

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

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Our working group was established to address gaps in substance use disorder (SUD) drug development, first among those being the continued reliance on outdated, statistically inefficient endpoints that fail to capture meaningful patient improvement.

In our first manuscript, we made the case that binary abstinence endpoints are misaligned with the chronic, fluctuating nature of SUDs and with FDA's endpoint definition "how patients feel, function, or survive". We demonstrated that the statistical inefficiency of dichotomous endpoints inflates sample sizes, increases costs, and deters industry investment - particularly in stimulant and opioid use disorder trials where abstinence rates are low. Drawing on the landmark 2025 FDA qualification of WHO Risk Drinking Levels for alcohol use disorder, we proposed a suite of innovations: continuous endpoints such as percent substance-free days; craving as a fit-for-purpose endpoint; deep phenotyping and enrichment strategies using assessment batteries like NIDA's PhAB; precision-medicine trial designs including adaptive enrichment and basket trials; and modern statistical approaches such as longitudinal modeling, hierarchical composites, and WIN statistics. The manuscript reframes treatment success as a continuum, arguing that meaningful improvement often occurs well short of full abstinence.

This year, our working group is developing a companion manuscript that expands the methodological scope beyond what the first paper could cover. Specifically, we will address five key areas.

First, we will map the regulatory landscape across FDA, EMA, PMDA, and NMPA, identifying points of alignment and divergence in evidentiary expectations for non-abstinence endpoints. Second, we will review the state of biomarker development — noting that while AUD benefits from validated markers such as PEth and CDT, stimulant and opioid use disorders lack comparable objective verification tools — and propose a biomarker development roadmap. Third, we will explore gatekeeping strategies, hybrid endpoints, and AI-enabled decision frameworks that can bring structure and transparency to early-phase Go/No-Go decisions. Fourth, we will tackle the requirement of drug–drug interaction studies as a barrier in the SUD drug development, proposing structured risk-management frameworks that allow promising mechanisms to proceed through development rather than being prematurely abandoned. Finally, we will outline a modernization roadmap for patient-reported outcomes, addressing the limitations of the Timeline Follow-Back and proposing alternatives including ecological momentary assessment, shorter recall windows, and hybrid PRO-digital endpoints.

Together, these two manuscripts are intended to provide the SUD field with a comprehensive, actionable framework for modernizing clinical trial endpoints and accelerating drug development.