nuttall women's health

XXcelerate

Turning Existing Research Into Impact for Women

Issued by: Nuttall Women's Health

Funding Scope and Duration

XXcelerate provides flexible support for projects that align with the objectives of this RFP. Applications for XXcelerate are on a rolling submission. Proposals can be submitted at any time through Proposal Central. No fixed budget ceilings are imposed. Project durations should not be longer than 3 years. For secondary analyses of completed trials, applicants are expected to propose timelines that allow for the most efficient completion feasible. For ongoing trials, the duration of support should be consistent with the goals and structure of the parent study. Initial funding requests should for no longer than a 3-year time period. Additional funding beyond that period will depend on achievement of metric and milestones. In all cases, proposed budgets and timelines should be proportional to the scope, ambition and developmental stage of the project. Applicants are strongly encouraged to ensure that their proposed activities are tightly aligned with the overarching goals of the RFP and to clearly articulate how the requested resources will enable substantive findings that impact women's health.

Goal

XXcelerate is committed to ensuring that clinical research findings are valid and relevant for women. Too often, exposures, interventions, diagnostics and treatments are evaluated without adequate attention to sex-specific biology.

XXcelerate directly addresses this gap by funding research that rigorously examines outcomes in female populations **leveraging completed or on-going clinical trials**. XXcelerate will advance its mission through two primary funding mechanisms:

1. Re-analysis of Completed Clinical Research Studies

- Secondary analyses of completed randomized clinical trials and cohort studies
- Projects should apply sex-specific approaches to determine whether outcomes are valid for women
- Any type of study is of interest if the findings will impact women including randomized clinical trials, pragmatic trials, cohort studies and/or other relevant study designs
- Special consideration will be given to studies where outcomes can be analyzed in the context of female-specific biology (e.g., menstrual cycles, reproductive history, menopause timing, hormone use)
- Any field of study is of interest if the outcome can be rigorously studied in women

2. Support of Ongoing Clinical Research Studies

- Funding is available for active randomized clinical trials and cohort studies to incorporate rigorous sex-specific analyses
- Proposals may include expanded recruitment of female participants, additional biospecimen/sample testing or enhanced analytical capacity
- Studies should be designed to rigorously evaluate outcomes, exposures and interventions in female populations

Desired Clinical Impact

XXcelerate is designed to close critical evidence gaps in health research by producing rigorous, sex-specific insights and accelerating the pace of discovery to improve health outcomes for women across the lifespan *leveraging existing and on-going studies*.

The Problem

Despite decades of progress in clinical research, women remain underrepresented and underserved in how evidence is generated and applied. Recent findings underscore how failure to provide for sex-specific analyses has resulted in incomplete or erroneous clinical recommendations for women.

The Missed Opportunity of Ignoring Sex in Clinical Trials

Many treatments used for women are based on trials that were performed mostly in men and/or were performed in both men and women, but outcomes were not analyzed in a rigorous sex-specific manner. Several examples are worth discussing.

Cardiovascular Health

Cardiovascular disease is a major cause of morbidity and mortality for women. As women enter mid-life, their risk for cardiovascular disease significantly increases. While women are more represented in contemporaneous clinical trials, there remains a lack of sex-specific analyses to understand how exposures and/or interventions specifically impact women. A recent re-analysis of a large randomized clinical trial illustrates this problem. For decades, international guidelines from the European Society of Cardiology and the American Heart Association have recommended beta-blocker therapy following acute myocardial infarction (MI) to reduce mortality, without distinction by sex. The REBOOT trial, a large pragmatic study conducted across 109 centers in Spain and Italy, re-examined this assumption by analyzing outcomes according to sex. Among the 8,438 participants, 1,627 were women (19%).

The results of the REBOOT trial were published in the New England Journal of Medicine in August of 2025. The study showed a neutral outcome in the total study population with no clear benefit or harm from the use of beta-blockers. An almost contemporaneous publication in the European Heart Journal, reanalyzed the REBOOT trial by sex. Consistent with the results of the parent study, this sex-specific analysis showed a neutral outcome for men. However, in women, use of a beta-blocker was associated with a significant **increase in mortality for women**. The sex-stratified analysis revealed that women treated with beta-blockers had **worse outcomes** than those who did not receive them, particularly in those with preserved left ventricular ejection fraction (LVEF) and in women receiving higher doses of the medication. Compounding these findings, the trial did not collect key female-specific data—*such as menopause timing, use of hormone therapy, or reproductive history (preeclampsia, infertility, PCOS)*—all of which are known to influence cardiovascular risk

The REBOOT findings underscore that therapies cannot be assumed to have the same benefit–risk profile in women as in men and that guideline recommendations built primarily on male-dominated evidence may inadvertently cause harm for women. Importantly, if women had constituted a larger proportion of the cohort, the overall results might have suggested that beta-blockers were harmful to all patients—*even though no adverse effect was seen in men*. Conversely, because men made up more than 80% of the cohort, the aggregate findings could have easily suggested a net benefit for beta-blockers, *masking the true harmful effect in women*. In other words, divergent responses by sex can confound trial outcomes, producing misleading conclusions and driving inappropriate use of therapies in both men and women.

Brain Health

Of all cases of Alzheimer's Disease, ~66% are women. Preventative and therapeutic approaches are needed to improve, if not prevent, this disease. To that goal, the Clarity AD trial was an 18-month, multicenter, double-blind, placebo-controlled trial involving individuals with early Alzheimer's disease. As published in the New England Journal of Medicine in November 2022, CLARITY AD demonstrated that Lecanemab, a monoclonal antibody, a significant 27% slowing of cognitive decline in Alzheimer's patients. In 2023, the drug received FDA approval for this drug for Alzheimer patients. Of note, in the NEJM publication, there was a supplementary figure that included an analysis of the primary outcome by sex. In those analyses, the confidence interval for the primary outcome crossed zero. In men, there was a statistically significant 43% slowing of symptoms (a greater reduction than observed when men and women were analyzed in the primary results). In contrast, in women, slowing of symptoms only occurred in 12% which was a non-significant finding. In the primary publication, the authors did not discuss the sex-specific findings. It was unclear as to whether these findings were 1) not robust as the study was not powered for these analyses or 2) valid as they were consistent with other reports demonstrating sex-specific differences in the presentation and progression of Alzheimer's. In November of 2024, Andrews et al used simulation methods to replicate the trial conditions over 10,000 runs; this study confirmed that this sex discrepancy in the CLARITY AD trial was highly unlikely to be due to chance. Despite this, regulatory approval proceeded without sex-specific labeling or guidance. As women comprise over 2/3rd of Alzheimer patients, it is worth asking if drugs hailed as important breakthroughs may deliver less benefit for the very population most burdened by the disease. Beyond Alzheimer's disease, there are many conditions and diseases that impact female brain health. To optimize women's health, the following questions should be asked: *Are there other trials focused on brain health have resulted in clinical recommendations that do not benefit women? Are existing clinical recommendations for specific therapies for migraines, multiple sclerosis, stroke and dementia as effective for women as the primary studies demonstrated? Is it possible that some interventions have greater efficacy while others have less or may cause harm for women?* While several studies have representation of women in their study, sex-specific analyses have not been rigorously pursued leaving these important questions unanswerable.

Gastrointestinal Health

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, affects men and women at roughly similar rates overall, though some studies show Crohn's disease is slightly more common in women while ulcerative colitis may be slightly more common in men. Globally, IBD affects more than 6.8 million people, with women representing about half of cases but often experiencing a greater burden during key life stages such as reproduction and menopause. In recent clinical trials focused on IBD, women constitute a significant percent of the study population; however, sex-specific analyses are lacking. In the ACCENT I trial of infliximab for Crohn's disease, women comprised more than 58% of participants. Other studies had a significant number of women in the trials (~40% in each of these trials): 1) ACT trials tested infliximab in ulcerative colitis and 2) the GEMINI I and II trials tested vedolizumab for ulcerative colitis and Crohn's disease. These studies were important studies that have defined biologic therapy in IBD. Despite women representing 40-50% of participants in these trials, no sex-specific outcomes were reported. In the GEMINI program, a post hoc pooled analysis (years later) revealed baseline sex-specific differences—men were more likely to present with severe endoscopic disease. Yet, this analysis did not examine whether treatment responses differed by sex. These omissions represent lost opportunities to optimize treatment strategies for women living with IBD.

The Missed Opportunity of Ignoring Sex in Cohort Studies/Biobanks

Outside of clinical trials, large longitudinal cohorts and population biobanks are increasingly being leveraged to identify environmental and biological exposures that shape long-term health outcomes. By following individuals across the lifespan, these resources provide critical insights into disease risk, aging trajectories and potential preventive interventions that traditional trials cannot capture. A leading example is the UK Biobank, which has enrolled more than 500,000 participants and generated transformative discoveries on cardiovascular disease, dementia, obesity, cancer and genetic risk. Importantly, while UK Biobank has enabled sex-based analyses at scale, it still lacks systematic capture of female-specific metadata—*such as age at menopause, real time capture of MHT use (type and for what length), reproductive outcomes and more*.

The size and scope of the UK Biobank have made it possible to uncover patterns impossible to see in smaller dataset and has enabled sex-specific analyses across tens of thousands of participants, identifying differences in dementia risk, obesity trajectories and cardiovascular disease burden. Yet, without rigorous data as to female-specific variables, some of these identified differences may be less related to differences between men and women and more impacted by female specific biology (e.g. genetic and/or gonadal) or female-specific conditions (e.g., preeclampsia, early onset of menopause, etc.) Without these variables, some of the most biologically relevant drivers of women's health and aging may remain invisible.

In the United States, the NIH *All of Us Research Program* is one of the most ambitious U.S. precision health efforts, aiming to follow over one million participants with linked surveys, electronic health records, biospecimens and genomic data. Early analyses demonstrate its potential for women's health: researchers have identified nearly 19,000 pregnancy episodes using multi-source EHR data, conducted studies linking menopause to chronic conditions such as rhinitis, and explored comorbidities like endometriosis in women with dermatologic disease. These examples highlight the program's ability to support sex-stratified and women-focused analyses at a scale rarely possible in U.S. cohorts.

At the same time, *All of Us* still lacks systematic capture of deep female-specific metadata. Age at menarche, menstrual abnormalities, age and type of menopause, years since menopause, hormonal contraceptive or MTH use/route and detailed obstetric histories—*including adverse outcomes such as infertility, premature ovarian failure and preeclampsia* —are inconsistently available or absent in the dataset. As a result, while the resource can reveal broad patterns by sex, it remains limited in its ability to interrogate how reproductive history and hormonal exposures shape women's health trajectories across the lifespan. This gap mirrors challenges in other major cohorts and underscores the urgent need for intentional design that prioritizes female-specific variables in precision health research.

A recent example of how large cohorts and biobanks can be leveraged to understand how exposures and/or therapeutics can impact women's health is demonstrated by the recent publication using the Canadian Longitudinal Study of Aging (CLSA). CLSA enrolled over 30,000 participants. Of those, 15,320 were women. In a recently reported study in Neurology (Puri et al 2025), the authors analyzed 10,291 women who had information on time of menopause, MHT use as well as outcomes for various cognitive tests. Notable strengths were that the cohort recorded these female specific variables (e.g., onset of menopause) that allowed for more in-depth and rigorous analyses. As noted by the authors in the discussion, other relevant female-specific variables, such as preeclampsia (which increases the risk for cardiovascular disease and cognitive impairment), was not captured and thus could not be interrogated for its potential impact. Overall, because CLSA captured critical information (genotype, medical history) along with female-specific metadata, the study was able to be leveraged to ask important questions regarding timing of menopause, route of MHT (not just use) and cognitive outcomes.

A Call to Action

Robust evidence demonstrates that male and female physiology are distinct. Differential drug responses, sex-specific effects of environmental exposures and variations in the predictive value of biomarkers highlight the importance of studying outcomes separately by sex. Moreover, exposures and conditions unique to women may further shape treatment efficacy and long-term health trajectories.

Nevertheless, most clinical studies are not adequately powered to investigate sex-specific outcomes. Historical underrepresentation of women in clinical trials compounds this gap, making it impossible to determine whether the evidence guiding medical decision-making is equally valid for women. This raises serious questions about the generalizability and optimality of current standards of care.

Notably, there is no uniform requirement across funding agencies, regulatory bodies or leading journals to ensure that studies incorporate sex-specific analyses with sufficient statistical rigor. While scientific advances and methodological innovations are accelerating, their translation into effective clinical practice is hindered unless sex differences are addressed *a priori*. Recognizing and integrating these differences is essential to advancing precision medicine and improving outcomes for women.

Specific Research Priorities

XXcelerate welcomes proposals across any area with potential to impact women's health, including but not limited to:

- Metabolic Conditions
- Cardiovascular disease
- Autoimmune and inflammatory disorders (e.g., IBD, lupus)
- Aging, longevity, long-term health
- Neurological disorders
- Mental health and psychiatric disorders
- Cancer

Clinical trials should have a sufficient number of female participants to allow for rigorous analysis. Cohort studies may focus on diagnostics, biomarker discovery, or identifying exposures and risk factors relevant to women. Intervention trials may be pharmacologic, behavioral, device-based or other modalities.

Criteria for Responsive Proposals

Proposals from both academic and commercial entities are welcomed. Proposals will be considered responsive if they meet the following criteria:

- **Clinical Impact:** The study must demonstrate potential to influence the diagnosis, treatment, or care of women
- **Female-Specific Relevance:** Projects that incorporate female-specific exposures and variables (e.g., menstrual history, reproductive outcomes, hormone use) will be viewed as particularly strong
- **Capturing additional female-specific metadata:** Applicants may request additional funding to capture these variables if they can be collected rigorously

- **Analytical Rigor:** Proposals must include a well-defined analytic plan and appropriate power calculations to ensure meaningful evaluation in female populations
- **Study Type:** Eligible projects include randomized clinical trials and cohort studies, whether completed (for re-analysis) or ongoing (for supplemental support)
- **On-going studies:** Applications seeking support for ongoing studies must provide clear details regarding recruitment strategies, retention and plans to achieve sufficient sample size for robust analyses in women
- **Biospecimens:** Funding may be requested for analysis of existing biospecimens or for collection of biospecimens not previously included in an ongoing trial
- **Biospecimen Discovery:** Support for biomarker discovery is permissible if it advances understanding of female-specific exposures and/or outcomes

Research that is not Considered Responsive

- Studies that cannot support rigorous analyses in female populations
- Re-analyses of studies where exposures are outdated or no longer clinically relevant to women's health (e.g., hormone therapies not in current practice)
- Projects led by research teams lacking adequate expertise in women's health to ensure sound study design and analytical approaches

References and Resources for XXcelerate: Link