DRUG DEVELOPMENT TOOL
LETTER OF INTENT DETERMINATION
DDT COA #000138

Cecilia Bergeria, Ph.D.
Behavioral Pharmacology Research Unit
Departments of Psychiatry and Behavioral Sciences
Johns Hopkins University School of Medicine
5510 Nathan Shock Drive
Baltimore, MD 21230

Dear Dr Bergeria:

We have completed our review of the Letter of Intent (LOI) for Drug Development Tool (DDT) COA #000138 received on May 21, 2020, and the revised LOI submitted July 8, 2020, by the CDER Clinical Outcome Assessments (COA) Qualification Program, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act.

The LOI is for the Opioid Craving tool, a patient-reported outcome (PRO).

FDA has completed its review and has agreed to accept your LOI into the CDER COA Qualification Program. The Agency is accepting this submission for the proposed context of use for the assessment of changes in opioid craving as an endpoint tool in clinical trials in individuals with mild to severe opioid use disorder (OUD). Please see the comments below regarding additional proposed contexts of use. In preparing to submit a Qualification Plan (QP), please ensure that the QP submission addresses the scientific issues and the recommendations outlined below.

Context of use:

1. We are accepting this tool for the context of use for the assessment of changes in opioid craving as an endpoint tool in clinical trials for individuals with mild to severe OUD.
    a. We recommend that you generate a more precise, clearly defined definition for the context of use for the Opioid Craving PRO. In the event that this tool is developed for two distinct endpoint definitions, another DDT submission may be required to address the second context of use.

2. Target patient population:
    a. The target population (currently defined as persons currently using opioids, persons meeting DSM-5 diagnostic criteria for mild-to-severe OUD, and individuals in recovery from opioid use) should be clarified to meet the level of precision required for an endpoint definition. It seems unlikely that these different populations would be enrolled in a clinical trial for the same purpose, such as medical product treatment efficacy. If the primary context

of use is with individuals diagnosed with OUD, additional populations would necessitate separate letters of intent.

b. The target patient population should be further clarified, such as adult and adolescent OUD patients, and differentiate among patients experiencing physical withdrawal versus those who are not.
c. Given that many medical product clinical trials are conducted globally, we recommend expanding the target population beyond English speakers. Additionally, about 13% of the US population primarily speaks Spanish at home (US Census 2018) and Hispanics comprise nearly a portion of the opioid misuse population (SAMHSA 2018) warranting consideration for Spanish-language translation and cultural adaptation. Translation and cultural adaptation include conducting qualitative work on the instrument within all languages and cultures in which the instrument is to be assessed. We refer you to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) principles for the translation and cultural adaptation process (Wild et al 2005). At a minimum, we recommend a translatability assessment as part of your PRO measure development to enable future translations.

Concept of interest:

1. We acknowledge the working definition of opioid craving provided in your response to the information request on July 8, 2020. We recommend evaluating and further refining this working definition with patients, clinicians, and other experts.

Instrument Development Process

1. Qualitative research and patient input are foundational to any instrument development to support the content validity of a tool intended for use in patient-focused medical product development. Direct patient input will help ensure that the resulting concepts, items, response options, and recall period of the tool adequately represent the experiences of patients with opioid craving. Evaluating and testing other measurement properties of a tool cannot resolve problems with content validity. We refer you to the ISPOR principles for concept elicitation and cognitive interviews (Patrick et al 2011a, 2011b) and the recently published guidance Patient-Focused Drug Development: Collecting Comprehensive and Representative Input https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.
2. While qualitative research can be conducted through focus group interviews, we recommend conducting one-on-one interviews with OUD patients to gather nuanced information about aspects of craving across a range of opioid use experiences, e.g., following acute withdrawal, craving during prolonged periods without opioid use.
3. We recommend that patients recruited for this instrument development research are broadly representative of geographic and racial/ethnic diversity within the United States.

4. We recommend that you submit protocols and interview guides for the qualitative research portion of this tool development for Agency comment and feedback prior to initiating the research.
5. We encourage you to consider modification of existing opioid craving items from previously identified tools in conjunction with the development of new items, as item modification can facilitate the instrument development process.
6. We refer you to the Roadmap to Patient-Focused Outcome Measurement in clinical trials for guidance as you develop this tool: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/roadmap-patient-focused-outcome-measurement-clinical-trials-text-version.
7. In addition, you may refer to the Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims ((http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf) regarding fit-for-purpose clinical outcome assessments.

Though the next milestone submission you would be working towards is a Qualification Plan (QP), we recommend that you submit your **qualitative protocol and interview guides** for FDA review and comment prior to submitting your QP.

The following weblink contains the contents to include in your submission to reach the next milestone (Qualification Plan): www.fda.gov/media/123245/download. Please contact the CDER COA Qualification Program at COADDTQualification@fda.hhs.gov should you have any questions (refer to DDT COA #000138).

Sincerely,

Elektra J. Papadopoulos -S

Digitally signed by Elektra J. Papadopoulos -S
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Elektra Papadopoulos, MD, MPH
Director (Acting)
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References

Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 1--eliciting concepts for a new PRO instrument. *Value Health.* 2011a;14(8):967-977.

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Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2--assessing respondent understanding. *Value Health.* 2011b;14(8):978-988.

Substance Abuse and Mental Health Services Administration (SAMHSA). 2018 National Survey on Drug Use and Health: Hispanics, Latino or Spanish Origin or Descent. Available at: https://www.samhsa.gov/data/report/2018-nsduh-hispanics-latino-or-spanish-origin-or-desce

Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.