clinical development for women's health are a small portion of the overall clinical development spend. According to a March 2021 report,[5] the 2020 estimated market size for the combined genitourinary and women's health therapeutic area was $582.7 million, approximately 1.2% of the total CRO services market. Similarly, of the nearly $42 billion the National Institutes of Health (NIH) spends

on medical research each year, only approximately $5 billion of that funding is directed specifically at women's health. However, the medical device market in women's health is growing rapidly; it is expected to be $42.5 billion by 2025.[6] The totality of spending on women's health product development is also difficult to tease out, unless the focus is limited to non-oncologic, reproductive health therapeutic areas, which may still not give the most accurate numbers.

The "femtech," or female technology market, includes a category of software, diagnostics, products, and services that use technology often to focus on women's health. This sector is growing at more than 15% per year and encompasses fertility solutions, period-tracking apps, pregnancy and nursing care, women's sexual wellness, reproductive system health care, and even electronic applications, such as online prescriptions and home delivery of contraceptives. The rapid expansion of femtech indicates that women continue to manage a myriad of health issues that are inadequately treated and that could potentially be addressed with advanced clinical solutions.

A Patient-Centric Approach to Women's Health Research

Fortunately, the recognition of the importance of including women across the spectrum of drug, device, and diagnostic product clinical trials is growing and reaching more stakeholders. There is a growing recognition of the need to make clinical trials accessible to women by considering the barriers to participating in a clinical trial. That includes everything from scheduling reasonable hours for appointments, including evenings and weekends, to providing on-site daycare facilities or playrooms and plenty of parking.

Telemedicine, technology, and the expanded use of decentralized trials are an essential part of the equation. Women of all ages are increasingly comfortable using mobile technology, whose higher adoption in clinical trials has been particularly fostered by the COVID-19 pandemic and its worldwide restrictions. It is now possible to individually review each protocol and identify opportunities for decreasing the patient burden by enabling some off-site visits. Scheduling an evening telemedicine appointment would allow women with childcare responsibilities to have more flexible visits to better match their daily schedule, reducing conflicts with childcare or working schedules.

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The FDA is also looking to expand the role of women's voices in drug development in their expanded Patient-Focused Drug Development initiatives, whose primary goal is to better incorporate the patient's voice in drug development and evaluation.[7] The FDA has outlined a series of indications across different therapeutic areas where it focuses on integrating the patient voice — especially those of underrepresented groups. This is important because drug developers sometimes choose the clinical trial objectives and endpoints that may be scientifically valid but not as meaningful to patients, caregivers, or patient advocacy organizations. To remedy that issue, researchers are viewing endpoints more critically through the lens of patients' perspectives earlier in the protocol design process. They are working to include or embrace the factors that are important and more meaningful from the patient's and caregivers' perspectives early on, and they are vetting protocols earlier in study development.

Decentralized Trials Boost Participation from Women

Decentralized trials that leverage digital technology can present a powerful opportunity to increase women's participation in clinical trials. Medication and other supplies can be shipped directly to each participant's home, and patient-reported outcomes (PROs) can be digitally recorded and better monitored through mobile applications and remote technology. Tele-visits can be scheduled with investigators instead of on-site. Nurses can make home-health visits, and telemedicine visits (assisted by the home-health nurse if necessary) can also be leveraged. These flexible options can dramatically reduce patient burden, increasing participation and retention rates.

We expect that many more studies will take this approach in the future. At the same time, we also know that offering different options is essential. Some patients still prefer in-person visits and can manage traveling to the clinic even frequently to maintain a direct (instead of remote) interaction with their treating physician. Others would prefer to

do everything from home or office and are enthusiastic about their telemedicine options. The power of decentralization provides flexibility and freedom to clinical trial participants to choose how they want to participate. That can be particularly relevant — and critical — for navigating the complexities of women's intense lifestyles.

It is Critical that Investigators Ensure Appropriate Representation of Women in Clinical Trials

There is an overall need to increase women's participation in clinical trials across different therapeutic areas. and this can be accomplished if both physicians and participants understand the importance of including clinically relevant populations in trials. For instance, hypertension studies have traditionally included predominantly male participants, but half of the people currently taking hypertension products, if not more, are women.[7,8] The medical community and clinical trial investigators should be thoroughly educated about the target patient population and be equipped to pursue a broader inclusion of all participants.

In addition to training around optimal communication, the medical community needs to learn strategies for talking to different groups of participants, known as cultural competence, including women and other underrepresented groups. Otherwise, the same barriers will remain. Some conversations can be challenging for topics directly impacting lifestyle, perception of others, or education taboos, such as those around urinary incontinence or sex, sexuality, and gender identification. Clinicians need to be hyper-aware of modern sensitivities and potential concerns of different participant groups to speak to them in a way that will ease, rather than exacerbate, negative feelings about participation in clinical trials.

There is also a need to increase awareness among women about getting proper diagnoses and treatment options. Although OTC products can be convenient, cost-effective, and a reliable treatment option, not all conditions are optimally managed with OTC medications; for example, an uncomplicated, presumed *Candida* (also known as yeast) infection can be treated effectively with an OTC product approved for that indication. However, the symptoms of *Candida* infections can also mimic other common vaginal infections, such as bacterial vaginosis. So, without a firm diagnosis, self-treatment can result in mistreating or inadequately treating a bothersome and potentially recurrent condition. Recurrent *Candida* infections require a different therapeutic approach, a definitive diagnosis, and a different management approach by an obstetrics/gynecology (OB/GYN) specialist.

Lastly, it's critical that drug developers continue to increase their awareness of and prioritize women's health conditions. Many women's health indications, such as osteoporosis or uterine fibroids, typically occur in otherwise healthy patients. Sometimes, the management of more life-threatening conditions, such as hypertension, diabetes, or asthma and other chronic more debilitating health issues, can be prioritized over the care and management of gynecologic conditions. Untreated, these indications can also have a significant negative impact on the health and overall quality of life for broad population of women.

Women's Health and PPD

PPD, part of Thermo Fisher Scientific, has a corporate focus and in-depth understanding of women's health disease areas, reproductive health and women's health drug, device, and diagnostic product development. We invest in developing our employees, with women representing approximately 70% of our personnel and 50% of the management team. PPD also invests in resources to support women's health studies with proven strategies to engage, recruit, and retain women into clinical trials.

Our internal teams are made up of experts in women's health across various indications. PPD has extensive experience in studies involving osteoporosis, *Candida* vaginitis, bacterial vaginosis, HPV-related cervical dysplasia, and urinary incontinence — and the expertise to address other important women's health conditions, such as gynecologic cancers, including breast, cervical, uterine, and ovarian cancer. Our clinical trial network also includes women's health experienced investigators and a library of training courses for key indications.

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This wealth of knowledge and experience allows us to recruit female patients and healthy female volunteers into studies, and our team members have a high level of excitement and passion for finding solutions to women's health issues.

One of the authors of this paper, Dr. Rose Blackburne, is a board-certified obstetrician–gynecologist. She has experience and expertise across several specialties and therapeutic areas, including women's health. She also brings her expertise and perspective as a specialist in women's health with over 25 years of experience, including as a practicing physician and clinical trial investigator and 17 years of drug, device, and diagnostic product development experience, to meet clients' needs in successful clinical trial design. Since 2016, Dr. Blackburne has served as Industry Representative to the FDA Patient Engagement Advisory Committee, and primary representative for the *Health of Women/Pediatrics (Vulnerable Population Groups)*, where she provides input on a range of issues relating to medical devices and their use by patients.

We review every step of a proposed trial protocol and every proposed assessment to determine how the burden on the patients — including female participants — can be minimized. Some examinations (e.g., radiology, biopsy) require an in-person visit, but we also consider opportunities to plan a visit at a local clinic rather than the more distant investigator site. In some cases, telemedicine or visits by a home-health nurse can substitute for in-person visits.

We also seek to provide patients with choices and flexibility whenever possible. We look for alternate ways to accommodate their needs, whether through a concierge service that offers transportation or help with childcare. We do whatever needs to be done to get patients to a site visit so they can meet other trial requirements without having to worry about how they will be able to participate without disrupting their lives and the lives of their families.

Finally, we provide enrollment solutions and improved recruitment through tailored and customized approaches for outreach to women of all races, nationalities, social groups, and other demographic categories and garnering their attention and interest in clinical trial participation. Our teams ensure the study messages resonate with the right segment of women and appear in places where the perfect candidate will see and notice them. ■

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