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October 4, 2018

Institute for Clinical and Economic Review (ICER)
Submitted electronically via: publiccomments@icer-review.org

RE: ICER’s Draft Report of Medication-Assisted Treatments for Opioid Use Disorder

Dear ICER Review Team:

Alkermes appreciates the opportunity to provide comments on the Draft Report for the ICER review of medication-assisted treatments (MAT) for opioid use disorder (OUD). Below, we summarize our comments and concerns.

1. Policy Implications of the Current Approach

Alkermes would like to reiterate the significant concerns we expressed to ICER in writing on August 9, 2018 on the Research Protocol and Model Analysis Plan. Specifically, ICER’s current approach has the potential to have substantial adverse policy, access, and public health consequences for persons with OUD. This analysis is concerning and potentially misleading in the following ways:

First, as the OUD epidemic continues to worsen and death rates from opioid overdoses continue to rise, treatment rates remain appallingly low, despite the strong evidence base supporting treatment with MAT. MAT—including methadone, buprenorphine-naloxone (BUP-NX), and VIVITROL® (naltrexone for extended-release injectable suspension, XR-NTX)—is effective and recommended for the treatment of OUD by the National Institute on Drug Abuse (NIDA), Substance Abuse and Mental Health Services Administration (SAMHSA), American Academy of Addiction Psychiatry (AAAP), American Society of Addiction Medicine (ASAM), and the American Association of the Treatment of Opioid Dependence (AATOD). Despite these treatment recommendations, only about 20% of those with OUD receive any treatment; notably, this figure does *not* include MAT (Saloner, 2015). Furthermore, 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, 2011). These data also indicate that there is tremendous geographic disparity in access to MAT across the US. In other words, during this epidemic, the delivery of evidence-based treatment for OUD remains fragmented, unbalanced, and underutilized (Morgan, 2018; Volkow, 2014).

On the face of it, ICER seems to accept these facts. In the Background section of its Draft Report dated September 7, 2018, ICER states: “Despite the essential role of MAT in treating OUD and in preventing harm, including death, an important gap persists between the need for and the availability of MAT. More than 30 million people live in US counties without a single prescriber for addiction treatment, and even if existing treatment capacity is reached, one

million people would still lack access to treatment.³⁶ Expanding access to OUD medications is considered an important public health strategy for countering the opioid epidemic.²⁰ Yet despite making these statements, ICER’s focus in the Draft Report is not expanding access to these essential medications, but comparing medications that are not approved for the same indication. Alkermes strongly encourages ICER to reframe the policy focus of the Report as **how can we improve equitable access to all MAT options for persons suffering from OUD.** The current focus has the very real potential of exacerbating the existing problem of access in the middle of an epidemic.

Secondly, the comparison ICER makes between opioid agonist and opioid antagonist medication does not make sense clinically. BUP-NX and XR-NTX are two quite distinct medications, used in different ways, in distinct patient populations at disparate times in patients’ treatment journeys. These medications do not even have the same FDA-approved indication. The Substance Abuse and Mental Health Services Administration (SAMHSA), the federal agency responsible for reducing the impact of substance abuse on our country’s communities, describes the differences between naltrexone and buprenorphine in Exhibit 1.2 in their Treatment Improvement Protocol 63 (TIP 63). In Exhibit 1.2: “Comparison of Medications for OUD” SAMHSA describes the “phase of treatment” for naltrexone as “[P]revention of relapse to opioid dependence, following medically supervised withdrawal”, while “phase of treatment” for buprenorphine is described as, “Medically supervised withdrawal, maintenance” (SAMHSA, 2018). Indeed, these differences are reflected in the FDA-approved indications for the products, where:

- XR-NTX 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, and
- SUBOXONE (sublingual film of buprenorphine and naloxone) is indicated for the treatment of opioid dependence.

As recognized by SAMHSA and articulated in the FDA-approved indications, these products are not interchangeable. Patients initiating treatment with BUP-NX are in a very different phase of the disease than the patients who initiate treatment with XR-NTX. In the clinical comparative effectiveness section, ICER acknowledges, “Differences observed between Vivitrol and buprenorphine/naloxone are due at least in part to differences in treatment intent and goals.” Further, under the section “Controversies and Uncertainties” at the end of the Comparative Clinical Effectiveness section, ICER states, “As noted by SAMHSA in the 2018 TIP, no evidence clearly predicts which patients are best treated with Vivitrol versus methadone or buprenorphine formulations. The treatment sequences for different subpopulations with OUD cannot be based solely on the available evidence, but rather must be informed by clinical knowledge and the local context.” Given these facts acknowledged by ICER itself, it is perplexing why ICER has chosen to compare these very different medications to each other. Again we strongly encourage ICER to reconsider the policy question, not to focus on how these quite distinct medications compare to each other, but rather on **how we can improve equitable access to all medications for persons suffering from OUD**, so that a person can choose the medication that is most appropriate for him/her at any given point in his/her journey with the disease.

2. Fundamental Flaws in the Cost-Effectiveness Analysis

Notwithstanding the points above, the conclusions of the cost-effectiveness analysis (CEA) are misleading at best, and at worst could serve to restrict access to these essential medications in the midst of an epidemic. The CEA violates several key principles of cost-effectiveness methodology, as summarized below.

ICER's conclusions from the comparative clinical section are that XR-NTX has comparable net health benefit to BUP-NX with a high degree of certainty. It is confusing to a reader who is not well versed in CEA that the conclusion from the CEA is that XR-NTX is "less effective and more costly" than BUP-NX. In other words, the conclusions from these two sections are inconsistent. Further, if XR-NTX and BUP-NX are equally effective (as the scientific data suggested [Lee et al., 2018; Tanum, 2017] and ICER concluded), a cost minimization analysis, not a CEA, is most appropriate according to traditional economic methods (Drummond et al., 1997). Finally, the conclusion from the CEA regarding "less effective" is based on inappropriate assumptions (summarized below in "Utility Values").

Patient Population. Standard cost-effectiveness analysis states that the target population under study be well-defined and consist of those who would receive the interventions being modeled (Roberts et al., 2012; Drummond et al., 1997). However, in this case the target population for the model is listed as "(P)articipants ages 16 years or older who are seeking detoxification, maintenance treatment, or long term recovery from OUD." Patients seeking "long term recovery from OUD" may seek *either* detoxification *or* maintenance treatment; however they typically do not seek them both together. As detailed above, patients seeking detoxification from opioids followed by XR-NTX versus maintenance therapy with an opioid agonist are distinct patient populations as these are very different treatment options. In fact the Surgeon General and SAMHSA recently stated that all patients with OUD who are detoxified from opioids should be offered XR-NTX (US HHS, 2018). These treatments are not substitutable and in fact as described by ICER, "initial pathways differed for each intervention based on trial design and FDA label..." The differences between opioid agonist versus antagonist medications are summarized in detail above. To include these distinct patient populations in the same cohort and consider them eligible for the same medications is contrary to the underlying principles of CEA.

Finally with respect to the patient population, we again remind ICER that XR-NTX is only indicated for patients 18 years and older; therefore it is not appropriate to consider 16- and 17 year-olds in an economic model of XR-NTX.

Comparators. In CEA, all relevant alternatives for the question under study should be included (Roberts et al., 2012; Drummond et al., 1997). Assuming it is appropriate to compare opioid agonist to opioid antagonist medications, ICER has omitted an important alternative—the one that most patients with OUD are currently receiving—no medication treatment.

Utility Values. Despite the very limited data available on utility values associated with OUD and its treatment, ICER has elected to estimate a cost-per-quality adjusted life year (QALY) as the

only outcome for the CEA. Importantly, ICER does not include a discussion of the significant limitations of this outcome in this disease area, nor does it include any alternative outcomes for the incremental cost-effectiveness ratio (e.g., cost per life-year saved or cost per abstinent day). The conclusions of the CEA with respect to XR-NTX are based on a marginal (0.03) difference in QALYs. However, the single study from which utility values were obtained included health states for persons on buprenorphine and methadone, but not for XR-NTX. The fact that utility values for buprenorphine were used as a proxy for utility values for XR-NTX was never stated in the ICER report; one would have to go to the original data source (Wittenberg et al., 2017) to understand this detail. In Wittenberg et al., the utility values associated with buprenorphine therapy were found to be significantly different from utility values associated with methadone; this is not surprising, as patient preferences are different for these medications (Uebelacker et al., 2016). Furthermore, given the differences between opioid agonist and antagonist medications, we should expect utility values for buprenorphine to differ from those associated with XR-NTX. Yet the ICER model assumes that the utility value associated with being stable on buprenorphine is equal to that of being stable on XR-NTX. This is not an appropriate assumption, and violates what we already know about these medications, i.e., that patients express specific preferences for one versus another at a given point in their disease (Uebelacker et al., 2016). This significant limitation is not discussed in the ICER report, nor did ICER attempt to assess the impact of this limitation on the CEA results by conducting a sensitivity analysis on differential utility values. This is not in keeping with good reporting practices in CEA (Drummond et al., 1997).

Handling of uncertainty and “societal” perspective. Good practice in CEA stipulates that researchers provide allowance for uncertainty and are clear on the extent to which uncertainty affects the results (Caro et al., 2012). The handling of uncertainty in ICER’s analysis is minimal at best. As summarized above, one of the critical inputs into the CEA is utility values. However, ICER did not assess results under an alternative, more realistic assumption that patients on buprenorphine and XR-NTX have different health-related quality of life outcomes (i.e., utility values). ICER used data from Shah et al. (2018) to estimate background healthcare costs, however the medication-specific costs from the study were not used. Rather, ICER states, “We calculated the population-weights average costs of inpatient, ED, and outpatient visits among the Vivitrol and buprenorphine treated populations at baseline and follow-up...” ICER used these estimates as background costs for 3 distinct health states. Yet nowhere in the report does it describe that results from Shah et al. indicate that XR-NTX patients experienced no increase in costs while buprenorphine patients experienced a statistically significant 43% increase in costs. ICER did not explore the impact of differential background costs in sensitivity analyses. In fact, the current structure of the economic model does not allow for differential costs and utility values for BUP-NX and XR-NTX to be tested.

Furthermore, while ICER conducted a “modified societal perspective,” they did not include potentially one of the biggest drivers and differentiators between generic BUP-NX and all of the extended release formulations: the risks and costs associated with diversion, misuse, and abuse. This is a glaring omission, as diversion is of importance to buprenorphine prescribers (Lin et al., 2018) and was one of the reasons extended-release buprenorphine products were developed (Rosenthal et al., 2017). In one study of opioid, polysubstance users seeking treatment in a drug-



free residential recovery center, researchers reported that less than 10% of former buprenorphine users obtained it through a medical prescription and over 90% obtained it via illegal means (Walker et al., 2018). Furthermore, over 70% of former buprenorphine users reported that they took other drugs or alcohol to get high while taking it, and over 80% reported selling, trading, or giving away their prescribed buprenorphine. The omission of the unwanted effects of generic BUP-NX from the ICER Draft Report is glaring and leads to inaccurate and misleading conclusions regarding the extended-release formulations of both agonist and antagonist medications.

3. Correction of Errors in the Draft Report

We have noted several inconsistencies and inaccuracies in the ICER Draft Report, and wanted to call attention to one in particular. On Page 23, ICER states that the 2012 AATOD Guidelines for using Vivitrol recommend monitoring and frequent liver function studies...“because Vivitrol carries a black box warning for liver complications...” Vivitrol does not carry a black box warning, and Alkermes requests that ICER correct this false statement in the Final Report.

4. Comments on Draft Voting Questions

To reiterate all the points above, Alkermes strongly recommends that the Voting Questions be reframed such that the focus is on evaluating whether the evidence is adequate to support increased education, awareness, and access to all MAT options for OUD. Only then can we begin to address the sizable gap that exists between the need and availability of MAT.

Thank you again for the opportunity to comment. We sincerely hope that ICER considers these comments for the Final Report, because the methodology and conclusions as they currently stand could have far reaching adverse public health consequences in the middle of an opioid epidemic that is only getting worse by the day.

Sincerely,

A handwritten signature in black ink that reads "Amy K. O'Sullivan".

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Comments on Draft Report

Thank you for the opportunity to provide comments to the draft report. Braeburn provides the following comments for your consideration.

1. Two relevant studies were left out of your analysis, and we urge you to include them.

The studies are:

- The first study is described in the poster entitled, “Transitioning patient from sublingual to injectable weekly and monthly buprenorphine” and can be accessed here:

<http://www.eventscribe.com/2018/posters/asam/PosterViewMOBILE.asp?PID=134169>

and then clicking on the “view poster” bar. This open-label study was designed to evaluate the long-term safety of CAM2038 in both patients who were new to treatment and converting from sublingual buprenorphine (SL BPN). A post-hoc, subgroup analysis of the patients who converted from SL BPN demonstrated that CAM2038 weekly and monthly were associated with high retention throughout the study for subjects that were transitioned from sublingual buprenorphine. This information is relevant to the model when assessing the retention of CAM2038 compared with SL BPN.

- The second study can be found here:
<https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2632987?redirect=true>

This study was a randomized, double-blind, controlled study to evaluate the degree and duration of the opioid blocking effects of CAM2038 weekly following administration of intramuscular hydromorphone (6 mg and 18 mg) compared to placebo on subjective opioid effects in patients with opioid use disorder, as measured by the Drug Liking visual analog scale (VAS). The findings show that CAM2038 weekly 24mg and 32mg produced immediate and sustained opioid blockade. The results support the use of CAM2038 for treatment initiation and stabilization without a need for SL BPN. Studies have shown that a substantial proportion of SL buprenorphine treatment failures occur during the first seven days of treatment, so being able to induct with injectable buprenorphine that is therapeutic with first dose is beneficial.

Note: Two articles that discuss the SL BPN retention can be found here:

- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2628995/>
- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1490248/>

This information is relevant when assessing and modeling the benefits of CAM2038 and SL BPN.

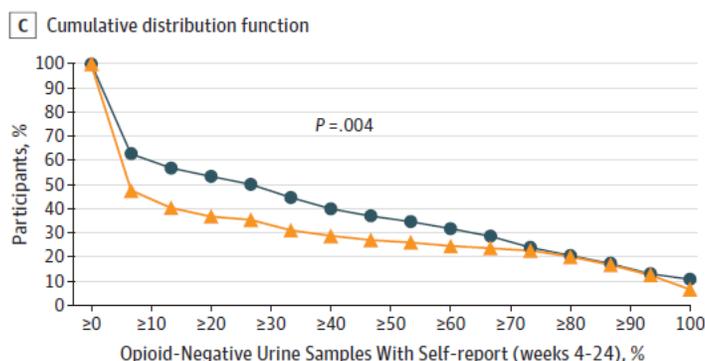
2. One study was included in your assessment; however, a critical finding of the study was omitted. The study can be found here:

<https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2681061>. It was the completed pivotal randomized, double blind phase 3 study in 428 patients with moderate to severe opioid use disorder. Phase 1 encompassed the first 12 weeks of the

treatment phase that included flexible dosing with weekly CAM2038 while phase 2 encompassed the second 12 weeks that included flexible dosing with monthly CAM2038 vs daily sublingual buprenorphine/naloxone (SL BPN/NLX). The primary endpoint was the responder rate based upon no evidence of illicit opioid use measured by opioid negative urine samples and self-report at prespecified time points. **A key secondary endpoint, which was omitted in your assessment, was the calculation of the cumulative distribution function (CDF) of percent urine samples negative for illicit opioids from week 4 through week 24 of the treatment phases 1 and 2.** It is important to note that this endpoint was controlled for multiplicity.

The primary endpoint met prespecified criteria for non-inferiority. Analysis **of the key secondary outcome of CDF of the proportion of opiate-negative urine samples from week 4 through week 24 demonstrated superiority of CAM2038 vs SL BPN/NLX (see figure C below).**

This statistical superiority of SC buprenorphine dosed weekly or monthly over the sublingual formulation is notable and should be taken into consideration when considering relative value of CAM2038. Because CAM2038 is an extended release formulation of buprenorphine administered as a subcutaneous injection given by HCPs only, there are other potential benefits of CAM2038 that are important to consider. HCP administration may mitigate risks related to abuse/misuse/diversion and unintended pediatric exposure. Additionally, its extended release profile provides for sustained therapeutic plasma exposure throughout the weekly or monthly dosing period and thus may improve medication adherence and increase treatment retention.



This key secondary endpoint is relevant to the model when assessing that value of CAM2038 compared to sublingual buprenorphine (SL BPN/NLX).

3. The issues of SL BPN being subject to misuse, abuse and diversion – and the issues resulting from this – do not seem to be addressed in the draft report. Because CAM2038 is administered by a healthcare professional and is intended to never be in the hands of the patient, the risk of misuse, abuse and diversion is mitigated. Some points from the paper which can be found here <https://www.ncbi.nlm.nih.gov/pubmed/29693427> include:

- Among those with a history of BPN use, one-third of the lifetime SL BPN/NLX group and 40% of the recent BPN/NX group had received SL BPN/NLX by prescription and over 90% of both groups had obtained BPN without a prescription at least once.
 - Among those who had received prescribed SL BPN/NLX over 80% said they had sold, traded, or given away their prescribed BPN at least once.

Please also see SAMHSA diversion

data: <https://www.samhsa.gov/data/sites/default/files/NSDUH-DefTabs-2016/NSDUH-DefTabs-2016.htm#tab1-97A> Note: You have to calculate Misuse (712k) as a percentage of Any Use (2,253k). Dividing Misuse by Any Use yields 32%.

4. We urge you to include in the clinical guidelines section the Treatment Improvement Protocol, TIP 63, entitled “Medications for Opioid Use Disorder: For Healthcare and Addiction Professionals, Policymakers, Patients, and Families” instead of older guidelines. It can be found here: <https://store.samhsa.gov/shin/content/SMA18-5063FULLDOC/SMA18-5063FULLDOC.pdf>



October 4, 2018

Dr. Steven D. Pearson
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Re: Draft evidence report of ICER's review of extended-release MAT for OUD

Dear Dr. Pearson:

Indivior welcomes a balanced discussion on the value of medication-assisted treatment (MAT) options for opioid use disorder (OUD), including SUBLOCADE™ (buprenorphine extended-release) injection for subcutaneous use (CIII). The opioid crisis costs the United States one life every 13 minutes and about \$504 billion annually.^{1,2} MAT is an essential part of the public health response to this crisis, which affects more than 2 million patients and their families.³

While the ICER draft evidence report acknowledges the value of extended-release MAT treatment options, the model has serious methodological flaws that compromise its results and imply overall poor value of these treatments for OUD.

Specifically, the draft evidence report:

- Does not capture the value of: improved medication adherence with monthly versus daily treatment, consistency in buprenorphine levels, reduced potential for diversion, misuse and abuse, and the societal benefits associated with patient recovery
- Does not recognize the chronic and relapsing nature of OUD
- Does not allow MAT users who stop treatment to re-enter treatment contradicting real world clinical practice
- Does not recognize that target patient populations for the treatment options are different
- Makes assumptions about real world use without current evidence
- Uses incorrect assumptions to calculate discontinuation rates
- Does not include all relevant studies/evidence in their indirect comparisons
- Does not use the correct price for available medications
- Does not differentiate medical spend between the various treatment options

If left uncorrected, the final report may be used at face value without further assessment and jeopardize access to treatment that could meaningfully impact the lives of patients, their families and society at this critical juncture in the opioid crisis.

In addition to the overarching weaknesses listed above, Indivior would like to raise the following specific concerns related to ICER’s conclusions about SUBLOCADE in the draft evidence report:

- *The analysis overstates discontinuation and miscalculates the abstinence rate of SUBLOCADE as compared to generic sublingual buprenorphine/naloxone (Generic SL bup/nal).*
- *The framework adopted by ICER does not explicitly include the numerous societal and contextual considerations critical to real-world treatment of patients with OUD such as misuse, diversion, and pediatric exposure.*

Consistent with our commitment collaboration and addressing unmet patient needs, Indivior submits the following detailed recommendations to that will improve the accuracy of ICER’s conclusions:

Recommendation 1: *The model should assume comparable rates of discontinuation between SUBLOCADE and Generic SL bup/nal during the induction and dose adjustment period.*

The model incorrectly assumes that nearly a quarter of subjects receiving SUBLOCADE in the US-13-0001 study immediately discontinued treatment. As a result, ICER assumes 24.2% of patients enter the model in the health state “off MAT with use of illicit opioids” (Table 4.1)—the equivalent of illicit use without recovery until death (Figure 4.1B). On the other hand, ICER assumes that a far smaller proportion (0.3%) of the cohort treated with Generic SL bup/nal start in the “off MAT with use of illicit opioids” health state. This assumption substantially mitigates SUBLOCADE’s projected incremental clinical benefit.

The US-13-0001 study included a 14-day “run-in” period prior to initiating treatment with SUBLOCADE to ensure that potential subjects could meet the requirements for participation in the study. As a result, around 25% of potential subjects did not advance to the full study. However, there is no evidence to suggest that subjects who did not complete the run-in period for non-medical reasons (e.g., inflexible work schedule or lack of transportation, etc.) would proceed to the “off MAT with illicit use of opioids” state more frequently than subjects who successfully completed the run-in period and entered the full study.

Of the 665 subjects in the US-13-0001 study who did not complete the run-in period, 23 (3.5%) failed for medical reasons (see Table 1, additional detail in the Appendix), which is consistent with the known safety profile of SL buprenorphine. Specifically, for the SUBLOCADE treatment arm, ICER should assume that 96.5% of the cohort starts in the “MAT with illicit use of opioids” state and 3.5% starts in the “off MAT with illicit use of opioids” state.



Therefore, we recommend that ICER reassign the subjects who did not complete the run-in period for non-medical reasons to the same initial health state as those who completed the run-in period (“MAT with illicit use of opioids”).

Recommendation 2: *The model should assume the discontinuation rate for SUBLOCADE is at least as good as or better than the discontinuation rate for Generic SL bup/nal.*

The report assumes that the discontinuation rate for Generic SL bup/nal is less than an extended-release injectable buprenorphine. However, there is no reason to believe that Generic SL bup/nal would have a lower discontinuation rate than SUBLOCADE. Both treatments contain the same active partial mu-opioid receptor agonist, buprenorphine. Moreover, SUBLOCADE was designed specifically to overcome limitations of sublingual buprenorphine products, including daily medication adherence, consistent therapeutic level of buprenorphine over time and the need for supplemental buprenorphine. The lack of adherence to oral MAT is well-documented.^{5, 6}

In its model, ICER uses a network meta-analysis (NMA) based on trial US-13-0001, which compares SUBLOCADE to placebo, and a trial by Rosenthal, et al. (2013), which compares PROBUPHINE with open-label SL bup/nal and placebo. ICER’s analysis estimates an odds ratio of discontinuation for Generic SL bup/nal relative to SUBLOCADE of 0.67 (95% CI of 0.28 to 1.61). Additionally, the confidence interval does not indicate a statistically significant difference in discontinuation rates for Generic SL bup/nal and SUBLOCADE.

There are several trial design characteristics for the Rosenthal, et al. study that further limit our confidence in the estimated discontinuation rates for Generic SL bup/nal vs. SUBLOCADE including: an open label design, more frequent urine analyses (3 per week vs. 1 per week in US-13-0001), and the route of administration in the placebo arm (implant). This design likely would decrease retention in the placebo arm of the Rosenthal study, which, in turn, would have inflated the retention estimate for SL bup/nal compared to SUBLOCADE. Finally, ICER’s NMA includes only Rosenthal et al. (2013), and does not consider evidence on SL bup/nal from 10 other available trials.^{4, 7-18} We recommend ICER add these 10 trials to the network, as was done in the full NMA report Indivior submitted to ICER in June 2018, which would result in a HR for study discontinuation of 1.1 (95% CI: 0.73–1.58) for SUBLOCADE (300mg/300mg) relative to Generic SL buprenorphine.^{4, 7-18}

Recommendation 3: *The model should estimate abstinence rates for SUBLOCADE and Generic SL bup/nal using four studies identified by a comprehensive literature review.*

To compare the clinical effectiveness of SUBLOCADE vs. Generic SL bup/nal, the model assumes an abstinence rate of 41.3% for SUBLOCADE based on study US-13-0001 and an abstinence rate for Generic SL bup/nal equivalent to that observed for the control arm in the CAM2038 trial (27.4%). Given the known differences in study design—which the draft report



acknowledges—a comparison based solely on these two studies offers more speculation than verification of abstinence.

Instead of comparing abstinence based on the comparison of two clinical studies, we urge that ICER develop an NMA consistent with the approach ICER uses to compare discontinuation rates. Using four studies identified by a comprehensive systematic literature review of all published clinical trials of opioid agonist therapies (Ling et al., 2010; Rosenthal et al. 2013; RB-US-13-0001; and Lofwall et al. 2018), we recommend that ICER conduct an NMA of “overall percentage of abstinence by urinalysis” to derive probabilities of abstinence at week 24 of 46.4% and 22.8% for SUBLOCADE and Generic SL bup/nal, respectively (details of the calculation are provided in the Appendix).^{4, 12, 16, 19}

The literature review protocol, as well as detailed methodologies for this NMA, are presented in the full NMA report we submitted in June 2018. A sample Win BUGS code and data inputs from the four studies ready for Win BUGS entry are included in the Appendix to this letter.

Recommendation 4: ICER should include additional evidence to capture the role of SUBLOCADE in supporting patients’ recovery journey.

- **Improved quality of life:** In the pivotal Phase III clinical trial, subjects receiving SUBLOCADE (both doses) versus placebo had significantly greater changes from baseline on the EQ-5D-5L visual analog scale (VAS) and SF-36 physical component score—demonstrating quality-of-life improvements. Differences in the EQ-5D-5L index with 300mg, VAS with 100mg, and SF-36 in both groups vs. placebo were found to be clinically meaningful based on published benchmarks established in other chronic conditions. Treatment satisfaction was reported by 88% of patients (both doses) of RBP-6000 and 46% of placebo-treated subjects (P<0.001 for both).²⁰
- **Impact on improving return to work and/or overall productivity:** For those receiving SUBLOCADE in the RB-US-13-0001 study, employment increased by 10.4% on average while decreasing 12.6% for placebo patients.²⁰ Those receiving SUBLOCADE worked approximately 4 hours more per week on average. Subsequently, in the long-term follow up of the participants of the SUBLOCADE Phase III programs, sustained levels of employment, low levels of health resource use and low prevalence of arrests throughout the 12 months of post-trial observation were observed among those who received SUBLOCADE.
- **Longer SUBLOCADE treatment durations were associated with higher rates of opioid abstinence over 12 months:** Twelve months following enrollment in the RECOVER study, approximately half of those who participated in the SUBLOCADE Phase III program and recruited to the RECOVER study demonstrated complete, continuous abstinence, despite a low prevalence of any use of MAT. Further, longer SUBLOCADE treatment durations were associated with higher rates of opioid abstinence. A summary of preliminary data from



RECOVER, a 12-month longitudinal analysis, has been submitted to ICER as “academic in confidence” under separate cover.

Indivior is committed to working with health system decision-makers including patients, providers, payors and policy makers to ensure access to MAT, including SUBLOCADE. Given the weaknesses in draft report, we urge ICER to revisit its model assumptions and inputs to improve the accuracy of their conclusions. While well intended, the draft report and model are scientifically inaccurate and could inadvertently impact millions of patients who could benefit from these treatments.

Sincerely,



Ponni Subbiah, MD, MPH
Chief Medical Officer
Indivior Inc.



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Appendix: Supplemental Data and Materials to Support Recommendations 1 and 3

Recommendation 1: *The model should assume comparable rates of discontinuation between SUBLOCADE and Generic SL bup/nal during the induction and dose adjustment period.*

Table 1. RB-US-13-0001 Run-in phase reasons for discontinuation

Reason for discontinuation	Discontinuation during run-in period	
	N = 665	
	n	(%)
<i>Medical</i>	23	3.5%
Adverse event	6	0.9%
Physician decision	6	0.9%
Withdrawn by physician	4	0.6%
Lack of efficacy	3	0.5%
Protocol deviation	4	0.6%
<i>Non-medical</i>	138	20.8%
Lost to follow-up	61	9.2%
Other	32	4.8%
Withdrawn by subject	41	6.2%
Non-compliance with study drug	4	0.6%

Recommendation 3: *The model should estimate abstinence rates for SUBLOCADE and Generic SL bup/nal using four studies identified by a comprehensive literature review.*

This appendix section will outline the following specific procedures for the recommended estimation of abstinence rates:

- Recommended steps for an NMA to compare abstinence rates for SUBLOCADE and Generic SL bup/nal
 - WinBUGS Code for Overall Abstinence
- Recommended steps for calculating 24-week abstinence rates for SUBLOCADE and sublingual buprenorphine/naloxone from NMA results

Recommended steps for an NMA to compare abstinence rates for SUBLOCADE and Generic SL bup/nal

Based on our systematic review of the randomized controlled trials of opioid agonist treatments (see the full protocol and report submitted to ICER in June 2018), we recommend using the “overall abstinence by urinalysis” outcome that measures the percentage of urine samples positive for opioids throughout the trial period, as no network analysis was possible using the weekly urinalysis data.

Measures of abstinence in each of these studies have been reported in different ways. After a review of comparability across different abstinence measures, it was determined that abstinence by urinalysis represented the most commonly and consistently reported analyzable outcome for abstinence that could be reasonably compared across studies.

We recommend using the 4 studies listed in Table 2 below. In order to ensure the outcomes compared were similar to each other, we summarize the following study characteristics in the same table.

- 1) Imputation of missing samples and study dropouts (consistent across 4 studies),
- 2) Timing of assessment for overall urinalysis (all available at 24 weeks), and
- 3) Timing of randomization and induction/dose stabilization (randomization after induction/stabilization for all but 1 study).

In total, there were 4 trials in addition to RB-US-13-0001 that reported on overall abstinence by urinalysis, for a total of 5 trials. One study (Petitjean et al., reference #6) was excluded, since it had a duration of only 6 weeks compared to the 24-week RB-US-13-0001 trial. Of the remaining 4 studies, all but the Lofwall study performed randomization after induction/dose stabilization. This was considered important as abstinence during the induction/stabilization period was thought to differ from abstinence that would be observed after this period. Although the Lofwall study performed randomization before induction/dose stabilization, overall urinalysis (as a percentage of urine samples negative) were consistent when evaluated in the weeks 1–24 time frame and the weeks 4–24 time frame. Inclusion of the Lofwall study in addition to the other studies would strengthen the analysis around comparisons of abstinence by allowing a greater amount of data to be used. Thus, 4 studies comprised of 1367 total subjects were included into the overall abstinence by urinalysis NMA (Table 2).



Table 2: Overall urinalysis abstinence data from the identified studies

Trial No.	Ref No.	Citation	Treatment Category	Subjects, N	Randomization Timing Relative to Induction/Stabilization	Reported Time Point(s), Weeks	Negative Urine Samples, %	Handling of Missing Data	Reported Missing Data Methodology
1	1	Ling et al. <i>Journal of the American Medical Association</i> 2010	Placebo BUP-IMP	55 108	After	16/24	28.3/22.4 40.4/36.6	Dropouts = positive Missing = positive	“The denominator for the primary end point was all possible urine samples that could have been collected from implantation through week 16. Missed samples were considered positive for opioids. After a subject was withdrawn from the study, urine samples from the point of withdrawal were also considered positive.”
2	2	Rosenthal et al. <i>Addiction</i> 2013	Placebo BUP-IMP BUP-V	54 114 119	After	24	13.4 31.2 33.5	Dropouts = positive Missing = positive	“The denominator for the primary end point was all possible urine samples that could have been collected through week 24. Missed samples were counted as opioid-positive. When a subject discontinued or was withdrawn from the study, urine samples from that point onward were considered positive.”
3	3	RB-US-13-0001	Placebo RBP-6000 300 mg/100 mg RBP-6000 300 mg/300 mg	99 194 196	After	24	10.1 47.4 44.9	Dropouts = positive Missing = positive	N/A, calculated directly from clinical trial data

Trial No.	Ref No.	Citation	Treatment Category	Subjects, N	Randomization Timing Relative to Induction/Stabilization	Reported Time Point(s), Weeks	Negative Urine Samples, %	Handling of Missing Data	Reported Missing Data Methodology
4	4, 5	Lofwall et al. <i>JAMA Intern Med</i> 2018 FDA Advisory Committee: CAM2038 Briefing Document	BUP-V CAM2038	215 213	Before	24	28.4 35.1	Dropouts = positive Missing = positive	“A total of 1988 of 7704 urine samples (25.8%) were missing and imputed as positive for illicit opioids because return to illicit opioid use is common when patients leave treatment. In specified sensitivity analyses, missing values were deleted and not imputed.

Abbreviations: BUP, buprenorphine; IMP, implant; KM, Kaplan-Meier; MET, methadone; N, number; N/A, not applicable; V, variable dosing. Because of differences in the denominator, the proportion of opioid positivity between the reported samples and the NMA inputs may not match exactly.

We recommend modeling the total number of positive urinalysis samples divided by the total number of samples scheduled to be collected using the binomial distribution with logit link (see the NICE Technical Support Document 2 Section 2, sample Win BUGS code, and data inputs from the 4 studies recommended ready in the Win BUGS format in page 3 of this appendix). Study designs varied with respect to the frequency of urinalysis sampling, so the number of subjects within each treatment arm should be used as the denominator of each of the proportions rather than the total number of samples collected so that the NMA would give more weight to larger studies rather than to studies that collected more frequent urinalysis samples. Only fixed-effect model results can be generated due to the inclusion of only 4 studies in the network, thereby prohibiting reliable estimation of the random-effect parameter.

Table 3 presents the results from the NMA. The odds ratio for overall opioid positivity for SUBLOCADE 300mg/100mg compared with sublingual buprenorphine was estimated to be 0.38.

Table 3. Overall opioid positivity NMA odds ratios (and 95% CrI) relative to each treatment

		Placebo	BUP-IMP	BUP-V	RBP-6000 300mg/100mg	RBP-6000 300mg/300mg
Odds Ratio, row compared to column	BUP-IMP	0.4 (0.21, 0.66)				
	BUP-V	0.38 (0.18, 0.69)	0.97 (0.55, 1.6)			
	RBP-6000 300mg/100mg	0.13 (0.06, 0.24)	0.35 (0.12, 0.78)	0.38 (0.12, 0.9)		
	RBP-6000 300mg/300mg	0.14 (0.06, 0.26)	0.39 (0.13, 0.86)	0.42 (0.13, 0.99)	1.13 (0.74, 1.66)	
	CAM2038	0.28 (0.12, 0.57)	0.72 (0.35, 1.34)	0.74 (0.48, 1.09)	2.54 (0.75, 6.54)	2.3 (0.68, 5.9)

Abbreviations: BUP, burprenorphine; CrI, credible interval; IMP, implant; mg, milligram; V, variable dosing.

Note: Bolded outcomes do not include 1 within the CrI and are considered to be statistically significant comparisons.

WinBUGS Code for Overall Abstinence

Overall urinalysis

Fixed effect model

```
model
{
  for (std in 1:noStudies)
  {
    mu[std] ~ dnorm(0,0.00001)
    for (i in 1:arms[std])
    {
      r[std,i] ~ dbin(p[std,i], n[std,i])
      logit(p[std,i]) <- mu[study[std]]+d[comp[std,i]] -
d[comp[std,1]]
    }
  }

  #priors
  d[1]<-0
  for (k in 2:noTx) { d[k] ~ dnorm(0, 0.00001)}

  #calculate weighted average of PBO OR
  for (std in 1:noPBO)
  {
    var[std] <- 1/r[std,1] + 1/(n[std,1]-r[std,1])
    weight[std] <- 1/var[std]
  }

  #calculate PBO prob
  ln_pbo <- inprod(mu[1:noPBO],weight[])/sum(weight[])
  logit(prob[1]) <- ln_pbo
  for (i in 2:noTx)
  {
    logit(prob[i]) <- ln_pbo + d[i]
  }
}
```



```

#calculate OR of RBP300 relative to other treatments
for (i in 1:noTx)
{
  lnOR_rbp300[i] <- d[rbp] - d[i]
  OR_rbp300[i] <- exp(lnOR_rbp300[i])
}
}

#STUDY INPUT DATA
study[] arms[] comp[,1] comp[,2] comp[,3] r[,1] n[,1] r[,2] n[,2] r[,3] n[,3]
1 2 1 2 NA 43 55 68 108 NA NA # Ling 2010
PBO BUP-imp
2 3 1 2 3 47 54 76 114 79 119 # Rosenthal 2013
PBO BUP-imp BUP-V
3 3 1 4 5 89 99 102 194 108 196 # RB-0001 PBO
RBP100 RBP300
4 2 3 6 NA 154 215 138 213 NA NA # Lofwall 2018
BUP-V CAM2038

END

```

Recommended steps for calculating 24-week abstinence rates for SUBLOCADE and sublingual buprenorphine/naloxone from NMA results

To estimate the probability of abstinence at week 24, Indivior recommends ICER use the following steps. First, using the methods described above, ICER can estimate the odds ratios of overall opioid positivity at week 24 for SUBLOCADE and SL buprenorphine compared with placebo (0.13 and 0.38, reported in Table 3 in the Appendix). Then, the odds ratios should be converted to relative risks using the formula $RR=OR/(1-risk_ref + [risk_ref*OR])$, where risk_ref stands for the risk of opioid positivity in the reference case (placebo).⁷ Using the odds ratios of 0.13 and 0.38 for SUBLOCADE and SL bup (Table 3 in the appendix) and the percentage of opioid positive subjects in the placebo arm (89.9%, see Table 2 in the Appendix for the % of subjects with negative UDS samples in each study arm) as risk_ref, the relative risks comparing SUBLOCADE and SL bup/nal are estimated to be 0.597 and 0.859, respectively. Applying these relative risks to the percentage of opioid positive subjects at week 24 in the placebo arm yields the % opioid positive samples at week 24 for SUBLOCADE and SL bup arms of 53.6% and 77.2%, respectively. Finally, the probability of abstinence at week 24 is estimated to be 1 minus the % opioid positive at week 24, i.e., 46.4% and 22.8%.



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, MDICER public comments:

My name is James L. Andersen, M.D. FASAM, ABAM. I am an addiction specialist physician in Lakeland FL as well as a principal investigator in clinical trials with Meridien Research also in Lakeland. I have 23 years experience in methadone treatment as Medical Director of Lakeland Centres, a federally licensed OTP, 16 years of buprenorphine prescribing in private practice, and 4 years with naltrexone ER in 2 different 6 month residential treatment programs. In particular, I was a principal investigator for the trials of what is now Sublocade, following 30 some subjects for over two years.

With the above in mind, I would like to comment on some values of injectable buprenorphine beyond the exhaustive statistics in your report. With sex, age, and some details altered for privacy, I offer these cases for your consideration:

A drug dealing, heroin addicted couple, incarcerated during the study, who were unable to keep their protocol defined visit windows. They both said “this was the best jail detox we’ve ever had. Didn’t even feel it.” Although neither designed nor powered to study this aspect of addiction, it was clear from this and other examples at the end of the trial that the drug eased out of the body so gradually that most subjects felt nothing. Four subjects which I followed post study in my office never even filled the end of study buprenorphine. They were not in withdrawal.

A girl who had multiple psych issues, successfully completed the study and entered a drug free residential program elsewhere in the state. She did well, and one year later is not using.

A gentleman who got a good job and promotions during the study, finished, didn’t fill the buprenorphine rx and was fine until he took up with a former girlfriend who had continued to use heroin and suffered relapse. He is now back on buprenorphine films at 16mg per day.

A 30 some year-old well- situated man who was drug free for over a year until he reacquainted with an old drug using “friend” who enabled him to use what he called “black tar heroin.” After he overdosed, was resuscitated, hospitalized, and discharged he came to see me; his initial drug screen 2 days later was still positive for fentanyl. He was placed back on buprenorphine films but missed his next appointment. When he came in a week late he revealed that in wanting to use he would stop the films for a few days and then shoot up, then resume films when starting back in withdrawal. He and his non- using pregnant girlfriend agreed that he needed to be back on Sublocade which is now scheduled.

Quality adjusted life year statistics do not reveal the quality of the life that is saved by the use of a non-divertible, non-forgettable, continuous action effective product. Just from these few examples, it is evident that there are uses beyond the package insert for Sublocade which should be researched: preparation for entry into drug free programs when a person is spiritually, clinically, and psychologically ready, maintenance of sobriety for long term situations, ER treatment for stabilized OD's (most survivors leave asap and return to their source of the very drugs which just almost killed them with 10% dead in a year), and better training for change to non-drug thinking (no having to take something every day to keep from "that feeling"- withdrawal).

If even half of the 60 000 or so persons who died of opioid overdose last year could have been successfully resuscitated and started on injectable long acting buprenorphine, the effect on families and friends and the nation would be incalculable. What can be calculated is the cost; I tend to look at the benefits in the cost/benefit ratio first. With 30 000 lives saved for another 30 earning years at just \$30 000 earned per person per year, I see a \$27 billion benefit. Adjusting for some subsidy, discount and insurance covering half the \$1500 price of injection, adding this treatment to the current emergency mix would be adding only \$22.5 million per year assuming no improvement in prevention strategies. Keeping all of those saved in a monthly (or longer) injection program would be expensive but not unrealistic at \$270 million per year considering the latest federal opioid budget bill was \$8.1 billion. I will leave it to ICER to work out the additional cost savings that could accrue from items such as reducing repeat OD'ers like one man who was recently reported to have been revived with ER Narcan 173 times in the last year at one Camden NJ ER which records 15 OD's per day.



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ICER MAT Draft Comments:

I was surprised that the issue of diversion of the sublingual and buccal formulations of buprenorphine was not mentioned, when discussing the subcutaneous formulations of buprenorphine. I would think that in addition to the usual outcome measures, the prevention of diversion is of paramount importance. Frequently patients are prescribed limited quantities of buprenorphine, necessitating frequent clinic visits, in an attempt to decrease the likelihood of diversion. The SC formulation would eliminate this concern, and in some cases allow patients more flexibility for work and educational activities.

David Schwartz
Head of Global Policy
Public Policy and Federal Government Affairs



October 4, 2018

VIA ELECTRONIC SUBMISSION TO www.publiccomments@icer-review.org

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Re: Draft Evidence Report, Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value

To Whom It May Concern:

Cigna welcomes the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report, *Extended Release Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value* ("the report"). We appreciate ICER's focus on treatment of opioid use disorders and the opportunity to comment on newer MAT interventions compared to currently approved interventions.

More broadly, we appreciate ICER's commitment to evidence-based, transparent determinations of the clinical and economic value of critical public health interventions. Cigna is a leader in the move to value-based care across the health care spectrum. Our experience has taught us how crucial the move from volume to value is to promoting competition, lower costs, and better outcomes in our nation's health care system. The right environment encourages innovation, collaboration, and choice to the benefit of consumers and the system as a whole

Cigna Corporation, together with its subsidiaries (either individually or collectively referred to as "Cigna"), is a global health services organization dedicated to helping people improve their health, well-being, and sense of security. Our subsidiaries are major providers of medical, pharmacy, dental, disability, life and accident insurance, and related products and services, covering 15.2 million customers in the more than 30 countries and jurisdictions in which we operate. Worldwide, we offer peace of mind and a sense of security to our customers seeking protection for themselves and their families at critical points in their lives.

Within the U.S., Cigna provides medical coverage to approximately 14 million Americans in the commercial segment, of whom almost 9 million receive integrated medical and pharmacy coverage. We also provide integrated coverage in the individual insurance segment to about 400,000 people.

"Cigna" is a registered service mark, and, "the 'Tree of Life'" logo is a service mark, of Cigna Intellectual Property, Inc., licensed for use by Cigna Corporation and its operating subsidiaries. All products and services are provided exclusively by such operating subsidiaries and not by Cigna Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company (CGLIC), Cigna Health and Life Insurance Company (CHLIC), and HMO or service company subsidiaries of Cigna Health Corporation and Cigna Dental Health, Inc.

Additionally, Cigna serves approximately 1.7 million people through our Medicare Advantage (MA), Medicare Prescription Drug Program (MA-PD and PDP), and Medicare Supplemental products.

Cigna is a leader in value-based contracting with health care providers, pharmaceutical manufacturers, and other service providers that help us achieve the goals set by, and with, our employer clients on behalf of their employees. Cigna has a long history of motivating providers to move away from a volume-driven view of health care delivery and reimbursement and helping them to align their financial incentives with patient health outcomes, resulting in joint success through collaborations which may include shared risk. We help prepare doctors and other providers not only to earn incentives for delivering better care at a lower cost, but also to assume greater financial risk while improving patient health outcomes across a variety of products and payers.

Cigna has long recognized that substance use disorders are complex, chronic conditions that are frequently accompanied by other behavioral or medical conditions. To address this growing public health issue, the company tapped into its extensive experience with prevention, wellness, and chronic disease management programs, and worked with clients, physicians, regulators, patient advocacy groups, and others to develop ways to increase prevention and treatment of substance use disorders. Cigna's achieved a significant step in the fight against the opioid epidemic by reducing opioid prescriptions among our customers by 25 percent. Having achieved that goal, Cigna is continuing its efforts by focusing on addressing overdoses, instituting safer prescribing measures, and helping to prevent opioid misuse before it starts. We have removed all prior authorization restrictions on MAT, increased access to opioid reversal agents (e.g., naloxone and Narcan), and increased access to opioids with abuse-deterrent properties.

Our comments on the report focus on the availability of the medications reviewed (Sublocade, Probuphine, and Vivitrol) on payer formularies. An important distinction missing from the report's *Summary of Coverage Policies and Clinical Guidelines* is the difference between medications prescribed by a physician and dispensed by a pharmacy which fall under a patient's pharmacy benefit, and medications administered by a physician, which generally fall under a patient's medical benefit. The report indicates that Sublocade, Probuphine, and Vivitrol are not on Cigna's 2018 formularies, leading to an assumption that Cigna does not cover these medications. However, these medications are covered under Cigna's medical benefit, due to the manner in which they are administered (i.e., injected or implanted by a physician).

Gathering coverage information is not a core function of ICER's mission to establish impartial value assessments. While we understand why ICER may want to include such information, we are concerned that ICER's summary of such information does not take into account the variety of benefit plans and funding arrangements across multiple plan sponsors or the impact of numerous state and federal regulations on coverage policies. Using the data cited in this report, any summary exposition of coverage policies may convey an incorrect or incomplete position, and ultimately create more confusion and cause more harm in the public discourse. If ICER continues to include coverage summaries, a more collaborative and effective approach might be to reach out to those whose coverage policies are referenced so that we may provide contextually accurate information relative to publicly available coverage policies. An appropriate disclaimer regarding coverage policies should also be considered to

ensure reviewers understand that references to a particular tier structure or coverage policy are not homogenous across benefit plans and/or may be heavily influenced by numerous state and federal regulations.

Thank you for your consideration of these comments. Cigna would welcome the opportunity to discuss these issues with you in more detail at your convenience.

Respectfully,

A handwritten signature in blue ink that reads "David Schwartz". The signature is written in a cursive style with a large, looping initial "D".

David Schwartz

To Whom It May Concern:

I am submitting comments with regard to the report that the Institute for Clinical and Economic Review released on September 7, 2018 with regards to “Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value”.

AATOD represents over 1,100 Opioid Treatment Programs throughout the United States. These are the specialty addiction treatment hub sites, which are monitored by accreditation mechanisms through the Substance Abuse and Mental Health Services Administration. The OTPs are also regulated by the Drug Enforcement Administration with regard to security issues and the State Opioid Treatment Authorities with regard to staffing and other operational responsibilities.

It is noted at the outset that the ICER report as referenced above does not provide any data with regard to how patients will respond to methadone maintenance treatment as utilized in OTPs. Perhaps the ICER report wanted to focus primarily on the use of partial agonists and antagonists.

General Overview

We support the ICER approach and how it characterizes Medication Assisted Treatment for Opioid Use Disorder. It is important to recognize that Opioid Use Disorder is a chronic, treatable illness and long term treatment generally produces favorable outcomes, as repeatedly demonstrated by the National Institute on Drug Abuse and the Substance Abuse and Mental Health Services Administration.

We also support the view as stated in the ICER report that “the primary aim of treatment is recovery rather than cure”. This is still misunderstood by many addiction treatment providers and individuals who manage Drug Courts and correctional settings.

We also support the view that the ICER report states that “all three drugs are to be used in combination with counseling and psychosocial support, described as a multipronged approach that includes counseling, vocational training, psychosocial therapies, family support, and building connections to community resources”.

In our experience and we believe that it is reasonable to conclude, that we do not have particularly good information on how clinical support services are being used at the present moment to supplement the use of medications when they are being used to treat this disorder, outside of the OTPs. While all of the OTPs are subject to tripartite regulation, as indicated above, we do know the range of services that are provided in the OTP setting in addition to medications.

We do not have comparable information on how support services are used when buprenorphine and other medications are used in a DATA 2000 practice or individual practices that decide to use long-term antagonists. All reasonable parties conclude, as ICER has, that such support services are needed to improve patient outcomes. Once again, it is important to go beyond the simple philosophic statements. We simply do not have the proper tracking mechanisms in place at the federal and state levels to determine how often such services are provided. This is a bottom line reality.

The ICER report also states that MAT is limited in the United States. This is true. At the present time, there are 1,600 OTPs operating in 49 states. A number of states including New York, Indiana, Georgia, Florida and Ohio have been seeing significant increases in access to treatment through the OTP settings.

It is also important to keep in mind that the number of patients that are being treated in the OTP setting has been steadily increasing over the last several years.

Finally, the report indicates that patients must attend daily to receive their dose of medication in OTPs. Patients typically get take-home medication, which progresses through the course of treatment. This is in accordance with the SAMHSA regulations, which specifies that OTPs must follow eight points of criteria when considering take-home medication. The point here is that it is not accurate to state that patients are always attending daily to get their treatment and medications in the OTP setting.

The Use of Medication in Criminal Justice

I am attaching the Fact Sheet that we wrote “Medication Assisted Treatment for Opioid Use Disorder in the Justice Setting”. This paper was developed at the behest of federal authorities in order to provide a straightforward set of principles when medications are used to treat Opioid Use Disorder in the Justice setting.

The progress of providing Medication-Assisted Treatment in correctional settings and Drug Courts has been slow although Drug Courts are increasingly providing access to Medication-Assisted Treatment for those individuals who come before their courts. The National Association of Drug Court Professionals published guidelines for Adult Drug Courts, recommending that such medications be used as appropriate.

The growth of MAT in correctional facilities has been much slower but we have been encouraged by the recent increase in access to treatment both in Connecticut and Rhode Island.

The ICER report also references the fact that the coordination of care is critically important in this domain by citing the Vermont Hub and Spoke Model. AATOD wrote three policy papers for SAMHSA, which were published during the summer of 2016, which focused on the importance of coordination of care at the state and local level.

We are also supporting recently introduced congressional legislation, which will support the increased use of Medication Assisted Treatment in correctional settings as sponsored by Congresswoman Kuster of New Hampshire. These two bills will both increase access to Medication Assisted Treatment in the correctional system and will eliminate the Medicaid exclusion. Both are critically important.

Summary

Our Association appreciates ICER’s interest in this area. We have been observing with great interest the number of entities that have a new interest in evaluating the importance of treating Opioid Use Disorder and providing effective recommendations for the future.

As individuals, who constructed this report will know, we have experienced several phases in this opioid use epidemic from prescription opioids to heroin and now more recently fentanyl. Services need to increase to respond to this demand but there needs to be much more focus on the quality of care that is delivered in addition to the harm reduction strategies that are being suggested. Medication alone is generally not adequate to respond to the many needs of patients who come into treatment. The focus has to be on ensuring that patients get access to good quality and coordinated care once medications are determined to be necessary in the treatment of this chronic disorder.

Thank you for taking these views into account.

With best regards,

Mark

Mark W. Parrino, M.P.A.

President

American Association for the Treatment of Opioid Dependence (AATOD)

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To: Institute for Clinical and Economic Review
From: Addiction Policy Forum
Re: Comments on Draft Report on Long Acting Injectable Medications for Opioid Use Disorder
Date: October 4, 2018

The Addiction Policy Forum is a 501(c)3 nonprofit organization based in Washington, DC committed to improving national policy and program delivery around substance use disorders through an evidence-based, comprehensive response that includes prevention, treatment, recovery support, overdose reversal and criminal justice solutions. Put simply, we envision a world where fewer lives are lost and help exists for the millions of Americans affected by addiction every day.

We thank and commend the Institute for Clinical and Economic Review (ICER) for undertaking an analysis of the effectiveness of long acting injectable medications for the treatment of opioid use disorders. As an organization working on behalf of millions of patients and families struggling with addiction, we know how critically important these medications are for promoting health and healing families and communities grappling with opioid misuse, addiction, and overdose.

We are also grateful to have an opportunity to submit comments as ICER moves forward with developing a final report. Our recommendations are below.

Incorporate the societal costs of opioid misuse, addiction, and overdose into the cost/benefit analysis

As ICER develops a final report, ICER should more closely examine and incorporate the societal costs of opioid use disorder into its cost effectiveness analysis. These costs include not only lost productivity (for patients as well as their family members who spend time caring for them and mourning them when they die from substance-related causes) but also health care expenditures, criminal justice costs, child welfare, education, social services, and other costs. The burden of addiction and the opioid epidemic is borne by all of society, and these costs should be reflected in any analysis of the cost effectiveness of medications for treating opioid use disorder.

Consider the importance of providing medications that reduce the potential for diversion

ICER should consider the importance of providing medications that reduce the potential for diversion. This is important for at least two reasons. First, reduced diversion means that fewer opioids are available in our communities to people for whom they have not been prescribed who may be at risk for developing an addiction, in active addiction, or treating themselves for substance use disorder rather than seeking care from a health care provider. Second, reduced diversion will increase the comfort level among health care providers for treating patients with opioid use disorder with medications. We have a shortage of

providers to treat patients on the scale required to arrest the opioid epidemic. In our conversations with providers, many are concerned about prescribing opioid medications for the treatment of opioid use disorder because they fear these medications may be misused or diverted away from their patients.

Examine the adherence and quality of life benefits of long acting medications

ICER should consider the substantial benefits of long acting medications for opioid use disorder to improve medication adherence and the quality of life of patients and families. Medication adherence and a reduction in the ups and downs of blood concentrations of opioid medications are major benefits of these medications. People with addiction, especially those in the early stage of recovery, have to make the difficult decision every day to adhere to their treatment plan and medications while their addiction continues to hijack their brain and push them back toward active addiction. By making the decision to stay on medications a decision they have to make only monthly or even less often, we ease their road to recovery. Not only that, for those whose recovery is further along, they do not have to think every day about their need for medication. This can be a huge psychological benefit. Reducing the number of doctor's visits, trips to the pharmacy, or visits to Opioid Treatment Programs to receive medication means patients can focus more of their time and energy on addressing psychosocial needs and can reduce the burden on families to support the needs of their loved ones in treatment.

Thank you for taking the time to consider our recommendations. These are informed by our expertise and experience with patients and families who have confronted this disease, including many who have become members of our staff or joined one of our forty-one chapters across the country. They know that we need more medications and better options now to address the opioid epidemic. We are looking forward to reading ICER's final report on long-acting medications for opioid use disorder.



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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 evidence report, *Extended-Release Opioid Agonists and Antagonists for Medication-Assisted Treatment (MAT) of Opioid Use Disorder: Effectiveness and Value*. Please find our comments below.

Draft Evidence Report

ASAM is in support of the overall approach and conclusions of the draft evidence report. ASAM believes that the approach to culling research appears to be within usual and customary practices, and that the statistical analysis appears to be accurate – but recommends a biostatistician or epidemiologist to also review the statistical analysis.

ASAM does recommend that the costs of medication should be an additional contextual consideration that will have an important role in the judgements of the value of the provided interventions.

Draft Voting Questions

ASAM believes the draft voting questions could potentially benefit from having some guidance as to how they are answered. It seems that asking whether LAI(X) is superior to transmucosal bup/nlx is simplistic, and one might struggle to answer without a definition of "superior." One suggestion is to pull this question apart into several questions with head-to-head comparison.

In addition, ASAM recommends providing more options for questions 6-7. One suggestion for a question is: "What is the first line medication for the treatment of OUD?"

Lastly, ASAM recommends separating questions 8-9 into each medication preparation. There may be specific considerations for each formulation, and ASAM believes that respondents should answer in the context of the specific formulation.

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,

A handwritten signature in cursive script that reads "Margaret Jarvis MD". The signature is written in black ink and is positioned to the right of the typed name.

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



October 4, 2018

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

Dear Members of the New England Comparative Effectiveness Public Advisory Council:

Mental Health America (MHA) thanks Institute for Clinical and Economic Review (ICER) for assessing the comparative clinical effectiveness and value of several new options for medication-assisted treatment (MAT) of opioid use disorder. MHA would like to reiterate its previous comment on ICER's approach to cost-effectiveness modeling in behavioral health.

In conducting the cost-effectiveness modeling, MHA asks that ICER consider cost-effectiveness from the perspective of both a generic payer and a public payer, i.e. Medicare and Medicaid. Medicaid and disability Medicare are the largest payers of behavioral health services in the United States. Poverty and disability contribute to the development of behavioral health conditions, and behavioral health conditions create burdens that can cause poverty and disability. Effective treatment and management of behavioral health conditions, on the other hand, can break this cycle and allow individuals to reach or maintain a level of community participation that positions them to stay on or purchase commercial insurance and not require public benefits – dramatically increasing cost-effectiveness from a public payer perspective.

For ICER's cost-effectiveness modeling, this is different than the increases in productivity that ICER currently evaluates. With Medicaid and disability Medicare, increases in productivity beyond a threshold uniquely reduce health care costs as the individual disenrolls entirely or never requires coverage in the first place, impacting ICER's primary cost-effectiveness calculations for these public payers. Where there might not be adequate evidence to allow for modeling, even scenario analysis would benefit the field. By making such analyses common practice, it can shift the paradigm for how CMS and state Medicaid agencies view costs and benefits, away from trimming health care costs and toward making critical investments that alleviate poverty and disability.

MHA thanks ICER for its consideration on including a separate cost-effectiveness analysis from the perspective of a public payer. For additional information, please do not hesitate to contact us.

Sincerely,

A handwritten signature in black ink, appearing to read "Nathaniel Z Counts, J.D.", is written over a light gray rectangular background.

Nathaniel Z Counts, J.D.
Senior Policy Director
Mental Health America



October 4, 2018

Steven D. Pearson, MD, MSc, FRCP
President, Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report “Extended-Release Opioid Agonists and Antagonist Medications for Addiction Treatment (MAT) in Patients with Opioid Use Disorder: Effectiveness and Value”

Dear Dr. Pearson:

Patients Rising Now welcomes the opportunity to comment on ICER’s September 7th draft evidence report about pharmacological treatments for Opioid Use Disorder (OUD). As you know, we advocate on behalf of patients with life-threatening conditions and chronic diseases for them to have access to vital therapies and services. Access to treatments is a matter of survival for those patients, and a requirement for them to have better and more productive lives.

As has become overwhelmingly clear over the past several years, opioid related deaths are truly a national emergency, and has been characterized as a crisis and a public health emergency.ⁱ Thus, our concerns about access equaling survival is exceptionally and unquestionably true for people with OUD. And the consequences of those people either receiving treatment or dying from their disease also extends to their families, their communities, and the country overall.ⁱⁱ

The opioid crisis in the U.S. is rapidly evolving and receiving widespread attention from government agencies, legislators, clinical organizations, law enforcement, other first responders, and judicial systems. All that attention underscores the complexity of appropriate responses. Therefore, unlike our other comment letters to ICER, we are going to make observations and recommends about how ICER can better contribute to the national response to the crisis without delving into many specific data or methodological issues. We feel that this is the appropriate patient-focused approach for our comments because with the rapidly changing nature of the crisis, what is true today, may only be partially true or of lesser concern tomorrow. For example, while the epidemic of opioid use and deaths was driven by prescription medicines only a few years ago, heroin and fentanyl are now of greater concern, and it was recently reported that the first time use of heroin appears to be waning.ⁱⁱⁱ

Language Choices and Terminology

Because words, phrases and terminology are so important for both clinical care and policy actions, at the outset, we want to urge ICER to use consistent language that both clearly conveys the meaning of choices and the seriousness of the opioid crisis for American families. As ICER notes, this epidemic is rapidly changing, and the “concepts and terminology around illicit drug use are constantly evolving,”^{iv} just as are our understanding of diseases such as OUD and related mental health and substance use disorders also continue to be refined. Two common themes in this advancement of knowledge are that those diseases are biological based disorders (and not

moral failings, or limitations of willpower), and that the language used to describe such medical conditions (and the people they affect) has real and significant consequences for how clinicians, payers, governments and others approaches those conditions and individuals, which can result in access and care limitations, or other problems. Therefore, because language can be part of the solution, (or part of the problem), we recommend ICER pay close attention to its word choices, particularly since ICER’s work is often cited by the popular and lay media.

First, we recommend that ICER mirror the phrasing that it uses toward the end of the draft report: “OUD is considered a public health emergency with an epidemic of deaths that decrease the overall life expectancy in the US and impacts all parts of society: families, the health system, social services, the judiciary system, and the economy. For the affected person, OUD is a chronic disease that is often compared to other chronic diseases, such as diabetes, but that carries a stigma affecting self-esteem, social relations, and work.”^v In contrast, the opening lines of the draft report characterizes the current crisis as an “increasingly common public health concern.”^{vi} We believe that this phrase – particularly at the start of the draft report – diminishes the significance and importance of the problem, and recommend that it be changed so as to not dilute anyone’s impression about the seriousness of the problem. Overall, we recommend that ICER use the terms crisis, epidemic, or public health emergency.

Second, one of the many challenges facing the U.S. in responding to the opioid crisis is the historical stigma of the misuse or illegal use of opioids, and particularly heroin. As ICER notes, “This stigma is rooted in a widespread belief that drug addiction is a moral failing rather than a medical condition that is best addressed through treatment.”^{vii} And very recently, the Surgeon General released a report that noted the problems with access to MAT related to “the use of some medications for opioid use disorder (methadone and buprenorphine) remains surrounded by misconceptions and prejudices that have hindered their delivery.”^{viii} Some of that stigma is dissolving with greater understanding – and public appreciation – of the biological basis of OUD, but it is still a problem. Stigma not only inhibits individuals from seeking treatment, but can reduce the attention and resources that governments, payers, and clinicians will devote to the crisis. Therefore, word choices and language that reinforce that stigma should be avoided and those that help dispel it should be used. For example, people with opioid use disorder is preferred over addicts, and by extension avoiding the term addiction is preferred even though it has a place in technical clinical usage – and particularly to distinguish addition from dependence, a distinction that ICER’s draft report touches upon.^{ix}

Third, consistent with using language that does not reinforce the stigma of OUD, we recommend that ICER not use the term “Medications for Addiction Treatment” when referring to MAT. That term is used only rarely in the literature^x and is not used in SAMSHA’s “Medications for Opioid Use Disorder”^{xi} nor in other major documents and recommendations.^{xii} In addition, we note in the draft report that MAT can be used by a person in recovery, i.e., in a state of dependence and not addiction: “A person in recovery refers to an individual who abstains from further use, reduces their substance use to a safer level, or takes steps to mitigate the potential physical and emotional harm resulting from continued use. A person can be considered in recovery while on MAT.”^{xiii} Therefore, we urge ICER to use “Medication Assisted Treatment” as a definition for MAT because it is much more commonly used and a much less controversial – although we do recognize that this term also has problems related to whether the medication is the treatment or is

assisting the treatment. That is, for other chronic diseases pharmacological therapies are also part of overall optimal treatment programs, e.g., diabetes, (where nutritional and exercise counseling are important), depression (where cognitive therapy can be important), and for other substance use disorders, such a nicotine dependence (where combining non-pharmaceutical therapies with a pharmacological agent can lead to better outcomes).

And lastly, we recommend that ICER not refer to treatment or abstinence from opioid use as “cure” as it does in Table 4.3 and other places in the report. We realize that by putting the word in quotation marks ICER may be attempting to change the context of the word from a full cure to something else, but we believe that it would be better to avoid the word altogether. SAMHSA states that “OUD is often a chronic medical illness. Treatment isn’t a cure.”^{xiv} And as AHRQ wrote in a recent report, “Like other chronic diseases, opioid addiction cannot be cured but can be effectively treated and managed.”^{xv} Therefore, we assert that as with almost all chronic, biologically-based conditions, people are not cured of OUD any more than they would be cured of diabetes or alcoholism even if they are able to manage their health without the use of medications, e.g., managing diabetes with diet and exercise is not a “cure” any more than having an acceptable hemoglobin A1C level with the use of medications is a “cure.”

Patient Perspectives and Need for Individualization of Care

We completely agree with ICER’s findings from talking to patient groups that “OUD needs to be considered a chronic disease that can affect widely varying populations in terms of age, background, and other factors.”^{xvi} We also completely concur with the statements from patient groups that “treatment is not one-size-fits-all,” and that it is critically important that patients have “access to different treatment options on their road to recovery.”^{xvii}

The need for better access to treatments for OUD is a priority for many organizations, including the FDA, which is devoting resources to both developing better patient-focused outcomes for treating OUD, as well as expanding access to approved treatments, i.e., “Supporting development, access, and adoption of medications for treatment of OUD is a key priority of the U.S. Food and Drug Administration.”^{xviii} Therefore, we urge ICER in its documents and meetings to stress the importance of increasing access to all treatment options currently available for people with OUD, as well as exploring the importance of new treatments – particularly those that may use novel mechanisms of action. Like most complex chronic conditions, there are many avenues for treatment, and individualization of care is crucial for achieving the best outcomes.

In addition, we also want to note that while outside of the scope of ICER’s draft report (and overall process), we share the concerns of many other organizations (including the NIH and the FDA) that better approaches to the treatment of acute and chronic pain are needed to both improve patient care and reduce the use of opioids, which not only have the potential for misuse and OUD, but can cause significant physiological side-effects for many patients.

Why Minimize Methadone?

As part of ensuring that access to all available treatments is recognized by ICER – and anyone who might come across ICER’s work – we believe that the current draft evidence report is deficient in its content by not fully recognizing methadone as a treatment option for OUD. Although, as ICER points out, access to Methadone is currently limited in the U.S., it is also

clearly a part of the treatment guidelines referenced in Section 2.2 of the draft evidence report. By only partially summarizing (i.e., not including those guideline recommendations for methadone as part of MAT), the draft report fails to provide a complete picture of the recommended treatment landscape. And further, while current Federal and state laws and regulations restrict access to MAT with methadone, because those restrictions are not based in medical rationale, they could be changed to enable broader access – as is the case in other countries. And since ICER has stated that its goal is for a “more effective, efficient, and just health care system,”^{xxix} providing information and insights about options for care that could move U.S. health care delivery in that direction would be appropriate. In contrast, excluding methadone from the presentation in the draft evidence report undermines that effort since not only has methadone been shown to be clinically and cost effective,^{xx} but with the tremendous need for individualized care, methadone should not be excluded from evaluations of treatment options by anyone – including payers, clinicians, or patients. We also note that both methadone and buprenorphine are in the WHO’s Model List of Essential Medicines.

Another area of the draft report where methadone is not appropriately incorporated is its essential absence from the discussion of the various treatment options in ICER’s quantitative analysis, i.e., it is not used alongside buprenorphine as a comparator even though the draft evidence report notes that it “dominated” buprenorphine in terms of cost and clinical effectiveness.^{xxi}

And on a technical note, we want to point out that ICER’s description of the access limitations for methadone are somewhat imprecise. Specifically, the statement that that “access to methadone treatment is very limited in the US, as it cannot be legally dispensed through community pharmacies or physician offices, but only as part of highly structured treatment programs that patients must attend daily to receive their dose of medication,”^{xxii} is technically incorrect because clinic visits of six days a week can be used at the start of treatment,^{xxiii} and after a person has been engaged with methadone maintenance therapy for a while (i.e., they are stabilized and felt to be low-risk), weekly (or less frequent) visits may be required.^{xxiv}

Additional Points

- Health care is still two words, not one.
- Footnote #67 has a typographical error – it is from 2015, not 2018.

Conclusions & Recommendations

Patients Rising Now believes that ICER’s draft report about pharmacological treatment options for OUD inadequately reflects society’s perspectives about this public health emergency by its broad use and misuse of terms and phrases that minimize the seriousness of the epidemic and mischaracterize the chronic nature of the illness. Therefore, we request that ICER tighten up the language it uses by indicating that at the current time for OUD, MAT refers to “Medication Assisted Treatment,” and that while recovery is the goal and abstinence is possible, there is no “cure” for OUD.

In addition, as part of our desire that ICER’s reports and statements contribute to solving this crisis, we recommend that methadone be given a more equal place in the report as part of the possible treatment options for OUD. While we recognize that access to methadone is limited in the U.S., that is partially due to government rules and not exclusively because of innate

physiological or pharmacological reasons such as those which would cause the FDA to establish distribution or use restrictions as they have for other medicines with inherent risks. And to the contrary, the FDA – and other parts of the Federal Government, including the U.S. Congress – are committing resources to increase access to all forms of MAT. We believe that these factors for how patients’ perspectives are included in addressing the OUD crisis are important and should be recognized by ICER and others.

Sincerely,



Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

ⁱ <https://www.whitehouse.gov/opioids/>

ⁱⁱ “Where have all the workers gone? An inquiry into the decline of the U.S. labor force participation rate,” Brookings Institution, Krueger, Thursday, September 7, 2017”; “The Economic Burden of Opioid Abuse: Updated Findings,” JMCP, Vol. 23, No. 4 April 2017; “HEALING MICHIGAN An Examination of State-Level Responses to the Opioid Epidemic in Michigan,” Greenberg, University of Michigan Gerald R. Ford School of Public Policy, December 2016.

ⁱⁱⁱ <https://www.samhsa.gov/data/report/2017-nsduh-annual-national-report>

^{iv} Draft Evidence Report, p. 9.

^v Draft Evidence Report, p. 82.

^{vi} Draft Evidence Report, p. 8.

^{vii} Draft Evidence Report, p. 19.

^{viii} “Facing Addiction in America The Surgeon General’s Spotlight on Opioids”, September 2018.

^{ix} Draft Evidence Report, p. 9.

^x “Medications for addiction treatment (MAT)” Letter to the Editor, Am. J of Drug and Alcohol Abuse, Feb, 2, 2018.

^{xi} Draft Evidence Report, Reference #20.

^{xii} Including, “Facing Addiction in America The Surgeon General’s Spotlight on Opioids”, September 2018.

^{xiii} Draft Evidence Report, p. 18.

^{xiv} SAMHSA. TIP 63: Medications for Opioid Use Disorder. Treatment Improvement Protocol (TIP) series, 2018.

^{xv} “Implementing Medication-Assisted Treatment for Opioid Use Disorder in Rural Primary Care: Environmental Scan Volume 1,” 2017.

^{xvi} Draft Evidence report, p. 19.

^{xvii} Draft Evidence Report, p. 81.

^{xviii} <https://www.fda.gov/Drugs/NewsEvents/ucm616564.htm>; and “Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment Guidance for Industry, DRAFT GUIDANCE” FDA, August 2018.

^{xix} Draft Evidence Report, p. iii.

^{xx} Draft Evidence Report, p. 78.

^{xxi} Draft Evidence Report, p. 78 citing “Cost Effectiveness of Injectable Extended Release Naltrexone Compared to Methadone Maintenance and Buprenorphine Maintenance Treatment for Opioid Dependence” Subs. Abus. 2015

^{xxii} Draft Evidence Report, p. 11.

^{xxiii} <https://arshealth.com/methadone-clinics/methadone-clinic-new-castle-de-delaware-addiction-recovery/>,

<https://www.nytimes.com/2018/01/12/nyregion/opioid-addiction-knows-no-color-but-its-treatment-does.html>

^{xxiv} <https://www.samhsa.gov/medication-assisted-treatment/treatment/methadone/>;

<https://americanaddictioncenters.org/methadone-addiction/clinic-facts/>;

https://www.crchealth.com/addiction/heroin-addiction-treatment/heroin-detox/methadone_life/



California Health Benefits Review Program

Garen Corbett
Director

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September 26, 2018

Institute for Clinical and Economic Review (ICER)

Dear Colleagues:

We appreciate the thoughtful and important work undertaken by ICER. Informing policymakers, payers and the public through robust evidence-based analysis is a mission that we share. I am writing regarding ICER's draft *Opioid Disorder Report*. The California Health Benefit Review Program's (CHBRP's) faculty and staff that completed CHBRP's analysis on *Medication-Assisted Treatment* would like to suggest a clarification on how CHBRP's work was cited in ICER's draft report (on Page 10). The ICER draft report currently states:

"A 2018 health technology assessment informing legislation in California that would require MAT for OUD concludes that "there is clear and convincing evidence that medications are more effective than a placebo or no treatment for retention of patients in treatment, abstinence from opioids, and a preponderance of evidence that receipt of medication reduces mortality."

We would suggest a slight adjustment to more accurately characterize our work:

"An analysis of legislation considered by the California State Legislature in 2018 concluded that "there is clear and convincing evidence that medications are more effective than a placebo or no treatment for retention of patients in treatment, abstinence from opioids, and a preponderance of evidence that receipt of medication reduces mortality."

I believe this wording accurately describes our work without labeling it as a "health technology assessment" or any other term of art and without getting the reader bogged down with the particulars of the particular legislation considered by California. This modest clarification ensures that readers understand the specific statutory role that CHBRP plays in supporting California policymakers.

We appreciate CHBRP's work being included in your report, and appreciate consideration being given to this suggestion.

Sincerely,

Garen L Corbett, MS
Director



October 3, 2018

Reiner Banken, MD, MSC
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Massachusetts Biotechnology Council
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RE: Extended-Release Opioid
Agonist and Antagonist
Medications for Addiction
Treatment (MAT) in Patients
with Opioid Use Disorder:
Effectiveness and Value

Dear Dr. Banken,

As President of the Massachusetts Biotechnology Council (MassBio), I am writing to offer comments on the above captioned draft report.

MassBio represents more than 1100-member organizations, including companies, teaching hospitals, and academic institutions, the majority of which are directly engaged in research, development, and manufacturing of innovative products that improve the lives of people around the world. The Commonwealth's vibrant biomedical research and development community, by most accounts, ranks first in the world for medical discovery and innovation.

The opioid crisis has gripped Massachusetts for almost two decades. I have been in my present position for 11 years and, during that time, the number of deaths due to opioid overdose has more than doubled.

Clinical and economic reviews are valuable and have an important role to play in healthcare; however, it is important to note that these analyses have limitations. When discussing opioid use disorder (OUD), in particular, choices around which medication is most appropriate must take the real-life needs and preferences of patients into consideration.

OUD is unlike other diseases, and the cost-effectiveness and value of specific treatment options needs to consider the differences between opioid agonist and antagonist medications. The draft ICER review fails to consider that each treatment is fundamentally different and that patients seeking each type of medication likely vary in their preferences, lifestyles, and where they are in their recovery journey. Each medication may offer unique value to the patient depending on these factors. To suggest that treatments are interchangeable based on cost can have negative consequences on limiting patients' access to these essential medicines.

ALL evidence-based treatments (including VIVITROL) have a role to play in turning the tide of OUD devastation, yet these treatments are significantly underutilized. Recent data reinforce that the conversation need not be about which medication is more effective but instead how we can improve

access to and awareness of all FDA-approved treatments.^{1,2} Only broad awareness and access will allow people with opioid dependence to work with their physicians to find the right treatment plan to meet their evolving needs.

As the only FDA-approved medication for the prevention of relapse for opioid dependence following opioid detoxification, VIVITROL represents a distinct and important medication option for this critical and challenging public health issue. The cost of VIVITROL must be viewed in context and balanced against the cost of *not* offering treatment. Failure to offer such individualized treatment—treatment that the healthcare provider and patient feel is best suited to the needs and expectations of the particular patient at that particular point in time—can have negative consequences on both health outcomes and costs.

At MassBio, we believe that our work and advocacy must be patient-driven. This current opioid epidemic is a true public health crisis. Any analysis must take into account a real-world context. I am concerned that certain aspects of this report do not reflect the realities that patients suffering from OUD face each day as they work toward their recovery.

Sincerely,

A handwritten signature in black ink that reads "RK Coughlin". The letters are cursive and fluid, with the first letters of "RK" and "Coughlin" being capitalized and prominent.

Robert K. Coughlin
President and CEO

¹ Tanum L, Solli KK, Latif ZE, et al. Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. *JAMA psychiatry* 2017;74:1197-205

² Lee JD, Nunes EV, Novo P, et al. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet* (London, England) 2018;391:309-18.