A Dual-Table Framework for Rigorous Definition of Integrated Interventions in CNS Trials

Submitter Collin Price

Affiliation Semel Institute for Neuroscience & Human Behavior at UCLA

SUBMISSION DETAILS

Methodological Issue Being Addressed Integrated interventions – pairing a centrally regulated drug/device with complementary components (e.g., behavioral intervention) – lack a standardized framework to characterize them systematically. We propose a standard framework for systematic characterization of integrated interventions to facilitate alignment of stakeholders (regulators, industry sponsors, academics, payors, and patients/advocates) around trial design and reporting.

Introduction Historically, regulatory labels for drugs intended to be used in combination with behavioral or psychosocial interventions have treated the latter as a background standard-of-care. As integrated interventions gain traction, clarity on the structure and purpose of these combinations is essential to formulate appropriate estimands, inform trial design aligned with those estimands, and guide regulatory decisions. Whereas drugs and devices must adhere to statutory and regulatory standards, complementary components may fall outside such oversight which provides explicit standards for evaluating risk and benefits (e.g., specific psychotherapy modalities certified by private entities). Consequently, when a regulated intervention is embedded in a specific practice setting which would not be described as background standard-of-care, there is a pressing need for a pragmatic, reproducible framework that clarifies how each treatment component is defined and implemented. This framework would facilitate evaluation and labelling of the regulated intervention.

Methods An ISCTM working group surveyed regulatory precedents (e.g. labels referencing psychosocial support), mapped key domains of integrated interventions, and developed a dual-table framework:
- Table A (Generic Schema): Specification of Description & Rationale, Mechanism, Timing, Control Conditions, and Fidelity Controls for each active component—Drug/Device and Behavioral/Technological Intervention.
- Table B (Component Role Taxonomy): Provides definitions for classification of each component's role (e.g., primary efficacy, efficacy enhancement, safety enhancement, adherence support).
Both tables were piloted on two exemplar interventions (D-cycloserine + exposure therapy; lisdexamfetamine + cognitive behavioral therapy [CBT]) to refine the structure and utility of the proposed framework.

Results The key regulatory concern is that an integrated intervention can overestimate the standalone benefit of the regulated component. Our framework ensures that any synergy is explicitly documented.
• Table A Clarifies Intervention Structure: For D-cycloserine + exposure, it captures dosing (50 mg), timing (1–2 h pre-exposure), contraindications, session structure (introductory + five weekly

exposures), and fidelity checks. For lisdexamfetamine + CBT, it documents titration (30→50→70 mg/day), concurrent weekly CBT (12 weeks), prohibited medications, and fidelity controls.
• Table B Clarifies Component Rationale: In D-cycloserine + exposure, D-cycloserine is conceived as an efficacy enhancer (potentiates extinction) and exposure therapy is primary efficacy. In lisdexamfetamine + CBT, lisdexamfetamine is conceived as providing primary efficacy (targets BED), while CBT functions as efficacy enhancer and adherence support.
By clearly specifying the structure and rational for the integrated intervention our framework supports estimand specification appropriate to the decision-making a trial is intended to inform. For example, a change in the non-regulated intervention may be an intercurrent event, and the precise formulation provided by this framework can inform how such intercurrent events should be handled in relation to a stakeholder's objectives for a trial.

Conclusions This structured, dual-table framework standardizes the description of integrated interventions, facilitating trial planning, review, and potential labeling.

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Co-Authors

Collin Price[1], Kiran Khirshid[2], Walter Dunn[3]

[1] Semel Institute for Neuroscience & Human Behavior at UCLA

[2] Division of Clinical Outcome Assessment, CDER, FDA

[3] Semel Institute for Neuroscience & Human Behavior at UCLA; West Los Angeles, VA

Keywords

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