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REDEFINING THE MENOPAUSAL TRANSITION

An analysis of menopause trial development following FDA clarification of hormone therapy benefit-risk considerations

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Navigating the intricate landscape of perimenopause and menopause in clinical research demands a comprehensive understanding of its multifaceted nature. This article delves into the complexities of menopause, reframing it as a prolonged, multisystem transition rather than a singular life event. With fluctuating hormone levels impacting various physiological systems, menopause extends its reach beyond immediate symptoms to influence long-term health risks. This necessitates innovative clinical trial designs that integrate patient-centered outcomes and consider additional implications affecting the body. By exploring both medical and operational strategies, this article highlights the importance of flexible, pragmatic trial approaches that accommodate the realities of women going through this transition, ensuring that research is both inclusive and reflective of those it aims to serve.

EXPLORING THE MEDICAL AND OPERATIONAL ASPECTS OF MENOPAUSE

Both the menopausal transition stage and postmenopause stage are best viewed as extended phases of biological change rather than discrete life events. Menopause marks the culmination of the menopausal transition and the onset of postmenopause, representing a pivotal milestone that influences a woman's endocrine, reproductive, and long-term health trajectory.

Across this continuum, fluctuating and ultimately declining hormone levels affect multiple body systems, creating diverse therapeutic needs and requiring clinical trial designs that address both immediate symptom burden and longer-term health risks, including:

- Vasomotor Symptoms
- Mood
- Sleep
- Cognition
- Urogenital and Pelvic Health
- Bone Health
- Insulin Sensitivity
- Lipid Metabolism

KEY DESIGN CONSIDERATIONS FOR PERIMENOPAUSE, MENOPAUSE, AND POSTMENOPAUSAL STUDIES

Menopause clinical trials require design strategies that align eligibility, endpoints, and visit schedules with dynamic hormonal transitions, integrate validated patient reported outcomes, and prospectively address long term risks while remaining operationally feasible for midlife women balancing life with clinical trial participation.

The menopausal transition can span several years, making the selection of eligibility criteria, that identify the intended reproductive-stage cohort while remaining operationally feasible, a central design challenge. These criteria should minimize burden on participants and sites and avoid assessments with prolonged turnaround times.

Although age cutoffs and time since the last menstrual period are appropriate in many settings, they may not reliably classify women with bilateral oophorectomy or those with prolonged amenorrhea or irregular menses associated with long-acting reversible contraception or continuous combined hormonal contraception. Established staging frameworks can support classification, but their limitations may require complementary clinical or laboratory assessments. Eligibility requirements should therefore be tailored to the intended study population and indication.

Additionally, hormonal fluctuations during the menopausal transition also creates a hormonal heterogeneity in this population which can impact endpoints. To optimize enrollment of the intended population, the study design needs to define what the target reproductive stage is, how it is defined for the study and adjust for anticipated heterogeneity of population if applicable.

Once the target population and anticipated heterogeneity are appropriately addressed, endpoint selection becomes the next critical design consideration. Traditional vasomotor symptom endpoints remain important but may not fully capture the broader impact of menopause on quality of life, cognition, mood, sleep, and sexual health^{1,2}. As a result, recent menopause trials have increasingly incorporated patient-centered outcomes alongside traditional symptom measures, including sleep disturbance, menopause-related quality of life, patient global impressions, sexual function, emotional well-being, and work productivity. The specific domains vary by intervention and development program, but this broader approach can provide a more comprehensive assessment of treatment benefit.

A comprehensive benefit-risk assessment should also consider relevant cardiometabolic outcomes. Secondary or exploratory endpoints may include changes in lipid profiles, inflammatory biomarkers, or insulin sensitivity. Composite endpoints that integrate symptom relief with changes in cardiometabolic risk factors may provide a more comprehensive assessment of benefit-risk; however, they require careful definition, appropriate statistical planning, and adequate power to support meaningful interpretation.

From an operational perspective, trial design must account for the social and practical factors that influence participation and adherence. Midlife women often balance substantial caregiving and workforce roles, which may affect their ability to meet study requirements. Practical barriers and overly restrictive eligibility criteria, particularly those related to comorbidities or concomitant medications, may limit participation and reduce representation of women likely to receive the therapy in routine clinical practice.

One way Medpace operationalizes these pragmatic principles is through a “design matrix” that maps each menopausal stage against key design domains, including eligibility, primary endpoints, safety endpoints and the operational model. This visual framework enables cross functional teams to quickly identify where scientific objectives and operational realities may not fully align and where targeted adaptations can bridge those gaps.

OPERATIONAL STRATEGIES TO MANAGE COMPLEXITY IN GLOBAL MENOPAUSE TRIALS

Menopause trial operations succeed when they are intentionally built around women's realities, combining investigator education, flexible visit models, data driven recruitment, and integrated safety monitoring to reduce participant burden while preserving scientific rigor across global sites.

Medpace addresses this by implementing layered visit strategies. Core safety and efficacy assessments are anchored at investigative sites, while lower intensity touchpoints (questionnaires, some vital sign checks, digital cognitive tasks) are migrated to home via ePRO, wearables, or telehealth.

A simple operational flow diagram, shared with both Sponsors and sites, maps each assessment to a mode (site vs virtual) and clarifies where flexibility is possible without compromising endpoints or data integrity.



Site and investigator preparedness are equally important. Because menopause intersects with multiple specialties, sites may vary widely in their baseline comfort with staging, symptom assessment, and long term risk counseling. Medpace's women's health experts routinely provide targeted training on hormonal staging, PRO administration, and management of common adverse events. Standardized source templates and visit checklists help ensure consistent data capture across regions.

Recruitment strategies must reflect both scientific and cultural nuances. For global programs, Medpace works with Sponsors to localize messaging so that it resonates with different health beliefs and levels of menopause literacy. In some regions, stigma around discussing sexual function or mental health may require more discreet communication channels and partnership with community organizations. In others, employer based outreach or digital campaigns focused on sleep and performance may be more effective. Real time analytics dashboards allow the project team to monitor enrollment by age, race, ethnicity, geography, and menopausal stage, enabling rapid course correction when representation goals are at risk.

Retention requires ongoing attention to burden, logistics, and trust. Practical measures (travel support, reminder systems, and rapid responses to symptom concerns) can have an outsized impact on midlife participants. Just as importantly, clear explanations of study rationale, safety monitoring, and post trial access are central to building confidence.

Finally, integrated governance structures help manage complexity across medical and operational domains. At Medpace, cross functional menopause study teams typically include therapeutic medical experts, regulatory strategists, clinical trial managers, central lab specialists, imaging experts when needed, and biostatisticians. Regular data review meetings bring these perspectives together to interrogate emerging signals, such as site level variability in PRO completion or unexpected cardiometabolic trends, and to implement protocol clarifications or operational adjustments swiftly.

By aligning deep medical understanding of the menopausal transition with disciplined operational execution, Sponsors can navigate the inherent complexity of this indication and deliver trials that are scientifically robust, globally feasible, and truly reflective of the women they aim to serve.

MAKING THE COMPLEX SEAMLESS® IN GLOBAL WOMEN'S HEALTH CLINICAL TRIALS

At Medpace, our dedicated women's health leadership team integrates medical, operational, and regulatory expertise to support Sponsors across Phase I-IV clinical development. This collaborative, full-service approach helps drive efficient trial execution, high-quality data, and informed decisions from study startup through closeout in a broad range of conditions.

Connect with our women's health team, Rujin Ju MD, MSCR, FACOG, Women's Health Medical Director, and Beth Tulip, Women's Health Senior Executive Director, to learn more about how Medpace supports global women's health programs.

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CONTACT OUR EXPERTS >



REFERENCES:

1. The Menopause Society (formerly NAMS) 2022 Hormone Therapy Position Statement
2. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials (JAMA, 2024) evaluated VMS frequency/severity plus PROMIS Sleep Disturbance and MENQOL.

