Cycle-Timed Design Considerations for Decentralized Neuromodulation Trials in Women's Health

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INTRODUCTION

Hormonal and neurophysiological dynamics across the ovarian cycle drive phase-dependent variation in mood, pain, and cognition. Estradiol, progesterone, and allopregnanolone modulate GABAergic signaling and cortical excitability - suggesting that cycle timing could meaningfully influence responses to neuromodulation.

Nonetheless, many neurotechnology studies still do not prospectively track or align procedures to cycle phase. Some exclude women entirely. Where women are included, uncontrolled hormonal variability may obscure treatment effects and contribute to the response variability widely reported across modalities.

In parallel, decentralized trial designs have become increasingly feasible and regulator-supported, offering the means to address both issues: cycle-sensitive scheduling with broader, more representative recruitment.

We present a device-agnostic methodological framework integrating cycle-timed scheduling with decentralized trial operations for neuromodulation research in women's health.

RESULTS

Evidence from prior remotely supervised neuromodulation studies demonstrates that home-based implementation is feasible, with high session completion rates and acceptable tolerability when structured training, adherence monitoring, and adverse event capture are embedded. A clinical usability study of a Bluetooth-controlled wearable neurostimulation device for primary dysmenorrhea reported excellent system usability scores (SUS > 90) in both active and sham groups, with no critical use errors and effective blinding maintained throughout.

METHODS

The framework comprises four pillars:

Cycle Tracking & Outcome Capture

Participants log menstrual onset and cycle length via a dedicated app, establishing an individualized cycle model.

Estimated ovulation is derived algorithmically from historical cycle data, enabling prospective phase-window assignment.

Daily symptom diaries capture pain, mood, and sleep quality.

Time-stamped entries enable cycle-day indexing of all study outcomes.

Phase-Aligned Scheduling & Interpretation

Cycle-phase indexing enriches every outcome measure with hormonal context.

Sessions aligned to predefined phase windows, targeting symptomatic periods.

Windows anchored to each participant's tracked cycle length and predicted ovulation day, creating a personalized schedule.

Session counts and stimulation parameters held constant across windows to isolate phase effects.

Usability & Human Factors

Self-administration at home follows IEC 62366-1-aligned formative and summative usability processes.

In-app training precedes first use.

Usability check-ins capture:
- Use errors
- Electrode/device placement confidence
- Handling feedback

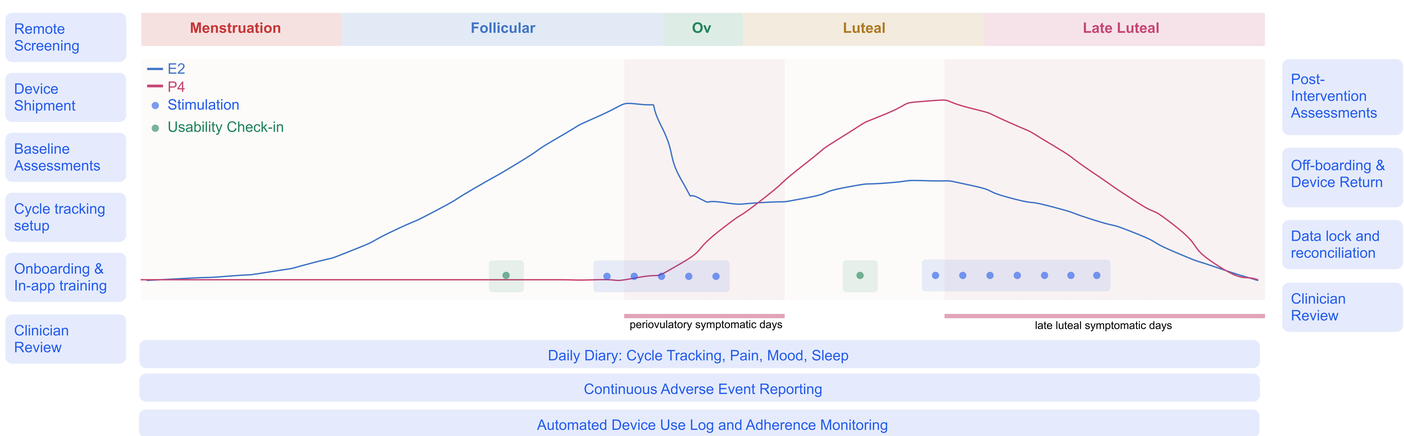
Findings linked directly to the risk management file.

Decentralized Trial Operations

Operationalized per FDA guidance on clinical trials with decentralized elements:

- Remote training
- Real-time adherence monitoring via time-stamped device logs
- Continuous adverse event capture with automated flagging
- Scheduled clinician reviews

All procedures conducted within GCP and human-factors frameworks.



DISCUSSION

Cycle-timed designs may reduce within-participant variability and improve interpretability when hormonal state plausibly modulates the target circuits or symptom domains under investigation - for example, affect regulation via prefrontal GABAergic networks, or dysmenorrhea-related pain via corticothalamic excitability.

Incorporating sex as a biological variable (SABV) and ovarian-cycle state directly addresses reproducibility challenges across the neuromodulation literature, where unexplained response variability has been a persistent limitation.

In addition, decentralized operations broaden access to populations historically underrepresented in neurostimulation research, while remote monitoring maintains data quality and participant safety within GCP and human-factors frameworks.

The framework is applicable across portable transcranial electrical stimulation methods suitable for home use - including tDCS, tACS, and tRNS - and is designed to complement and enhance rather than replace existing trial methodologies.

CONCLUSIONS

Cycle-sensitive, decentralized methodologies represent a practical and underused dimension of clinical trial design in women's neurohealth. Aligning neuromodulation sessions to menstrual cycle phase may reduce uncontrolled neurophysiological variability, while decentralized operations expand access and representativeness. The framework is device-agnostic and ready for adoption across neuromodulation trial designs.

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