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## Submitter Information

**Name:** T. Dorina Papageorgiou

## General Comment

See attached file(s)
Request for Information on the Development of a 2025 National Artificial Intelligence (AI) Research and Development (R&D) Strategic Plan
Authored by:
T. Dorina Papageorgiou, Ph.D., M.H.Sc, FAAN
Assistant Professor of Psychiatry, Neuroscience,
Physical Medicine and Rehabilitation
PI, Investigational Targeted Brain Neurotherapeutics
Faculty Member: Center for Space Medicine
Dan L. Duncan Comprehensive Cancer Center
Adjunct Assistant Professor
Electrical & Computer Engineering
Neuroengineering Research Initiative
Rice University

Amanda M. Buch, Ph.D.
Simons Foundation (SFARI) Independence Fellow
Department of Psychiatry and Brain and Mind Research Institute
Weill Cornell Medicine, Cornell University

Disclaimer: This comment for an action plan reflects the individual perspective of the authors rather than the affiliated institutions.
Title: AI-based Neuromodulation in Clinical Trials – Improving Rigor, Reproducibility and Economic Efficiency by Eliminating Traditional Shams
Summary
Neuromodulation is an expanding field in precision medicine, and includes therapies ranging from invasive deep brain stimulation (DBS) to non-invasive transcranial magnetic stimulation (TMS), transcutaneous electrical nerve stimulation (TENS), fMRI neurofeedback, transcranial focused ultrasound (tFUS), and individualized neuromodulation (iNM).

Traditional sham methods involve deception, misleading participants into believing they receive neuromodulation or receive incorrect neuromodulation. This deceptive practice undermines trust in clinical trials, raises ethical concerns about informed consent, and reduces the interpretability and generalizability of findings. In contrast, improved "sham" control conditions eliminate deception. Improved "sham" controls refer to any control condition that is characterized by transparency, and methodological rigor, and reproducibility. The goal is to ensure participants are informed in advance that they will eventually receive treatment while eliminating deceptive interventions and boost economic efficiency.

Improved "sham" control designs in AI-based neuromodulation clinical trials can enhance ethical integrity, economic efficiency, interpretability, and generalizability by ensuring transparent informed consent, optimizing resource allocation, and improving access to treatment. This approach not only enhances patient trust but also improves reproducibility of results, facilitating broader application across

broad patient populations.

How can we forego traditional sham conditions? AI can enhance study design by addressing placebo effects while improving causal inference.
Linear and/or non-linear AI models provide invaluable guidance for planning neuromodulation, especially real-time closed-loop neuromodulation interventions. These AI models are crucial for increasing sensitivity and specificity to improve therapeutic outcomes or to enhance human performance.

Predictive modeling for placebo effects involves training AI models on past neuromodulation studies to estimate expected placebo responses based on participant demographics, baseline neural activity, and prior response patterns. This enables statistical adjustments for placebo-like effects without the need for a sham group. Additionally, causal inference techniques, such as Bayesian Causal Networks and Dynamic Causal Modeling (DCM), can identify causal relationships between neuromodulation, physiological, and behavioral changes, even in the absence of a sham condition. These AI-driven approaches strengthen the study's ability to detect true neuromodulatory effects while maintaining methodological rigor.

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## Attachments

AI-based Neuromodulation and Sham Clinical Trials_Papageorgiou and Buch_NSF_RFI

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Physical Medicine and Rehabilitation
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Faculty Member: Center for Space Medicine
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**Action Plan Attached as pdf**

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**Forgoing Unnecessary Regulatory Roadblocks**
Eliminating outdated traditional sham protocols that involve misleading interventions benefits ethical, medical efficacy and safety, and regulatory frameworks by reducing administrative hurdles. Aligning with federal policies such as the "2-for-1" executive order (EO 13771) aimed at cutting excessive regulations, improved "sham" controls eliminate the need for deceptive interventions that often require complex regulatory oversight. This could help fast-track FDA approvals for neuromodulation therapies, and enhance the generalizability of results by reducing variability introduced by misleading placebo conditions. A sham condition introduces additional variability because participants may respond differently based on their expectations, even in the absence of an actual treatment effect. Without a sham, all participants in the treatment arm receive the active intervention, which can lead to more consistent neurophysiological responses. This could reduce inter-subject variability and improve the ability to detect true treatment effects. By implementing transparent control designs, this approach maintains regulatory compliance without compromising scientific integrity or trial efficiency.

**Cost, Transparency & Economic Efficiency**
Mandating upfront cost disclosures for trial participation extends the administration's healthcare price transparency initiatives, reinforcing financial accountability in research. Traditional sham-based control arms increase costs and undermine the interpretability of results. This can result in participant attrition, delay trial completion, and reduce meaningful scientific and clinical results – the inability to offer the treatment arm to the sham-based control arm is often fiscally and practically infeasible. By eliminating deceptive control arms and replacing them with ethically sound methodologies, clinical trials can optimize resource allocation, prevent unnecessary expenditures, and enhance data reliability. AI-driven predictive models and improved control designs can ensure cost-efficient, scalable methodologies while maintaining scientific rigor and leading to more generalizable conclusions. To conclude, removing unnecessary sham arms can accelerate participant recruitment, reduce trial durations, improve patient outcomes, and boost economic efficiency.

**Public-Private Partnerships & Industry Incentives**
Encouraging industry collaboration through tax breaks for trials using non-deceptive, improved "sham" controls foster innovation and strengthen public-private partnerships. Venture capital firms investing in AI-driven healthcare solutions are more likely to support methodologies that reduce regulatory burden, enhance scientific validity, improve clinical trial feasibility and efficacy, and increase generalizability. By shifting toward market-driven models that emphasize ethical rigor and data transparency, this approach ensures that private investment supports reproducible, scalable research outcomes. Furthermore, improved "sham" controls increase the interpretability of AI-driven neuromodulation models, making trial findings more applicable to broader patient populations.

**Implementation Strategy & Regulatory Adjustments**
The U.S. Department of Health and Human Services could issue regulatory guidance allowing clinical trials to use no-treatment control (improved "sham" control) arms instead of sham procedures with associated risks (Johnson and Goebel, 2023; i.e., *If participation in a clinical trial imposes risks that subjects would not have been exposed to otherwise, those risks must be disclosed* https://www.govinfo.gov/content/pkg/FR-2014-10-24/html/2014-25318.htm). Thus, we can replace sham controls with no-treatment control arms when:

1. The sham procedure introduces novel risks (e.g., invasive placebo surgeries).
2. The risks are deemed unreasonable relative to the study's societal value.

In neuromodulation trials, traditional sham controls often involve invasive or deceptive interventions, such as implanting a device but not activating it or delivering simulated but ineffective stimulation. While these methods aim to serve as a placebo comparison, they can introduce unnecessary risks, including infection, procedural complications, and ethical concerns. By replacing traditional shams with no-treatment control arms in cases where the sham intervention poses a risk, clinical trials could eliminate unnecessary exposure to harm while maintaining scientific integrity.

How no-treatment control arms compare to sham procedures in terms of patient outcomes:
For example, in ophthalmology trials measuring self-reported quality of life (e.g., NEI-VFQ scores for macular degeneration patients), no significant differences were found between sham and no-treatment controls when:

- Participants were matched on baseline prognostic factors (e.g., visual acuity, age) (Hawkins BS, Bressler NM, Reynolds SM. Patient-reported outcomes among sham vs no-treatment controls from randomized trials. Arch Ophthalmol. 2011 Feb;129(2):200-5. doi: 10.1001/archophthalmol.2010.359. PMID: 21320967; Hawkins BS, Bressler NM, Reynolds SM. Visual acuity outcomes among sham vs no-treatment controls from randomized trials. Arch Ophthalmol. 2009 Jun;127(6):725-31. doi: 10.1001/archophthalmol.2009.101. PMID: 19506188).
- Outcome assessors were masked to treatment assignment (Hawkins et al., 2009).

This suggests sham procedures may be unnecessary for subjective outcomes when alternative bias-reduction methods (masked assessors) are used.

**Ethical and Safety Tradeoffs in Control Design**
Traditional sham controls versus no-treatment controls (improved "sham" controls) present distinct ethical and practical tradeoffs in clinical trials, particularly when evaluating medical devices and neuromodulation interventions. Traditional sham procedures typically expose participants to a higher level of risk (Sutherland, 2007). In contrast, no-treatment controls pose minimal risk since they do not involve unnecessary procedures. Traditional sham controls often require some level of deception regarding treatment status, raising issues of informed consent and participant autonomy, whereas no-treatment controls allow full transparency. Additionally, traditional sham controls tend to be more expensive due to the costs associated with device preparation and procedural interventions, while no-treatment controls are more cost-effective.

**Practical Considerations in Trial Design**
Traditional sham-controlled trials may face recruitment challenges, as potential participants might be deterred by perceived deception or the risks associated with unnecessary interventions (Hawkins BS, Bressler NM, Reynolds SM. Patient-reported outcomes among sham vs no-treatment controls from randomized trials. Arch Ophthalmol. 2011 Feb;129(2):200-5. doi: 10.1001/archophthalmol.2010.359. PMID: 21320967; Hawkins et al., 2009).

It is imperative that medical devices undergo rigorous, controlled testing to confirm their efficacy and reproducibility, but this should not come at the expense of patient safety through high-risk traditional sham procedures. Instead of exposing participants to unnecessary risks without therapeutic benefit, clinical trials should prioritize ethical, minimally invasive control conditions that maintain scientific validity while protecting patient welfare (Wright, Yale Law and Policy Review, 2016). This approach would also help streamline regulatory approval processes by reducing institutional review board (IRB) delays. Furthermore, eliminating high-risk traditional sham interventions aligns with the improved "sham" control model,

which advocates for ethical, transparent, and scientifically valid alternatives, such as AI-driven predictive neuromodulation models and interventions. By shifting toward safer and more efficient control strategies, clinical trial costs can be reduced, regulatory approvals can be accelerated, and the overall ethical standards of neuromodulation research can be enhanced -- reinforcing the Administration's AISIC objectives of promoting economic efficiency, scientific integrity, and responsible innovation.

**Long-Term Impact on R&D and Industry Standards**

Improved "sham" controls enhance the sustainability of neuromodulation research by reinvesting clinical trial savings into future R&D. This transparent, no-treatment control design, which can leverage AI-enhanced methodology, sets a new industry standard -- prioritizing medical safety, scientific reproducibility, cost efficiency, and ethical transparency. By eliminating deceptive placebo conditions, improved "sham" controls ensure that clinical trial results accurately reflect neuromodulation's true physiological effects, while strengthening both interpretability and generalizability in clinical research.

**Interpretability** refers to that study's results being explainable, reproducible, and scientifically valid. Traditional sham-controlled neuromodulation trials obscure true treatment effects, making it difficult to distinguish real neuromodulation responses from placebo-driven changes. Improved "sham" control designs remove deceptive and misleading interventions, allowing clear identification of causal relationships between neuromodulation and patient outcomes.

**Generalizability** determines how well clinical trial results are similarly efficacious in broader patient populations. Traditional sham clinical trials create artificial conditions that fail to reflect real-world treatment effects, limiting their clinical relevance. Improved "sham" controls maintain valid control conditions while financially affording all participants eventually receive active treatment -- making findings more applicable across patient groups. AI-driven monitoring in clinical trials further enhances generalizability by dynamically adjusting treatment protocols based on real-time physiological responses rather than traditional, rigid sham conditions.

By optimizing clinical trial designs to maximize **interpretability** and **generalizability**, improved "sham" controls establish a scientifically rigorous, medically safer, ethically sound, and clinically-robust approach. We can achieve this by:

1. **Enhancing Interpretability:** Eliminating deceptive placebo conditions allows researchers to directly assess neuromodulation's effects. This can improve regulatory decision-making and accelerate the process from the "bench-to-bedside."
2. **Improving Generalizability:** Results reflect real-world therapeutic outcomes, which expands applicability to patient populations.
3. **Optimizing AI-Driven Predictive Models:** Adaptive AI monitoring refines treatment protocols, improves responder identification, and provides individualized, effective neuromodulation therapies.

Adaptive trial designs enable individualized neuromodulation adjustments (e.g., dosage, treatment duration) using AI analysis of patient data. This reduces trial failure risks and improves patient safety. (BioPharma Trend. 2024, October 11. The Pivotal Role of AI in Clinical Trials: From Digital Twins to Synthetic Control Arms. Retrieved March 12, 2025, from https://www.biopharmatrend.com/knowledge-center/the-pivotal-role-of-ai-in-clinical-trials-from-digital-twins-to-synthetic-control-arms/3; Ponce H, Martínez-Villaseñor L, Chen Y. Editorial: Artificial intelligence in brain-computer interfaces and neuroimaging for neuromodulation and neurofeedback. Front Neurosci. 2022 Jul 15;16:974269. doi: 10.3389/fnins.2022.974269. PMID: 35911982; PMCID: PMC9336526.)

This shift not only advances neuromodulation research but also aligns with broader industry trends toward ethical, efficient, and data-driven clinical trial methodologies.

**Conclusion**

Improved "sham" control designs in neuromodulation trials enhance medical safety, clinical trial efficacy, rigor, and reproducibility, while also improving deregulation, economic efficiency, and market-driven innovation. Unlike traditional placebo methods, improved "sham" controls eliminate unnecessary medical risks for patients, and ensure they receive active interventions rather than deceptive or ineffective procedures. AI-driven optimization and clinical trial monitoring enhances interpretability and scalability, making trials more ethical and cost-effective. By reducing bureaucratic burdens and clinical trial costs while minimizing risk, we can optimize federal research investments and accelerate access to transformative treatments.