

Pragmatic Considerations for Assessing Physical
Withdrawal in Phase 2/3 Studies

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Pragmatic Considerations for Assessing Physical
Withdrawal in Phase 2/3 Studies

- Operational Considerations
- Relevance of Subject Reported Instrument Metrics in Various Patient Populations
- Statistical Analysis Considerations of Captured Data

Operational Considerations:
Physician Principal Investigators (PIs)

- Subjects in outpatient studies are not logistically available on a daily or continuous basis for physician related clinical drug withdrawal assessments such as the COWS.
- Many PIs may not feel competent or comfortable-in the role of properly evaluating clinical exam metrics of physical withdrawal (ie: pupil diameter, skin temperature; perspiration assessments, etc since these are not assessments typically conducted by many physician specialties in their routine practice and/or during safety/efficacy clinical trials in various types of indications
- PIs can be expected to assess a subject for an overall clinical diagnosis of drug withdrawal, but there is no CTCAEv5 “Drug Withdrawal” AE term. – PI has been instructed to record the diagnosis of drug withdrawal and then to separately list AE related symptoms separately and assess grade severity.

Operational Considerations:
Subject Reported Data

- AE reporting is a different clinical trial activity from elicited symptom assessment through SOWS instruments.
- Traditional AE reporting is an “open ended” non-bias discussion between PI and subject to prevent any suggestive or leading language in the solicitation of AE events.
- The SOWS assessments are elicited specific questions from the subject

Clinical Trial Management Consequence:

- Subjects have reported symptoms of SOWS in e-diary format but deny AE related complaints during PI assessment and vice versa—a challenge in the study safety data analysis

Relevance of Subject Reported Instrument Metrics in Various Patient Populations

- Most widely used instrument - Subjective Opiate Withdrawal Scale presented in the original publication states: "...validity of the scales was administered to patients before and after pharmacological interventionmet DSM III criteria for opioid abuse" (Handelsman 1987).
- Short Opiate Withdrawal Scale was "...developed for opiate addicts..." (Gossop 1990)

Question:

- Since the instruments are not extensively studied in published literature in other subject populations, do opiate experienced subjects complete these forms differently from other types of populations of subjects ?
- Example: Question 16 on Handelsman (1987): "I feel like using now" has elicited clarification from many study subjects in our clinical trials that were conducted in non-addict study populations.
- Example: Question 10 on Handelma (1987): "My Bones and Muscles Ache" – how is that question analyzed in subjects with ongoing chronic arthritis ?
- Note: Handelsman (1987) version displayed on American Society of Addiction Medicine WEB site modified Question 6 word "goose flesh" to "goosebumps"; Question Question 16 "shooting up" to "using".

Statistical Analysis Considerations of Captured Data

- Review of the statistical methodology underlying Handelman 1987 paper on the SOWS shows:
 - The main test of interest was using Wilcoxon signed-rank tests to distinguish tests taken at two different times (6-8 hours after last use—expected to be high-withdrawal—and after 48 hours of methadone treatment—expected to be lower-withdrawal) in order to establish the test validity.
 - The Wilcoxon signed-rank test has no concept of scale; the test operates simply on comparing whether measurement A is higher/lower than measurement B and then assigning it a score, of, essentially, “+”, “-“, or “0” depending on whether A is higher, lower, or the same as B. So if, for example, most subjects had a SOWS score 1 higher at 14 days post-treatment than they did on treatment, the Wilcoxon signed-rank test would flag that as extremely significant (since all subjects experienced a + change in score), but it may not be very clinically significant.
 - If for example, most subjects had SOWS score similar or slightly lower at 14 days post-treatment but a small number had scores **much** higher at 14 days post-treatment, the Wilcoxon test wouldn’t necessarily catch this (as it would only see these in terms of “a lot of – and a few +”), whereas a test for mean change from baseline may give a different perspective on the data
- Handelman was not concerned about treatment effect, only that the test captured withdrawal as expected for validity—but for a clinical trial purposes the assumption generally being tested is whether the study arms show statistical separation on withdrawal scales.

Questions:

- Should a baseline score(s) be obtained prior to drug withdrawal – if so, when? (study start, periodically during the study on drug, last day on study drug, etc.)
- What is a clinically significant finding for an individual subject in physical withdrawal assessment ?
- Although not designed for this purpose, statistical analysis of SOWS by study arms may be done, but the clinical importance of the finding may be unclear..
- Different visual presentations of the SOWS scale are used by a variety of institutions found on the internet – can they all be considered interchangeable if they ask the same questions although the presentation of how the data is collected from the subject vary ?

Handelsman (1987) - The Subjective Opiate Withdrawal Scale (as appears in text)

Table 1. The Subjective Opiate Withdrawal Scale (SOWS)

1. I feel anxious
 2. I feel like yawning
 3. I'm perspiring
 4. My eyes are tearing
 5. My nose is running
 6. I have goose flesh
 7. I am shaking
 8. I have hot flashes
 9. I have cold flashes
 10. My bones and muscles ache
 11. I feel restless
 12. I feel nauseous
 13. I feel like vomiting
 14. My muscles twitch
 15. I have cramps in my stomach
 16. I feel like shooting up now
-

The Subjective Opiate Withdrawal Scale Visually Displayed as Study Instrument (from American Society of Addiction Medicine internet site- https://www.asam.org/docs/default-source/education-docs/sows_8-28-2017.pdf)

Name: _____

DOB: _____



Subjective Opiate Withdrawal Scale (SOWS)

Instructions: We want to know how you're feeling. In the column below today's date and time, use the scale to write in a number from 0-4 about how you feel about each symptom right now.

Scale: 0 = not at all 1 = a little 2 = moderately 3 = quite a bit 4 = extremely

DATE					
TIME					
	SYMPTOM	SCORE	SCORE	SCORE	SCORE
1	I feel anxious				
2	I feel like yawning				
3	I am perspiring				
4	My eyes are tearing				
5	My nose is running				
6	I have goosebumps				
7	I am shaking				
8	I have hot flushes				
9	I have cold flushes				
10	My bones and muscles ache				
11	I feel restless				
12	I feel nauseous				
13	I feel like vomiting				
14	My muscles twitch				
15	I have stomach cramps				
16	I feel like using now				
TOTAL					

Mild Withdrawal = score of 1 – 10

Moderate withdrawal = 11 – 20

Severe withdrawal = 21 – 30

Possible Ways to Consider in Performing Statistical Analysis of Physical Withdrawal Data:

- Data can be tabulated per WHO Guidelines (2009) which partition the Short Opioid Withdrawal Scale scores into three buckets giving the data a clinical assessment of mild (0-10), moderate (10-20) or severe (20-30).
- Aggregate score can also analyzed by the day number off drug when maximal score occurred.
- Adverse Events of Special Interest (AESI) using CTCAEv5 that would be possible candidates for a withdrawal symptomatology and analyzed across study arms.
- Incidence across study arms of the Clinical diagnosis of AEs of drug withdrawal as assessed by the physician investigator