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May 16, 2018

Institute for Clinical and Economic Review (ICER)
Two Liberty Square, Ninth Floor
Boston, MA 02109 USA
Submitted electronically via: publiccomments@icer-review.org

RE: ICER's Review of Medication-Assisted Treatments for Opioid Use Disorder

Dear ICER Review Team,

Alkermes appreciates this opportunity to provide comments on the draft scope for the ICER review of medication-assisted treatments (MAT) for opioid use disorder (OUD). We commend ICER for expanding its 2014 review of the management of patients with opioid dependence. In light of the ever worsening public health crisis, ICER's plan to evaluate and compare the available treatment options in an objective and pragmatic way will be an important contribution. Alkermes is a pharmaceutical company committed to developing medicines to help address unmet medical needs and challenges of people living with debilitating diseases, including opioid use disorder. Alkermes would like to offer the following considerations as ICER finalizes the scoping document.

1) Population

ICER has defined the population for the review as patients aged 16 years and older seeking outpatient treatment in office-based settings. Alkermes strongly encourages ICER to include patients seeking treatment in inpatient, residential, partial hospitalization, and intensive outpatient settings as well, since any of these settings may serve as an entry point to MAT (SAMHSA, 2017; ASAM, 2001). Benefits of more intensive levels of care for OUD include medically supervised withdrawal, removal of the individual from the environment in which the substance use was taking place, and establishment of ongoing psychosocial treatment and self-help participation after discharge (Nunes et al., 2018). In omitting these settings of care, ICER would be excluding a subgroup of the OUD population seeking treatment.

ICER further proposed two distinct populations in the review: one seeking MAT for "harm reduction" ("Population 1") and one seeking MAT for withdrawal from opioid use ("Population 2"). Alkermes encourages use of alternative terminology, as "harm reduction" applies to all forms of MAT (not only the therapies to be assessed for Population 1) (ASAM, 2015). In addition, ICER stated that VIVITROL® (extended-release injectable naltrexone, XR-NTX) will be the treatment of interest for Population 2, the persons seeking MAT for withdrawal. However, this is contrary to the indicated use of XR-NTX. According to its FDA-approved Prescribing Information, XR-NTX is indicated for the prevention of relapse following

detoxification.[1] If ICER decides to employ two populations in its final analysis, we suggest characterizing the populations as follows: 1) patients seeking opioid partial agonist maintenance therapy and 2) patients seeking to prevent relapse following detoxification with antagonist therapy. Finally, it is important for the analysis to recognize that opioid partial agonist medications may be used prior to a patient's initiation on to XR-NTX. Opioid partial agonists are often used to manage opioid withdrawal (SAMHSA, 2018; ASAM, 2015). Given the well-established risk of relapse following withdrawal from opioids (SAMHSA, 2018), practice guidelines recommend patients be transitioned to opioid antagonist therapy following detoxification (SAMHSA, 2015). In this manner, opioid partial agonists are used to stabilize the patient for some period of time, and then XR-NTX is initiated following detoxification. While some patients may remain on opioid partial agonist therapy for life, results from at least one study suggest that most will cease opioid agonist maintenance in less than a year (Hser, 2014). Consequently, opioid partial agonists and antagonists represent two profoundly different forms of medications which may be initiated at the outset of therapy, but in many instances, are used sequentially.

2) Interventions

Alkermes supports the stated interventions of interest for the ICER review.

3) Comparators

In the summary of the Comparative Value Analysis (cost-effectiveness model), ICER states that XR-NTX will be compared to oral naltrexone for Population 2. Alkermes disagrees that oral naltrexone is an appropriate comparator (for either population). In the recent SAMHSA Treatment Improvement Protocol (TIP 63), the expert panel does not recommend using oral naltrexone except in limited circumstances. Authors state, "This view is in keeping with expert reviews for the United Kingdom's National Health Service (Adi et al., 2007), a clinical practice guideline published by the Department of Veterans Affairs and Department of Defense (2015), and a Cochrane review (Minozzi et al., 2011)" (SAMSHA, 2018). In addition, although the evidence is clear that MAT leads to better treatment outcomes relative to no medication, only 41% of all drug addiction treatment programs in the US offer even one type of FDA-approved medication for OUD, and less than 3% offer all three of the FDA-approved treatment options (Jones, 2018; Roman et al., 2011). Thus psychosocial therapy with no MAT should be included as a comparator, as this remains a frequently used treatment strategy (Roman et al., 2011).

4) Outcomes

Alkermes commends ICER for incorporating a range of relevant outcomes in the draft scope. We recommend that ICER also consider the following outcomes: relapse to illicit opioid use, inpatient hospitalization, and cravings (an important patient-reported outcome). Furthermore, Alkermes recommends that ICER carefully consider the definitions of abstinence and relapse in

[1]VIVITROL® (extended-release injectable naltrexone, XR-NTX), Alkermes' FDA-approved, once-monthly, injectable medication, is indicated for the prevention of relapse to opioid dependence, following opioid detoxification, as well as for the treatment of alcohol dependence in patients able to abstain from alcohol in an outpatient setting prior to initiation of XR-NTX treatment. XR-NTX is approved for use with psychosocial support, such as counseling. Please see the Prescribing Information and Medication Guide for important product safety information.

the review, since definitions vary widely in the literature. A recent comparative effectiveness trial of buprenorphine-naloxone and XR-NTX defines relapse as 4 consecutive weeks of any non-study opioid use by urine toxicology or self-report, or 7 consecutive days of self-reported use (Lee et al., 2018). (In other words, abstinence on XR-NTX is treated the same as using illicit opioids up to 6 days a week, 3 weeks in a row on buprenorphine-naloxone.) In an open-label study of XR-NTX versus usual treatment among adult criminal justice offenders, relapse was defined as 10 or more days of opioid use in a 28-day period, assessed by self-report or by testing of urine samples obtained every 2 weeks; a positive or missing sample was computed as 5 days of opioid use (Lee et al., 2016). The XR-NTX pivotal trial considered proportion of weeks of confirmed abstinence (defined as no self-reported opioid use and a negative urine drug test) between the two groups as well as a secondary endpoint of "relapse to physiological opioid dependence," defined as failing a naloxone challenge (Krupitsky et al., 2011). Some buprenorphine trials have compared percentage of urine samples negative for opioids (other than buprenorphine) between groups (Fudala et al., 2003; Johnson et al., 1992). For a summary of the various definitions of abstinence used in the literature, please see Hser et al. (2015).

In the draft scoping document, ICER notes that while the primary analysis will include direct medical costs, productivity costs and outcomes and costs associated with the criminal justice system will be included, data permitting. Alkermes would like to refer ICER to the large body of literature on the use of XR-NTX in criminal justice-involved individuals (Lee et al., 2016; Friedman et al., 2018; Gordon et al., 2015; Springer et al., 2018; Springer et al., 2015; Crits-Christoph et al., 2015; Finigan et al., 2011; Lincoln et al., 2018; Chandler et al., 2016; Gordon et al., 2017; McDonald et al., 2016).

5) Timing

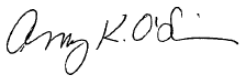
Alkermes commends ICER for considering a lifetime time horizon, as OUD is a chronic illness that has medical, personal, and societal impacts throughout patients' lives.

6) Setting

Alkermes recommends inclusion of additional settings, as summarized above in the "Population" section.

Again, thank you for the opportunity to comment. Alkermes looks forward to sharing additional data to support the review during the next phase of engagement with ICER.

Sincerely,



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Braeburn's Comments on ICER's Draft Scope for Extended-Release Opioid Agonists and Antagonists for Medication-Assisted Treatment (MAT) of Opioid Use Disorder: Effectiveness and Value

Product

CAM2038 is a subcutaneous extended-release injection of buprenorphine – not an intramuscular extended-release injection. CAM2038 has not been approved by the FDA, therefore, the safety and efficacy of the product has not been reviewed by the FDA for approval. Braeburn received a Complete Response Letter from the FDA for CAM2038 in January 2018. The date for resubmission has not been established.

Analytic Framework

- Outcomes
  - Reduction in illicit opioid use should be added. Adding reduction in illicit opioid use is consistent with the introduction of the sentence in the draft scoping document starting with "Diminishing non-medical opioid use..." (page 2).
  - Separating the effect of abstinence from illicit opioid use into the short and long term is relevant as is indicated in the framework. One potential approach would be to have 0-3 months to be considered as short term and 3- 6 months to be considered as long term.
- Key Benefit
  - Add in diminished number of overdoses
  - Add craving suppression (cravings are associated with subsequent lapse to illicit use)

Terminology

There are several instances where the terminology is unclear or could be considered pejorative. We recommend that terms be well-defined when used for the first time as well as the inclusion of a glossary of terms.

- On page 1 the document uses the term "agonists" for methadone and buprenorphine. The document should utilize the terms full agonist and partial agonists to be more precise.
- On page 5 the document states that patients on buprenorphine products will be evaluated as those "seeking MAT for 'harm reduction.'" The term "harm reduction" should be omitted. This term means different things to different people; in some instances, harm reduction refers to a disease management philosophy rather than a type of treatment. For example, not everyone that prescribes MAT is a "harm reductionist." (Please see ASAM's "Terminology Related to Addiction, Treatment, and Recovery" which can be found here: https://www.asam.org/docs/default-source/public-policy-statements/1-terminology-atr-7-135f81099472bc604ca5b7ff000030b21a.pdf?sfvrsn=0). The use of the term may perpetuate the stigma that individuals prescribed buprenorphine for OUD are substituting one drug for another – a sentiment that has been repudiated by SAMHSA, NIDA, and FDA.[1] Therefore, if the term is being used to define individuals seeking treatment with buprenorphine, the term

[1] https://www.drugabuse.gov/publications/principles-drug-addiction-treatment-research-based-guide-third-edition/frequently-asked-questions/use-medications-methadone-buprenorphine; https://www.samhsa.gov/medication-assisted-treatment/treatment; https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm582031.htm; https://www.ama-assn.org/ama-welcomes-secretary-azar-s-notable-comments-opioid-treatment

"harm reduction" should be replace by something more accurate, such as "detoxification or maintenance treatment" or "long-term recovery".

- On page 5 the use of the term "withdrawal from opioid use" is confusing and ambiguous in light of the population under discussion (i.e., withdrawal could mean either withdrawal symptoms or discontinuation of opioid use). The term should either be defined or written in different, clearer language.
- On page 8 the document states, "the health outcome of each intervention will be evaluated in terms of number of days of abstinence from opioid use..." Clarify the term "abstinence"; does "abstinence" in this context refer only to illicit opioid use or also MAT therapy that contains buprenorphine?

Treatment Considerations

- On page 5 Population 1:
  - Probuphine is indicated for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent). [2] Because of this more narrow indication, care should be taken to evaluate Probuphine in terms of maintenance therapy rather than direct comparison with other medications indicated for induction and stabilization as well.
- On page 5 Population 2:
  - Patients on naltrexone will be evaluated as "patients with OUD seeking MAT for withdrawal from opioid use." Naltrexone is not indicated for withdrawal. In fact, Vivitrol's labeling specifically states that "prior to initiating VIVITROL, an opioid-free duration of a minimum of 7–10 days is recommended for patients, to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization."[3]

Measures of Effectiveness

- On page 2 the document mentions that "stakeholders also mentioned that complete absence of non-medical opioid use (abstinence) should not be the only measure of effectiveness. Diminishing non-medical opioid use and better daily functioning should also be considered as measures of treatment success." Yet, the document also states, "the health outcome of each intervention will be evaluated in terms of number of days of abstinence from opioid use." What other measures of effectiveness will be used?
  - Although several outcomes are listed on page 5, in addition to those listed, other direct healthcare benefits of MAT therapy such as hospitalizations, as well as, reduction in endocarditis and skin and structure infections such as severe abscess should be included.
  - It is important to include special populations such as pregnant women or women of child-bearing years.[4]

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[2] https://probuphine.com/wp-content/uploads/2018/02/NDA-204442_Probuphine_Package-Insert-02.2018.pdf
[3] https://www.vivitrol.com/content/pdfs/prescribing-information.pdf
[4] https://store.samhsa.gov/product/SMA18-5054; https://www.acog.org/About-ACOG/ACOG-Districts/District-II/Opioid-Use-Disorder-in-Pregnancy; https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Opioid-Use-and-Opioid-Use-Disorder-in-Pregnancy

- Injection drug users is a relevant sub-population to examine.

Measures of Value

- On page 5 Population 1 Comparing HCP-administered products to oral formulations
  - Interventions of interest will include buprenorphine extended-release injection (CAM2038 - investigational), buprenorphine extended-release injection (Sublocade), and buprenorphine implant (Probuphine®), each compared to buprenorphine/naloxone (sublingual and buccal formulations) in patients diagnosed with OUD.
  - How does the report hope to examine the value associated with increased treatment adherence, reduction in diversion, reduction in misuse, and reduction in accidental pediatric exposure?
- On page 8 it says the report "will take a health system perspective (i.e., focus on direct medical care costs only)." The perspective is far too narrow. Such a perspective will fail to account for a large portion of the benefits that are associated with treating OUD – that is the economic benefits. Some examples that illustrate these benefits of treatment or cost of OUD include:
  - Florence et al estimate the following costs:
    - $7.8 billion in increased criminal justice costs
    - Reduction in productivity of $20.8 billion.[5]
  - Another tool to examine the impact that substance use disorder has on employers can be found here: https://www.nsc.org/forms/substance-use-employer-calculator
  - The impact of substance use disorder on the child welfare system can be found here: https://aspe.hhs.gov/system/files/pdf/258836/SubstanceUseChildWelfareOverview.pdf Therefore, we urge ICER to take a societal perspective.

- On page 8 with respect to the sentence which includes "on MAT and off opioids, off MAT and off opioids…": The use of this model structure is poorly aligned with what the draft scoping document is mentioning as important outcomes in MAT. In maintenance treatment there is clinical and economic relevance in reducing illicit opioid use and models can be structured around categories of frequency of illicit opioid use (e.g., 0-25%, 25-50%, 50-75% and 75-100%). Having a structure like this has the potential to be more informative than the binary choices laid out in the document.

Low Value Services

- On page 1 the document mentions that the number of patients treated with MAT in the US has approximately doubled overall. This study is designed to compare available and future MAT treatment, but only briefly considers that while growing, the vast majority of patients struggling with addiction to opioids and heroin are being treated without medication. The costs associated with poor outcomes with untreated, fully abstinent-based therapy should be included in your analysis of "Identification of Low-Value Services" (pg. 9)

[5] Florence, C. et al. "The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013." Medical Care, 54(10):901-906.

May 14, 2018

Dr. Steven D. Pearson
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Re: ICER evidence review of MAT for opioid use disorder draft scoping document

Dear Dr. Pearson:

Indivior appreciates the opportunity to participate in ICER's review of the evidence for medication-assisted treatment (MAT) for opioid use disorder (OUD). We have a long history of partnership in evidence-based research in this area of unmet need. It is with our commitment to patients in mind that we submit our comments on the draft scoping document.

Below is a list of recommendations related to ICER's proposed scope of analysis. We believe that incorporating these recommendations will make ICER's evaluation of MAT for OUD more representative of the patient journey and clinical practice, and therefore more informative.

- Revise the Populations, Interventions, Comparators, and Settings outlined in the Analytic Framework to reflect the OUD patient journey and clinical practice.
- Add key health and economic outcomes.
- Assess comparative value from the societal perspective and present alongside the base case from the health system perspective.
- Consider expanding the stakeholder list.

Revise the Populations, Interventions, Comparators, and Settings outlined in the Analytic Framework to reflect the OUD patient journey and clinical practice.

The Populations, Interventions, Comparators, and Setting proposed in the current Analytic Framework are inconsistent with clinical practice. Dividing the patient population into two categories ("harm reduction" and "withdrawal from opioid use") does not reflect OUD treatment objectives, as the overarching goal of OUD treatment is sustained recovery. Patients in recovery may not maintain complete abstinence from illicit opioids (which includes heroin and prescription opioids), as OUD is a chronic relapsing condition. Further, the concept of abstinence is frequently misunderstood. Most patients who "taper" or "detox" from short-term use of MAT will relapse.[1] Therefore, the intermediate goal of OUD treatment is to increase the frequency of illicit opioid-free weeks as a step toward long-term abstinence and recovery, which requires keeping patients on treatment. Harm reduction does occur as a result of decreased illicit opioid use and retention in treatment.

Choice of treatment is driven by access, availability of resources, treatment setting, and patient characteristics including disease severity. Along the patient journey to sustained recovery, which can include periods of recovery and relapse, patients may use different MATs and seek treatment

in various settings. Given these considerations, we recommend the following changes to the PICOTS/Analytic Framework:

Population/Setting: We recommend the use of only one population in the Analytic Framework: individuals seeking treatment for OUD with a long-term goal of sustained recovery from OUD. We also recommend that the setting be expanded beyond office-based settings, as there are several other treatment setting options available to patients with OUD. The ASAM Criteria defines a range of treatment services that vary by intensity.[2] Patients seeking MAT for OUD can seek treatment from: (1) residential treatment centers/programs, hospital ERs, other healthcare facilities (inpatient), (2) certified Opioid Treatment Programs (OTP), or (3) office-based opioid treatment (OBOT) programs. The treatment options offered within each of these settings differ.[3] As such, we recommend that ICER expand its analysis to include all settings of care, in addition to OBOT.

Interventions: We recommend that the list of interventions for consideration in this ICER evaluation include the following partial mu-opioid receptor agonists: (1) buprenorphine subcutaneous extended-release injection (Sublocade®, Indivior), (2) buprenorphine implant (Probuphine®, Braeburn/Titan), and (3) buprenorphine subcutaneous extended-release injection (CAM2038, Braeburn), as well as the following mu-opioid receptor antagonists: naltrexone intramuscular extended-release injection (Vivitrol®, Alkermes).

Comparators: We agree that all interventions should be compared to each other, as currently planned. In addition to the mu-opioid receptor partial agonist buprenorphine/naloxone, available as sublingual film, buccal, or tablet formulations, we recommend that the list of comparators for all interventions also include the mu-opioid receptor full agonist, methadone.[4] These comparators reflect real-world treatment options for OUD. Methadone and buprenorphine-based MATs should not be grouped together as mu-receptor agonists. Rather, they should be differentiated into full mu-opioid receptor agonists (methadone) and partial mu-opioid receptor agonists (buprenorphine).

Add key health and economic outcomes.

We appreciate ICER's acknowledgment of stakeholder feedback regarding abstinence as the only measure of efficacy and the recommendation to also use diminished opioid use and improved daily functioning as measures of treatment success. However, several key outcomes appear to be missing from the Analytic Framework:

- Emergency department (ED) and primary care physician visits are listed as outcomes of interest, but inpatient admissions and utilization of other treatment facilities are omitted. We recommend measures of health care utilization include ED visits, inpatient hospitalizations, outpatient visits, out/inpatient rehabilitation, accidental pediatric poisoning by oral buprenorphine, and costs of new HCV/HIV infections. Inclusion of these outcomes is supported by existing cost-effectiveness models (e.g., Carter et al., 2017 and references therein).[5]
- The mortality outcome is listed as "overdose deaths," but we suggest also including deaths from other potentially drug-related causes including homicide, suicide, and HIV/AIDS.[6, 7] Since mortality is an outcome, the value of loss of life and productive years lost can also be quantified.[8, 9]

- We recommend that arrest, abuse, misuse, and diversion be included in the comparative effectiveness model. This is supported by existing cost-effectiveness models (e.g., Carter et al., 2017 and references therein).[5]
- We also recommend that the employment-related outcomes include lost wages from absenteeism, presenteeism, incarceration, and premature death. This is supported by existing literature and cost-effectiveness models.[4, 7, 9-11]

We request that ICER add the outcomes listed above to its Analytic Framework to fully capture the benefits and costs of MAT. In addition, we recommend that craving, withdrawal signs and symptoms, and treatment satisfaction be included as other patient-reported outcomes.

Assess comparative value from the societal perspective and present alongside the base case from the health system perspective.

The opioid epidemic has been declared a national public health emergency, and OUD is a significant societal issue.[13] Given the large societal burden associated with OUD, the impact of treatment with MAT on societal benefits is expected to be substantial in proportion to the health system benefits.[14] As such, evaluation from the societal perspective in the base case is warranted. This perspective includes benefits from reduced crime, incarceration, child welfare/social services, public health/infectious disease, abuse, misuse, and diversion.[7, 14-19] Inclusion of these other sources of benefits is supported by current guidelines for cost-effectiveness analysis.[9]

Consider expanding the stakeholder list.

In addition to the list of stakeholders included by ICER, we recommend the following additional organizations for consideration: academic institutions with addiction expertise, Academy of Managed Care Pharmacy (AMCP), and International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Summary

Indivior has been committed to developing innovative evidence-based medicines for the treatment of addiction for two decades. The recommendations outlined above are meant to ensure that ICER's assessment of the comparative effectiveness and comparative value of different MATs for OUD reflects the patient journey and clinical practice in the United States. Other recommendations include incorporating additional relevant health and economic outcomes and presenting results from the societal perspective alongside the health system perspective in the base case analysis.

Indivior appreciates your consideration of our comments and thanks you for the opportunity to collaborate in your review of MAT.

Sincerely,

Ponni Subbiah

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ADDICTION POLICY FORUM

Extended-Release Opioid Agonists and Antagonists for Medication-Assisted Treatment (MAT) of Opioid Use Disorder: Effectiveness and Value

Addiction Policy Forum's Report on Draft Background and Scope

We at Addiction Policy Forum are appreciative of the opportunity to weigh in on ICER's drafted background and scope document 'Extended-Release Opioid Agonists and Antagonists for Medication Assisted Treatment of Opioid Use Disorder: Effectiveness and Value'. The Addiction Policy Forum is a 501c3 non-profit organization dedicated to building comprehensive solutions and serving as a patient advocacy voice for the millions of individuals and families affected by substance use disorder. We work to translate the science of addiction, help build a deeper understanding of addiction as a health condition, and work to integrate the treatment of this disease into our healthcare system. We also work to address stigma and counter misinformation and outdated ideas that limit access to evidence-based treatment and recovery services.

Medication Assisted Treatment (MAT) is one of our key areas of focus. For the treatment of opioid use disorders, MAT has been found to be more effective than solely behavioral approaches, yet there still exists prejudice and discrimination about this proven form of treatment among the general public, policymakers, and portions of the recovery community. All too often MAT is written off as "just giving addicts more drugs" or "moving someone from one drug to another". This viewpoint ignores the volume of research and the experiences of the thousands of people who have been able to overcome their illness and achieve a better life through use of these life-saving treatments. It is clear that in addition to the need for new medications and further research into existing medications, it is necessary to change the way we think and talk about the disease in order to correct misinformation.

Addiction Policy Forum's Feedback:

It is exciting to see the development of new medications. Addiction Policy Forum sees a great deal of value in the research ICER is performing around MAT, particularly long-acting formulations. In the introduction of the draft, it is clear that ICER is aware of the significance of the disease and the clear benefits of MAT. ICER proposes an impressive method of conducting this research that takes into account the individual and social effects of the application of these medications. We appreciate the opportunity to give input into this project. We work on the ground level of this epidemic and have seen and experienced first-hand the trials of the families and individuals suffering from or affected by this disease. Our feedback falls into three main comments:

1) Acknowledge Confounding Variables in the Sample Population
2) Examine Fidelity of Program Implementation and the Treatment Setting
3) Expand Patient Outcomes to Reflect Individualized Metrics Broader than Sobriety

1 - Acknowledge Confounding Variables in the Sample Population

Although the evidence ICER is using mostly comes from randomized controlled trials, there are still numerous confounding variables present. These are variables outside of the researcher's control that may interfere or effect the outcomes. The medications received may be standardized, but the backgrounds of subjects in the sample populations, the treatment settings, and the application of individual treatment programs are all out of the researchers control, and may affect outcome variables. ICER's access to participant information may be limited, but it is essential to understand individual-level factors may influence the treatment outcomes. Some examples are the level and frequency of past discrimination due to their illness, their external support structure, previous attempts at treatment, obstacles faced in their environment, previous involvement with MAT programs, and their specific opioid of use and route of administration (ROA). Being able to look at these factors in relation to outcome measures will allow ICER to better understand why different people achieve different results. For stronger research validity we suggest including individual-level data to improve the collection and evaluation of treatment outcomes.

2 - Examine Fidelity of Program Implementation and the Treatment Setting

The second area of concern is the MAT programs themselves and program implementation. Even with similar settings and methods, individual treatment programs offer patients unique experiences. By its definition, MAT includes behavioral and counseling therapies, in addition to the medications provided. It is important to note the services offered, the details of the programs' functions, and beyond a formal design, how the program has actually been implemented.

3 - Expand Patient Outcomes to Reflect Individualized Metrics Broader than Sobriety

Another critical element is the individual level and social outcomes considered in ICER's study. Just as individual's experiences with substance use disorder are unique, treatment is not one-size-fits-all, and there are many roads to recovery. As a result, choosing outcome measures is not clear-cut.

It is critical to understand the concepts of sobriety and recovery and to utilize measures that reflect both areas. Whereas sobriety refers to ceasing use of mind-altering substances, recovery refers to a more comprehensive array of outcome measures that indicate overall health, wellness, return to core activities, family relationships and stability. For many people, sobriety is necessary for recovery, while others can achieve their recovery while either decreasing their substance use or using other substances in moderation. Successful recovery is specific to the patient, and we therfore recommend expanding the outcomes ICER examines related to both sobriety and recovery.

ICER is currently considering both short-term abstinence from illicit opioid use and long-term abstinence as key patient outcomes. We recommend adding the following outcome measure:

- Short-term and long-term abstinence from other or all illicit or mind-altering substances.

- Frequency and severity of opioid, or other substance, use throughout the treatment process.

We also recommend the consideration of both subjective and objective outcome measures. Other important patient outcome measures include:

- Perceived quality of life
- Perceived self control
- Self esteem
- Hope for the future
- Confidence
- Feelings of guilt
- Acceptance
- Sense of purpose

We also recommend building upon the current objective outcome measures (health-related and employment outcomes), to include components such as:

- Stable housing
- Independence and self care
- Social functioning with friends, and family
- Stability and quality of parenting (if applicable)

Some of these examples also fall into the categories of risk and protective factors for the development of a substance use disorder and would be relevant to ICER's study. The vast body of research around risk and protection is underutilized in examining patient populations in treatment settings and recovery. These factors can serve as indicators for both the immediate quality of life as well as the potential for long-term sobriety and recovery. Risk and protective factors can be internal (positive self-image, self-control, and social competency) as well as external (pro-social relationships, familial involvement, and a supportive community and social environment). Specific risk factors can provide important context for service needs of patients as well, including mental health conditions, early exposure to substance use, association with antisocial peer groups, and current environmental exposure.

The Addiction Policy Forum represents thousands of individuals and families impacted by addiction, and we commend ICER for its efforts in this crucial area. We are available as a resource for ICER's work in this arena to build in the perspectives of patients and families. New medications give us hope to see better outcomes for our patients and how we can deploy new tools and practices.

Milon Waththuhewa, Pharm. D., M.Sc
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mcwath@icer-review.org

Dear Dr. Waththuhewa:

On behalf of the American Society of Addiction Medicine (ASAM), I am pleased to present to you our review of the Institute for Clinical and Economic Review (ICER)'s draft scoping document, *Extended-Release Opioid Agonists and Antagonists for Medication-Assisted Treatment (MAT) of Opioid Use Disorder: Effectiveness and Value*. Please find our comments below, categorized by the specific areas ICER requested feedback on.

Feedback on appropriateness of ICER suggested PICOTS

ASAM recommends changing the way populations are divided and the PICOTS are described. For example, it may be inaccurate to look at different medications for the different populations. In each population, individual patients hoping to reduce or quit heroin use may continue to struggle with opioid use on any of the medications that are FDA approved. In addition, referring to the use of opioid treatment medications as "harm reduction" in the description of population one may be inaccurate as harm reduction is generally viewed as injection sites for consumption and needle exchanges. The population two description "withdrawal from opioid use" may also be confusing because all patients do not want to continue to experience opioid withdrawal, and so it may not delineate a specific population for the purpose of the review. ASAM therefore suggests renaming the populations and recommends considering the following population labels respectively: "opioid agonist maintenance" and "opioid antagonist relapse prevention."

In the interventions list of all medications, ASAM suggests clearly stating the duration of action for each product as well as the doses available. For example, the duration of the buprenorphine implant is 6 months, it is FDA-approved for two rounds of treatment, and it is approved as a single dose of four rods (80 mg each/320 mg total) for patients who are on the equivalent of 8 mg of buprenorphine daily. The subcutaneous buprenorphine injection is available as once-weekly and once-monthly injections in several different doses (not currently FDA-approved; possible approval by end of 2018). The most recent FDA-approved buprenorphine formulation for OUD is a monthly subcutaneous injection available in two doses (300 and 100 mg) with a current FDA label recommending that the first two months dose are 300 mg followed by 100 mg monthly. Trans mucosal buprenorphine (SL tabs and film, buccal) has a variety of doses available and only one of these medications is given as a prescription to

the patient. Dosing is typically daily, although sometimes it can be less (e.g. thrice weekly).

Intermediate outcomes to consider adding include the number of hospitalizations (e.g., for infections like sepsis, endocarditis and osteomyelitis all related to IVDU), criminal activity, days of IVDU, overdose (fatal and non-fatal), and days of employment. HIV and Hepatitis C could be other key measures to include. ASAM also suggests considering the inclusion of pediatric exposures (pertinent for trans mucosal buprenorphine) as reports of harm to children who get hold of this medication.

In regards to the settings of care aspect of the PICOTS framework, the new injectables of buprenorphine may have expanded use in other settings such as hospitals, ERs, and criminal justice settings that should be considered.

In the introduction, ASAM suggests rewording the last sentence that states, "Many experts *feel*…" – as the term "feel" may imply that it is not science. ASAM suggests listing the experts (e.g., NIDA, SAMHSA, ASAM, AAAP) whose research shows that addiction and moderate to severe opioid use disorder is a brain disease that is often chronic in nature and requires long–term maintenance treatment in order to achieve remission and recovery. Please be sure to include "remission" when talking about recovery as this is a disorder that physicians are trying to put into remission, much like other illnesses, and also trying to get people into long-term recovery which is difficult to do without having the illness in remission. The duration of medication treatment may be months, years or lifelong as long as the patient is benefiting (TIP 63 cite).

Feedback on the economic analysis approach broadly described in the draft scope
No additional comments.

Feedback on the information about low-value services that may be eliminated or reduced to allow re-allocation of resources to newer drugs and technologies
It may be possible that injectables formulations decrease the need for supervised dosing/frequent prescriber visits as some supervised dosing is done in office-based settings as a way of holding patients in treatment when Opioid Treatment Programs are not accessible for a variety of reasons. Injectables may also decrease the need for quantitative urine testing for buprenorphine and its metabolites that is often done frequently to prove to payors that the medications are being taken and not diverted.

Thank you again for inviting ASAM to review this important document. If you have any questions, please feel free to reach out to Taleen Safarian via email (tsafarian@asam.org) or by phone (301-547-4123).

Best,

Margaret Jarvis
Chair, Quality Improvement Council
American Society of Addiction Medicine

LEGAL ACTION CENTER

May 16, 2018

Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Extended-Release Opioid Agonists and Antagonists for Medication Assisted Treatment (MAT) of Opioid Use Disorder: Effectiveness and Value, Draft Background and Scope

Dear Reviewers,

Thank you for the opportunity to submit comments on the Draft Scoping document for the review on effectiveness and value of extended release opioid agonists and antagonists for medication assisted treatment.

The Legal Action Center is a national non-profit legal and policy organization whose sole mission is to fight discrimination against people with histories of addiction, HIV/AIDS, or criminal records, and to advocate for sound public policies in these areas. A major focus of our work over the past forty-five years since our founding has been on improving access to evidence-based addiction treatment. Patients with substance use disorders (SUD), similar to patients who suffer from any other chronic illness, benefit from a wide variety of treatment options. A variety of treatment options is particularly important to patients with SUD as treatment is most effective when it is individually tailored to a patient's condition and unique needs.

Not all patients respond to medicines in the same way. Physicians may need to change medications over the course of an illness as patients suffer side-effects or their illness is less responsive to a particular drug, and patients requiring multiple medications may need access to alternatives to avoid harmful interactions. Furthermore, there are numerous factors such as patient motivation, desired treatment outcome, and access to various forms of medication that may need to be considered in determining the most appropriate medication for individual patients.

To that end, we applaud the Institute for Clinical and Economic Review for undertaking this important review of the effectiveness and value of various forms of extended release opioid agonists and antagonists for the treatment of opioid use disorders. We are particularly encouraged by the statement in the draft scoping document that the review will consider "full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities and unmet clinical needs". We believe that this type of comprehensive evaluation will be enormously valuable in assessing the value of the medications from different perspectives and in advancing clinical knowledge about which medications may be the best fit for individual patients.

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Numerous studies have shown that use of medications to assist in SUD treatment (MAT), including injectable naltrexone, buprenorphine and methadone, reduces drug use and disease rates. MAT for opioid addiction utilizes medications to normalize brain chemistry, block the euphoric effects of opioids, relieve physiological cravings, and normalize body functions. One study found that those receiving MAT as part of their treatment were 75 percent less likely to experience a mortality related to their addiction than those not receiving MAT. Other research shows that those in MAT programs experience dramatic improvements while in treatment and for several years following.

Unfortunately, despite existing evidence supporting the effectiveness and value of medication assisted treatment for opioid use disorder, access to these interventions remain problematic.

There are three types of medications that are currently used for the treatment of opioid addiction: agonists, partial agonists, and antagonists. Agonists are opioids that have a less intense and longer lasting effect than opioids that are commonly misused. Agonists turn on the same receptors as other opioids but the lower intensity and longer duration prevent the cycle of withdrawal and escalation that are part of addiction. As the name implies, partial agonists work similarly but produce an even weaker effect. Conversely, antagonists work by blocking the receptors in the brain on which opioids act, so that if a patient does relapse and use the formerly misused drug, it will have a completely blocked or diminished ability to trigger that receptor. Just as with medications for other chronic diseases, certain addiction medications are more appropriate and effective than others based on the specific clinical needs of the individual.

Currently, conflation of all three medications for opioid addiction into one singular U.S. Pharmacopeial Convention (USP) classification, despite those medications having different pharmacologic properties and each not being appropriate for all patients, has contributed to many patients not being able to receive the medications they need and overall poor coverage of SUD medications. We hope that the ICER evaluation addresses this critical problem of access and differentiation.

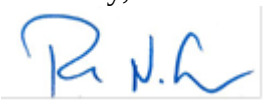
We are unclear as to why the review does not evaluate the effectiveness and value of all reviewed interventions for both populations, and urge the reviewers to consider evaluating outcomes for patients in each population for each of the included medications or formularies. It is important to understand the value and effectiveness of each according to patient incentives for seeking treatment and desired treatment goals.

It is well known that only a small percentage of patients with opioid addiction receive MAT and new measures are needed to help close this gap. Several significant barriers, including insufficient treatment capacity, inadequate reimbursement and stigma against these medications must be overcome. Stigma against opioid agonists and partial agonists is particularly strong and rooted in the misunderstanding that these medications “substitute one addiction for another.” While these medications

may cause physical *dependence*, when taken appropriately these medications do not cause addiction. More education about the nature of these medications and the distinction between dependence and addiction is needed among the public and providers. Limiting ICER's review of buprenorphine formularies to those patients who are seeking harm reduction might inadvertently reinforce that stigma against the medication.

Thank you very much for your willingness to receive and consider our comments and for your commitment to ensuring that your review of extended-release opioid agonist and antagonists is inclusive of both quantitative and qualitative comparators, as capturing key factors related to access, stigma and disparities.

Sincerely,



Paul N. Samuels
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Anthem

Submitted electronically via: publiccomments@icer-review.org

May 16, 2018

Institute for Clinical and Economic Review (ICER)
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Extended-Release Opioid Agonists and Antagonists for Medication-Assisted Treatment (MAT) of Opioid Use Disorder: Effectiveness and Value: *Draft Background and Scope*

To Whom It May Concern:

Anthem is committed to delivering high-value, affordable care that improves the lives of our members. We are working to transform health care with trusted and caring solutions, and our health plan companies aim to deliver quality products and services that give members access to the care they need. With over 73 million people served by its affiliated companies, including more than 40 million within its family of health plans, Anthem is one of the nation's leading health benefits companies. For more information about Anthem's family of companies, please visit www.antheminc.com/companies.

Anthem commends the Institute for Clinical and Economic Review (ICER) on its attention to the opioid use disorder epidemic and the widespread public health challenge posed by opioid use disorders (OUDs). We share ICER's commitment to identifying effective strategies for reducing opioid misuse and promoting value-driven OUD treatments. Anthem appreciates the opportunity to provide comments in response to ICER's draft scoping document for its assessment of extended-release opioid agonists and antagonists as part of MAT for OUD.

To ensure that recommendations resulting from this assessment are actionable and can be effectively implemented, Anthem would like to share the following high-level comments with respect to this *Draft Background and Scope*.

Outcomes

ICER intends to evaluate a number of outcomes, including, but not limited to: short-term and long-term abstinence from illicit opioid use, opioid withdrawal syndrome, health-related quality of life, employment-related outcomes, and other harm/adverse events. Given the causal complexity of many of these outcomes (including confounding social determinants of health, etc.), Anthem requests clarification of any assumptions used to infer the relative effectiveness of MAT. Furthermore, evaluated outcomes should reflect clinically meaningful endpoints, and use of surrogate outcomes such as short term abstinence should be utilized thoughtfully.

Population

Anthem requests that ICER consider patients in their analysis that are reflective of the intended treatment population in the "real world" setting; for example, in the "harm reduction" analysis, patients who have previously not been successful on short-acting treatments or who had

experienced challenges with treatment adherence. If extended release MAT formulations are being evaluated as first-line use, ICER should include all MAT formulations (short- and long-acting) in the analysis. Clarification around the parameters of patient groups included in the evaluation will help payers and providers better understand the results of the effectiveness assessment.

Interventions

Importantly, the medication component of MAT is typically only one part of a more comprehensive treatment plan. Comprehensive MAT encompasses a behavioral health component which plays a key role in a patient's road to recovery. Anthem believes that it is important that information about behavioral therapy components be included in the analytic value and effectiveness framework, and that use of such services be provided as part of the findings from the assessment. Additionally, Anthem would like clarification on how real-world evidence will be incorporated into the evaluation. This is especially important, considering that one of the drugs being evaluated has not yet been approved by the FDA.

Anthem values ICER's important work in this area and appreciates its commitment to providing information on cost-efficient and effective treatments for OUDs. ICER's goals in this analysis are aligned with our ultimate commitment to safeguard the affordability of healthcare for all of our members and to continue to improve health outcomes. We believe that ongoing engagement from all stakeholders is critical to combatting the opioid epidemic, and we look forward to working with ICER as it moves through the review process.

Should you have any questions or wish to discuss our comments further, please contact Dr. Geoff Crawford, at (443) 812-5001, or geoffrey.crawford@anthem.com.

Sincerely,

Geoffrey B. Crawford, MD, MS Medical Director – Office of Medical Policy and Technology Assessment

Weill Cornell Medicine

Sean M. Murphy, Ph.D.
Associate Professor of Research in Healthcare Policy and Research

Milon Waththuhewa, Pharm. D., M.Sc.
Program Manager
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Dear Dr. Waththuhewa,

Thank you for the opportunity to provide input on the Medication-Assisted Treatments for Opioid Use Disorder Draft Scoping document. My comments are below, please feel free to follow up with any questions you may have.

- As a general comment, I encourage you to reconsider the use of the term “Medication Assisted Treatment”. Although commonly used in political circles, many addiction experts dislike the term as it implies that the medication requires "assistance" from the behavioral therapy, when in reality there is a fair amount of evidence that the medications are effective without the behavioral therapy.[1-3]
- Page 1, Background, Paragraph 2, Sentence 2: I suggest using the he number of overdose deaths attributed to opioids (~42,000),[4] since that is the focus of the report.
- Page 1, Background, Paragraph 3: In relation to my first comment, I suggest breaking this discussion up and focusing on the evidence of effectiveness and efficacy of the three FDA-approved pharmacotherapies, then introducing the notion that they are commonly required to be prescribed alongside behavioral therapy.
- Page 2, Stakeholder Input, Paragraph 1, Last sentence: The comment regarding a particular lack of social skills among adolescents with OUD seems to come out of nowhere. Moreover, this is not something I have heard before. Do you have a reference to support this statement?
- Page 5, Populations: I encourage you to reconsider the two study populations as they are currently defined. The use of the term “harm reduction” makes it sound as if Population 1 is interested in continuing opioid use for non-medical purposes. I would also say that Population 2 is not seeking “withdrawal,” they are perhaps seeking “discontinuation.” The comparisons that make the most sense to me are a) short-acting buprenorphine versus long-acting therapies, b) short-acting buprenorphine versus long-acting buprenorphine versus long-acting naltrexone, and perhaps c) implantable versus subcutaneous injection versus intramuscular injection.
- Page 6, Outcomes, Bullet 3: What about other forms of healthcare service utilization; for example, behavioral healthcare, residential treatment, inpatient hospitalizations, etc. The detox/residential piece would be especially important given that many individuals being inducted onto extended-release naltrexone are initially detoxified in a residential setting.
- Page 6, Outcomes, Bullet 7: May also want to consider the value associated with increased school productivity, especially given that your population consists of individuals 16 years of age, and older.
- Page 6, Outcomes: I would also suggest criminal activity as part of the societal perspective.
- Table 1.1, Row 1: This is typically the argument used for assessment of QALYs, so I'm not sure what this is referring to.

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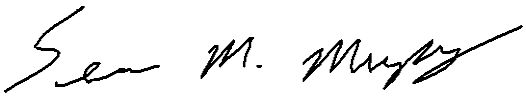
- Table 1.1, Row 3: This will depend on the price relative to the comparator, and the relative extent to which third-party payers are willing to cover it. For example, I posit that the long-acting buprenorphine products will be substantially more expensive than oral buprenorphine, which will result in many of the same availability issues that underlaid the buprenorphine vs. extended-release naltrexone debate.
- Table 1.1, Rows 4 and 6: This will depend on the comparator, induction model, and relative adherence. For example, I would only foresee a significant reduction in negative externalities to caregivers/family members relative to extended-release naltrexone if the long-acting buprenorphine therapies reduce time in detox and improve adherence.
- Table 1.1, Row 10: The comment that this intervention is the first to offer any improvement for patients with this condition, is not true. I would suggest deleting this statement.
- Page 8, Scope of Comparative Value Analyses: Regarding the literature of previously published studies of pharmacotherapy for OUD, I would also consider Murphy and Polsky (2016).[5]

Sincerely,



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I assume you are excluding oral naltrexone and methadone for a reason. Since oral is not so effective perhaps that is ok but it would be worth comparing costs and outcomes to methadone.

One outcome to focus on is initiation of treatment with medication. The issue is that with antagonists it is hard to initiate treatment, much moreso than with agonists. So even if outcomes are the same for those able to get on the medication, many fail before even starting NTX (see the X-BOT trial in Lancet).

I would not study these for withdrawal symptom outcomes. That is a different issue.

I would look carefully for relapse/return to use and many measures of abstinence (beyond complete)—frequency of use for example, and also at fatal and nonfatal overdose and overall mortality.

Lastly, as I mentioned to your colleague, I would avoid "medication-assisted treatment" as a term. It is widely used but it is odd, unlike the rest of medicine (?medication assisted treatment of diabetes? Cancer?), and stigmatizes the treatment and may in part be responsible for how addiction specialty treatment programs that choose not to offer it to patients get away with withholding a life saving treatment because they do not believe in it.

Instead, at first use say "medication for addiction treatment (MAT) or simply medication (a.k.a. 'medication-assisted treatment')….so that people looking for the acronym MAT will find it and so it will be found by those search on "assisted". But the medication doesn't "assist" anything. It is treatment in and of itself. And using it doesn't mean other treatments also cant be given but some have withheld medication when patients do not agree to go to frequent counseling and then those patients die. And there is little evidence that counseling consistently adds to meds re benefit.

A lancet paper by samet and Fiellin, a paper in ASCPjournal.org by friedmann, and a paper in J Addict Med by Wakeman all explain this in further detail, why we should abandon the misnomer.

Lastly, I am not sure how you will handle it but usually these meds are studied with a platform of psychosocial treatments and the detected effectiveness of the med could vary by what else patients are receiving for treatment. It should at least be reviewed. Robert Schwartz wrote a letter / commentary for J Addiction medicine a year or two ago about the lack of detectable benefit but most studies do include some sort of counseling or other attention beyond medication.

Really lastly, I think it is key to distinguish between studied of people showing up to emergency rooms or hospitals vs those who calmly and after some hoops jump through including requirements to abstain first for a while, receive care in specialist programs. Results at least initiation will be different I think

--Rich Saitz

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To Whom It May Concern:

I am writing to comment upon the Draft Background and Scope document, "Extended-Release Opioid Agonists and Antagonists for Medication-Assisted Treatment (MAT) of Opioid Use Disorder: Effectiveness and Value." I am pleased that the ICER is again addressing this issue, given the devastating toll of Opioid Use Disorder (OUD) in the United States, and the changes in treatment options that have occurred in recent years. These comments contained in this letter are my personal opinion, and do not represent a recommendation from my institution.

I have three primary comments. The first comment regards the listed outcome measures. I would suggest that the ICER consider utilization of outcomes that reflect the DSM-5 criteria, or that are organized to reflect these criteria. Improvements in OUD should indicate remission in symptoms of the disorder, and these would be reflected in criteria no longer being active. While it may be the case that there are limited data directly relevant to DSM-5 OUD criteria remission, the proposed report is an opportunity to highlight this approach and acknowledge that the field should consider studies that focus on symptom remission as an outcome measure. Treating OUD should decrease active symptoms and hopefully produce downstream improvements in other areas, but medications such as buprenorphine and naltrexone do not directly "treat", for example, employment.

My second comment relates to the scope of the work. Specifically, it was not clear if the plan is to look at opioid withdrawal, as implied in the definition of Population 2. If withdrawal will be considered, then the report should specifically address maintenance treatments (on-going, long-term care with a medication) as a separate topic from medically supervised withdrawal. (I would also note that maintenance treatment with naltrexone is technically still treatment with an opioid – naltrexone is an opioid medication. At present, it appears that Population 2 implies that treatment with naltrexone is not with an opioid, which is technically incorrect.)

My third comment is my primary feedback, and relates to the proposed analytic framework that creates two different populations. I would urge the ICER to look at all patients and studies, include methadone as a comparison medication, and not create this distinction between maintenance medications. The relative efficacy of buprenorphine compared to extended release naltrexone (XR-NTX), and to methadone, I would note, should be examined and directly addressed. There are data that now look at direct comparisons of XR-NTX and buprenorphine, and there is ample data looking at buprenorphine compared to methadone, and this artificial distinction between the two populations runs the risk of failing to address the relative value of each medication – and the research needs that still exist to further address comparative efficacy and safety. Differences and challenges when inducting patients on to NTX versus buprenorphine and methadone have high clinical relevance. Naltrexone products have a critically valuable role to play in the treatment of OUD, but there is a need to find more effective methods to induct patients on to this medication, and to highlight that buprenorphine and methadone can be more successful using current protocols. By creating two populations, the report runs the risk of obscuring these differences.

I want to close by noting that I am a strong advocate for all three current OUD treatment medications and their use. I would urge the ICER to consider all three in its review, and address direct comparisons of efficacy and safety for each, and that it focus on maintenance treatment with each. This can help to guide current practice, inform policy options, and assist in setting an agenda for research needs moving forward.

Thank you,

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