Measuring Patient Improvement in Symptom Criteria for Substance Use Disorder

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Disclosures

- None

The Problem of Endpoints in SUD trials

- Abstinence is difficult to achieve and difficult to measure

- Outcomes typically based on frequency of use/abstinence, but . . .
  - Biological measure of drug consumption is only a surrogate marker of disorder
  - **Frequency of substance use is not a criterion for disorder**

- Desired effect is improvement in physical and psychosocial consequences that characterize the disorder

DSM-5 Criteria for SUD

A problematic pattern of use leading to clinically significant impairment as manifested by at least 2 of the following occurring within a 12-month period:

1. Substance taken in larger amounts or over longer period than intended
2. P
3. A
4. C
5. F
6. P
7. I
8. U
9. Physical or psychological problem caused or exacerbated
10. Tolerance
11. Withdrawal

Criteria count for grading severity:

2-3 = Mild

4-5 = Moderate

6+ = Severe

Why Not Use DSM-5 as Endpoint in SUD Trials?

- Change in disorder severity or remission commonly used in treatment trials for other psychiatric disorders
  - Depression

- **Lengthy timeframe for symptom criteria (12 months)**
- **Lack of valid and practical measure of SUD symptom severity**

- SUD diagnosis needed for enrollment in trial
  - But assessment of diagnosis not repeated
  - **Count of criteria, not severity of symptoms**

FDA Guidance

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Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2020
Clinical/Medical

FDA Guidance

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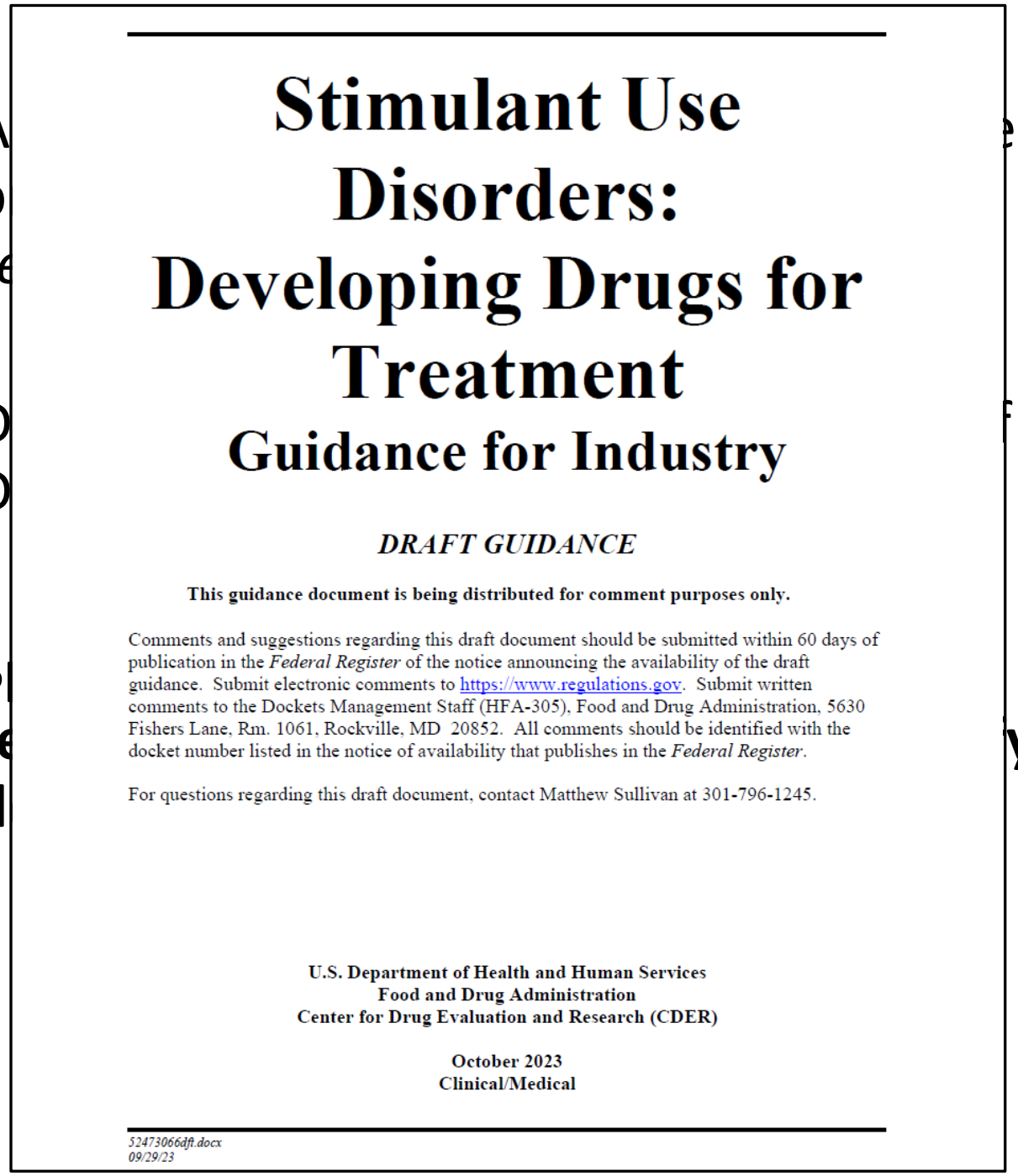

Stimulant Use Disorders: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Matthew Sullivan at 301-796-1245.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical

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FDA Drug Development Tools (DDT)

- Methods, materials, or measures that have potential to facilitate drug development
  - FDA created a Qualification Program for DDTs
- Clinica
  - Con *ssessment*
    - Results can be relied upon to measure a specific concept and have a specific interpretation and application in drug development and regulatory decision-making

DDT Qualification shortens path to medication approval

FDA Qualified - Clinical Outcome Assessments

Disease/Condition	DDT COA Instrument Name	Concept of Interest	Type
Chronic Heart Failure (CHF)	Kansas City Cardiomyopathy Questionnaire	CHF Symptoms and impact on health	PRO
Irritable Bowel Syndrome (IBS)	Diary for Irritable Bowel Syndrome Symptoms – Constipation	Symptom experience of IBS	PRO
Asthma	Asthma Daytime Symptom Diary	Asthma symptoms	PRO
Chronic Obstructive Pulmonary Disease (COPD)	Evaluating Respiratory Symptoms in COPD	Respiratory symptoms of stable COPD	PRO
Major Depressive Disorder (MDD)	Symptoms of Major Depressive Disorder Scale	Overall symptoms of MDD	PRO
Substance Use Disorder??			
Opioid Use Disorder (OUD)*	Opioid Craving	Changes in Opioid Craving	PRO

*** Under development (letter of intent accepted)**

https://www.fda.gov/drugs/clinical-outcome-assessment-coa-qualification-program/qualified-clinical-outcome-assessments-coa

Benefits of measure of SUD symptom severity

- Variation in severity of individual DSM criterion unknown
- Advance measurement-based care approach
- Shorter time frame (past month)

- Symptoms of Major Depressive Disorder Scale (SMDSS)
  - 16-item PRO
  - Depressive symptoms according to DSM-5
    - "Over the past 7 days . . ."
      - Intensity items ("not at all" to "extremely")
      - Frequency items ("never" to "always")

Opioid Use Disorder Severity Scale (OUDSS)

NIDA U01DA051639

- **Stage 1: Item Generation**
  - Initial pool of 110 items (8-12 items per DSM-5 criterion)
    - Guided by other instruments

Reduced to 64 items following expert consensus

  - Patient Reported Outcome Measurement Information System (PROMIS) methodology
    - First-person, past tense format
    - Response options reflecting frequency over past 30 days (“0 – never” to “4 – almost always”)
    - Items are series of statements
      - “I spent more time using opioids than I wanted to”

Opioid Use Disorder Severity Scale* (sample items)

In the past month...

	Never	Rarely	Sometimes	Often	Almost Always
I ended up using more opioids than I meant to	○	○	○	○	○
I used opioids for a longer amount of time than I meant to	○	○	○	○	○

* Currently being developed and validated

Opioid Use Disorder Severity Scale (OUDSS)

NIDA U01DA051639

- **Stage 2: Content Validity – Patient input**
  - Cognitive interviews ('think aloud') with 10 patients with OUD in treatment < 6 months
    - 1st round n=5
    - 2nd round n=5

Reduced to 46 items following patient input

    - Soliciting patient interpretation and thought process when selecting response
  - Interviews audio-recorded, transcribed, and summarized with tracking matrix

Opioid Use Disorder Severity Scale (OUDSS)

NIDA U01DA051639

- **Stage 3: Reliability and Validity**
- **Participants** (n=200)
  - Seeking or enrolled in OUD treatment < 6 months
  - Meet DSM-5 criteria for OUD
  - Opioid use during past 3 months
- **Assessment Battery (with OUDSS)**

Final participant enrolled Dec 23, 2024

  - Subjective Opioid Withdrawal Scale (SOWS)
  - Opioid Craving Scale (OCS – 3-item)
  - Addiction Severity Index (ASI)
  - Short Inventory of Problems (SIP)
  - WHO Quality of Life – Brief (QOL-BREF)
- **Schedule**
  - Baseline → 7-day retest → 3-month follow-up

Planned Analyses

OUDSS outcome	Type	Calculation	Range
Diagnostic Threshold	Binary	Rating ≥ 2 (“somewhat”) on at least 2 of the 11 items, consistent with SDSS scoring threshold for item endorsement of DSM criterion	Yes/No
Total Criteria Count	Count	Sum of items endorsed for diagnostic criteria (rating ≥ 2)	0 - 11
Severity Rating	Categorical	Based on total criteria count (2 or 3; 4 or 5; ≥ 6)	Mild-Moderate-Severe
Total Symptom Severity	Continuous	Sum of all item severity ratings	0 - 44

- Evaluation of Change
  - GLM to examine change in Total Symptom Severity (baseline → 3-months)

Conclusions

- Endpoints in SUD trials have neglected disorder criteria or severity
- DSM-5 OUD Threshold or Severity may be FDA accepted endpoint
- No FDA-Qualified COA for SUD
  - Craving instrument under development

- **1st PRO measuring OUD Symptom Severity**
  - Electronic, self-administered
  - Adhering to FDA Guidelines
    - LOI accepted into FDA Qualification Program
  - Ongoing validation study

Thank You

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