Patient-Reported Outcomes in Opioid Use Disorder (PR-OUD): Recommendations and Barriers in Clinical Trials and Studies

Ibrahim N[1], Walker M[1], Waris H[1], Litcher-Kelly L[1]

[1]Adelphi Values Patient-Centered Outcomes, Boston, Massachusetts, United States

Background

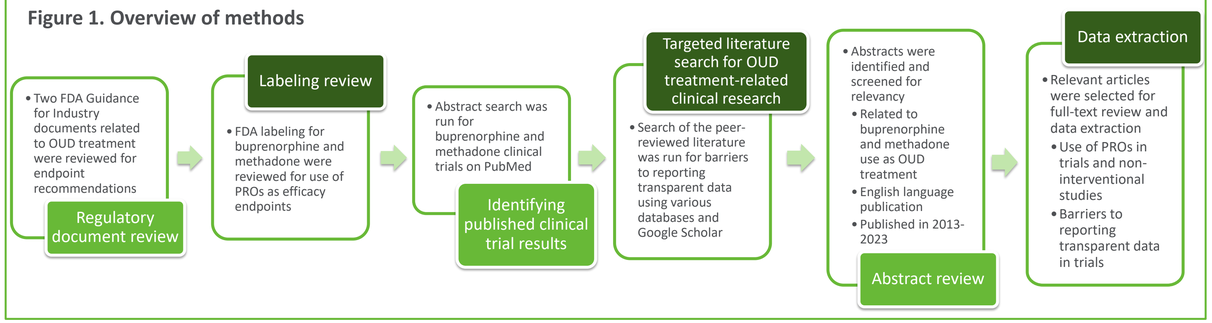
- Opioid use disorder (OUD) is a chronic disease that impacts millions of people in the United States.[1]
- OUD is treatable, and **buprenorphine and methadone** are two of the three current FDA-approved treatments that are **recommended** by the American Society of Addiction Medicine (ASAM).[2]
- Regulatory agencies **encourage patient engagement** and the **inclusion of patient-centric outcomes in clinical trials**, which are articulated in the 21st Century Cures Act.[3]
- Patient-Focused Drug Development (PFDD) guidance documents published by the FDA, including two specific to OUD,[4,5] provide Sponsors with recommendations and suggestions for **ensuring regulated clinical trials evaluate whether new treatments have a meaningful impact** on how patients feel and function (as measured by patient-reported outcome [PRO] assessments).
- The goal of this research is to **explore the current use of PRO questionnaires in clinical trials for individuals with OUD**.

Objectives

- Based on **regulatory interest in utilizing patient-centric outcomes** in clinical trials for treatments of OUD, a review of the published literature was conducted to understand current use of PROs in clinical trials and non-interventional studies. Additionally, **patient barriers to providing transparent PRO data** within the target patient population (TPP) were investigated. Therefore, this research focuses specifically on answering the following research questions:
  - **Should PROs be used** in clinical trials for OUD treatment?
  - Are PROs **currently used** in clinical research and trials for OUD?
  - What are the **barriers to the use of PROs** in clinical trials for OUD treatment?

Methods

Figure 1. Overview of methods



Conclusions

- Our targeted literature search indicated that **PROs have been utilized** in OUD-related clinical research, but **no PROs were identified in the labeling documents** for buprenorphine and methadone.
- **Patient-centric endpoints**, including PROs, should be **included at the forefront** of OUD-related clinical trials to **assess treatment efficacy**.
- **Full transparency** regarding the **use of PRO data** and **ensuring that data is safeguarded** whenever possible may **mitigate inaccuracies in PRO data** reported by each clinical trial's TPP.

Results

- Both regulatory guidance documents include information on potential novel patient-centric endpoints, though they note that **additional research is needed to support PROs**,[4,5] including:
  - Reduction in craving (or severity of urge to use opioids)
  - Improvement in sleep or mood
  - Work or school productivity
- **No use of PROs** were found in the FDA labelling for buprenorphine[6,7] and methadone.[8]
- Use of PROs in clinical trials and other studies:
  - One trial used PROs as a **primary endpoint**,[9] and two as a **secondary/additional endpoint**[9,10]
  - One longitudinal study utilized a PRO **throughout various timepoints**[11]
  - No other PROs were found to be used as endpoints
- Despite regulatory documents recommending the utilization of PROs in clinical trials for this population, significant barriers exist:
  - Opioid **use is highly stigmatized**, as is medication-assisted treatment.[11,12]
  - **Criminalization** and other adverse consequences of opioid use can serve to **prevent patients from being transparent** with their healthcare providers.[12,13]

Recommendations

Figure 2. Recommendations for inclusion of PROs in OUD-related clinical trials

Suggested PRO use

- PROs should be used, per regulatory guidance. FDA **regulatory guidances**[4,5] include information about **inclusion of patient-centric endpoints** in clinical trials.

Recommendation

- We recommend that patient-centric endpoints, including PROs, should be used at the forefront of OUD-related clinical trials, which **aligns with current FDA guidances**. Specifically, PROs should be used to **assess how patients feel and function**, and any **health-related quality of life (HRQoL) changes** that patients experience as a result of the clinical trials. As PROs have been confirmed as **feasible and acceptable**[11,14] for OUD-related clinical trials, these should be included as endpoints in order to **better assess the patient experience.**

Current PRO use

- PRO **use is limited** in OUD clinical trials, and PROs are **rarely utilized as a primary endpoint** in trials.

Recommendation

- We recommend **additional research** be done to further assess the **reasons for poor rates of retention** in clinical trials, in order for clinical trials to have **increased inclusion** of various patient groups, as the groups that **risk serious negative consequences of relapse** consist largely of **working professionals** and **criminal justice populations.**

Barriers to PRO use

- Various **challenges** with utilizing PROs include **stigmatization** (both of opioid use itself and of medication-assisted treatment) and **criminalization**.

Recommendations

- We recommend that **all necessary information is provided** to patients in a clinical trial regarding the **safeguarding of data** when disclosing substance abuse to providers in order to **decrease the fear of being criminalized** for their opioid use. Patients should have **accurate guidelines** on the **use of their information**, any **reporting procedures**, and any **consequences** that may occur in **specific populations** (e.g., pregnant persons) when disclosing an opioid use disorder.
- We recommend that Sponsors **disseminate educational materials** regarding OUD and its treatments to the public to **reduce the stigma** associated with the diagnosis of OUD, so patients **feel more comfortable** disclosing information about their experiences during a clinical trial, including on PRO assessments.

References

1. Centers for Disease Control and Prevention. Opioid Use Disorder. https://www.cdc.gov/dotw/opioid-use-disorder/index.html. Published 08/30/2022. Accessed 04/14/2023.
2. American Society of Addiction Medicine. National Practice Guideline 2020 Focused Update. https://www.asam.org/quality-care/clinical-guidelines/national-practice-guideline. Published 2020. Accessed 12/22/2022.
3. US Food & Drug Administration. 21st Century Cures Act. https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act. Published 01/31/2020. Accessed 04/14/2023.
4. US Department of Health & Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. *Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment – Guidance for Industry.* Silver Spring, MD: Office of Communications, Division of Drug Information;10/2020.
5. US Department of Health & Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. *Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment – Guidance for Industry.* Silver Spring, MD: Office of Communications, Division of Drug Information;02/2019.
6. Invidior Inc. *SUBUTEX, Package insert.* 2021.
7. Invidior Inc. *BUPRENEX, Package Insert.* 2019.
8. Roxane Laboratories Inc. *DOLOPHINE, Package Insert.* 2015.
9. Lintzeris N, Dunlop AJ, Haber PS, et al. Patient-Reported Outcomes of Treatment of Opioid Dependence With Weekly and Monthly Subcutaneous Depot vs Daily Sublingual Buprenorphine: A Randomized Clinical Trial. *JAMA Netw Open.* 2021;4(5):e219041.
10. Ling W, Nadipelli VR, Solem CT, et al. Patient-centered Outcomes in Participants of a Buprenorphine Monthly Depot (BUP-XR) Double-blind, Placebo-controlled, Multicenter, Phase 3 Study. *J Addict Med.* 2019;13(6):442-449.
11. Smith LR, Mittal ML, Wagner K, Copenhaver MM, Cunningham CO, Earnshaw VA. Factor structure, internal reliability and construct validity of the Methadone Maintenance Treatment Stigma Mechanisms Scale (MMT-SMS). *Addiction*. 2020;115(2):354-367.
12. Stone R. Pregnant women and substance use: fear, stigma, and barriers to care. *Health & Justice*. 2015;3(1):2.
13. Carroll KM, Nich C, Frankforter TL, et al. Accounting for the uncounted: Physical and affective distress in individuals dropping out of oral naltrexone treatment for opioid use disorder. *Drug and alcohol dependence*. 2018;192:264-270.
14. Hawk K, Malicki C, Kinsman J, D'Onofrio G, Taylor A, Venkatesh A. Feasibility and acceptability of electronic administration of patient reported outcomes using mHealth platform in emergency department patients with non-medical opioid use. *Addict Sci Clin Pract*. 2021;16(1):66.