



International Society for CNS Clinical Trials and Methodology

Development of Novel Endpoints for Clinical Trials in Substance Use Disorders Working Group

First Manuscript Draft and Second Manuscript Development

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Disclosures:

Tanya Ramey – nothing to disclose. Usona Institute Chief Medical Officer. Previously served as NIDA medical officer.

Martin S Mumenthaler- nothing to disclose. Adjunct Professor at the Department of Psychiatry and Behavioral Sciences at Stanford University School of Medicine in Stanford, California.

Agenda

- Current status of first manuscript:
What we cover, what we left out, and suggestions for manuscript #2
(20 min)
- Development of second manuscript (85 min)
 - Discuss our suggestions and potential topics for ms #2
Find section leaders (25 min)
 - Break out in groups to develop outline of sections (25 min)
 - Groups present outlines (25 min)
 - Finalize next steps (10 min)

Manuscript #1 Summary (Part 1): Why Modernization Is Needed

- Public-health urgency + therapeutic stagnation
- Rising overdose deaths; limited approved medications; no StUD pharmacotherapies.
- Binary abstinence endpoints are outdated
 - They ignore meaningful improvement; harm reduction and functional gains.
- Misaligned with FDA's "feel, function, survive" framework
 - Abstinence alone doesn't capture craving, functioning, quality of life, or overdose risk.
- Statistically inefficient and costly
 - Low abstinence rates → underpowered trials; dichotomization inflates sample sizes.
- AUD's WHO RDL qualification shows a path forward
 - Demonstrates regulators accept non-abstinence endpoints when linked to functional outcomes.
- Recovery exists on a continuum
 - Meaningful improvement often occurs without full abstinence; binary endpoints miss this.

Manuscript #1 Summary (Part 2): Proposed Innovations

- Continuous endpoints to improve sensitivity
 - % substance-free days, frequency-of-use measures; require functional validation.
- Craving as a fit-for-purpose endpoint
 - Central DSM-5 symptom; strong predictor of relapse; validated PROs in development.
- Addressing heterogeneity through deep phenotyping
 - DSM-5 symptom combinations, comorbidities, route of administration, motivation.
 - NIDA PhAB / PhAB-B enables enrichment for mechanistically relevant subgroups.
- Precision-medicine trial designs
 - Adaptive enrichment and basket designs to align mechanisms with phenotypes.
- Modern statistical approaches
 - Longitudinal models, multiple-endpoint strategies, hierarchical composites, WIN statistics.
- Emerging continuous severity measures
 - DSM-5 symptom-based PROs (e.g., OUDSS) as direct measures of disorder severity.

What Manuscript #1 Left Out

- Regulatory science gaps
 - No comparison of FDA vs EMA vs PMDA/NMPA guidance and expectations.
- Biomarkers and objective verification
 - AUD biomarkers exist, validated, frequently used; not so for stimulants or opioids.
- Gatekeeping, hybrid endpoints, and AI-enabled decision frameworks
 - Not covered despite relevance for early-phase decision-making.
- Drug–drug interaction (DDI) barriers
 - No structured risk-management frameworks.
- Modernization of PROs
 - TLFB limitations acknowledged but no digital PRO roadmap / EMAs.
- Tables from Beatrice Setnik
 - Existing Pharmacotherapy: intended as addendum of MS #1; Novel Pharmacotherapy: MS #2

Manuscript #2: Why Part 2 Is Needed

- Address methodological gaps not covered in Manuscript #1
- Build on recent regulatory momentum
 - AUD's WHO RDL qualification provides a template.
- Propose actionable early-phase decision frameworks
 - Gatekeeping, hierarchical composites, AI-assisted Go/No-Go logic.
- Integrate emerging tools into a coherent vision
 - Biomarkers, digital PROs

Start with Regulatory Landscape: FDA, EMA, and Beyond

- Divergent expectations across agencies
 - FDA emphasizes PFDD; EMA prioritizes harm-reduction framing.
- AUD provides precedent but not a template
 - WHO RDL qualification shows feasibility of non-abstinence endpoints.
- Opportunities for harmonization
 - Identify alignment, divergence, and evidence needs.
- Expanding scope beyond US/EU
 - PMDA and NMPA have emerging frameworks but limited SUD guidance.

Biomarkers: Lessons from AUD and Gaps in Other SUDs

- AUD has better validated biomarkers (PEth, CDT)
 - Extensively used in both clinical trials and clinical monitoring because they objectively capture recent or chronic alcohol use. Enable hybrid endpoints.
- No well-established biomarkers for stimulants or opioids
 - Major gap for objective measurement and early-phase decision-making.
- Opportunity to define biomarker categories
 - Exposure, pharmacodynamic, adherence, digital biomarkers.
- Role in hybrid endpoints and early-phase Go/No-Go
 - Objective measures strengthen decision quality.

Gatekeeping, Hybrid Endpoints, and AI-Enabled Decision Frameworks

- Gatekeeping is underused in SUD trials
 - Sequential testing improves decision quality.
- Hybrid endpoints capture multidimensional effects
 - Combine traditional endpoints with biomarkers, PROs, behavioral measures for early (Ph1, 2) decision making
- AI/ML can support composite construction
 - Integrate multiple weak signals into stronger decision rules.
- AI-assisted gatekeeping improves transparency
 - Depersonalizes difficult Go/No-Go decisions.

DDI Barriers and Suggestions /Solutions

- DDI concerns often halt development prematurely
 - Agencies default to risk-avoidance. Example: ibogaine with CV risk
- Structured frameworks can mitigate risk
 - Protocol-mandated risk management strategies could allow trial continuation (example in AUD: topiramate – cognitive + seizure concerns)
 - Structured Risk-Management Frameworks (SRMF)
 - Adaptive Risk-Mitigation Protocols (ARMP)
- Opportunity for a practical DDI decision model
 - Supports rational development without abandoning mechanisms.

Modernizing PROs: Beyond Timeline Follow-Back

- TLFB remains entrenched despite limitations
 - Retrospective, recall-dependent.
- EMA offers greater sensitivity
 - Real-time assessments capture fluctuations.
- Validation gaps limit regulatory acceptance
 - Need psychometric rigor and cross-population validation.
- Roadmap for PRO modernization
 - Hybrid PRO-digital endpoints; shorter recall windows; ecological capture.

Closing & Next Steps

- Comments from the Group / additional topics?
- Experts on specific topics to lead chapter groups?
- Break out in groups to develop chapter outlines
- Present to all

Title

- Text

