



Abuse-Deterrent Formulation of Opioids in Pain Management: Effectiveness and Value

Draft Background and Scope

September 8, 2016

Stakeholder Input

This draft scoping document was developed with important input from chronic pain patient organizations, and pain and addiction clinical experts who discussed the potential contribution of abuse-deterrent formulations of opioids (ADFs) as part of integrative pain management. Patient organizations stated a desire for continued patient access to opioid therapy for daily function, while also recognizing the need to curb opioid misuse and addiction. ICER also received several comments during the three-week “Open Input” period from specialists in the treatment of chronic pain and in addiction medicine, as well as input from pharmaceutical manufacturers and payers. ICER looks forward to continued engagement with these stakeholders throughout its review of abuse-deterrent formulation of opioids in the setting of pain management.

Background

Opioids are used to treat cases of acute and chronic pain that arise from a variety of causes, ranging from trauma to palliative care for advanced illness. Every year, 100 million people in the United States suffer from pain, 9-12 million of whom have chronic or persistent pain.¹ Although opioid therapy is an important component of pain management for many patients, the addictive and euphoric properties of these drugs make them liable to misuse, abuse, addiction, and diversion.

In an effort to help tackle the public health crisis of opioid dependence, misuse, and addiction that has emerged over the last decade, drug manufacturers have begun to develop abuse-deterrent formulations of these medications. In April 2015, the FDA issued non-binding recommendations encouraging manufacturers to produce abuse-deterrent formulations (ADFs) of opioids. In July 2016, Congress passed the Comprehensive Addiction and Recovery Act (CARA), including incentives to manufacturers to develop these products. In many states, legislation has been introduced to combat the opioid epidemic, often with language

encouraging consideration use of ADFs.² In New England specifically, legislation in Maine and Massachusetts mandates insurance coverage of ADFs.

Multiple ADFs are on the market or in clinical development. ADFs may deter users from chewing, inhaling or injecting opioids based on a variety of approaches including physical/chemical barriers, agonist/antagonist formulations or non-oral delivery systems. Technologies using prodrugs and other novel approaches are also currently under development.³ Questions remain, however, as to the impact of these formulations on rates of abuse, misuse, and diversion, as well as their effects on the most common form of abuse—swallowing a number of intact capsules or tablets to achieve a feeling of euphoria.³

In addition, because ADFs are more expensive than generic opioids, many carriers restrict access to ADFs in their coverage policies through step therapy protocols. Based on clinical input received, this can sometimes act as a barrier to necessary care. Patient groups agree that policies aimed at reducing opioid prescriptions can limit therapeutic and appropriate access to opioids, particularly in primary care and some rural settings.

ICER will review available evidence on the comparative clinical effectiveness and comparative value of ADFs in order to inform decision-making by patients, clinicians and policy-makers, within the context of multiple efforts being undertaken to combat the opioid crisis. ICER's review will also analyze the potential of ADFs to reduce the burden of prescription opioid abuse by evaluating their benefits and market penetration based on coverage policies and legislation.⁴ It is beyond the scope of this evidence review to compare the benefits of ADFs to non-opioid pain management strategies or to addiction treatment programs. Discussion of different strategies for combating the opioid crisis, and the potential role of ADFs, will be part of the policy roundtable discussion at the meeting of the New England Comparative Effectiveness Public Advisory Council on March 23, 2017.

Report Aim

This project will evaluate the health and economic outcomes of abuse-deterrent formulations of opioids in pain management. The ICER value framework includes both quantitative and qualitative comparisons to capture the full range of benefits and harms. This includes evaluating evidence that is not typically captured in the clinical trials, including public health effects, reduction in disparities, innovation and patient experience. These factors are considered in the judgments about the clinical and economic value of the interventions. Detailed protocols for both the evidence review and economic evaluation will be posted to the ICER page on the Open Science website (<https://osf.io/7awvd/>) following the posting of the final version of this scoping document.

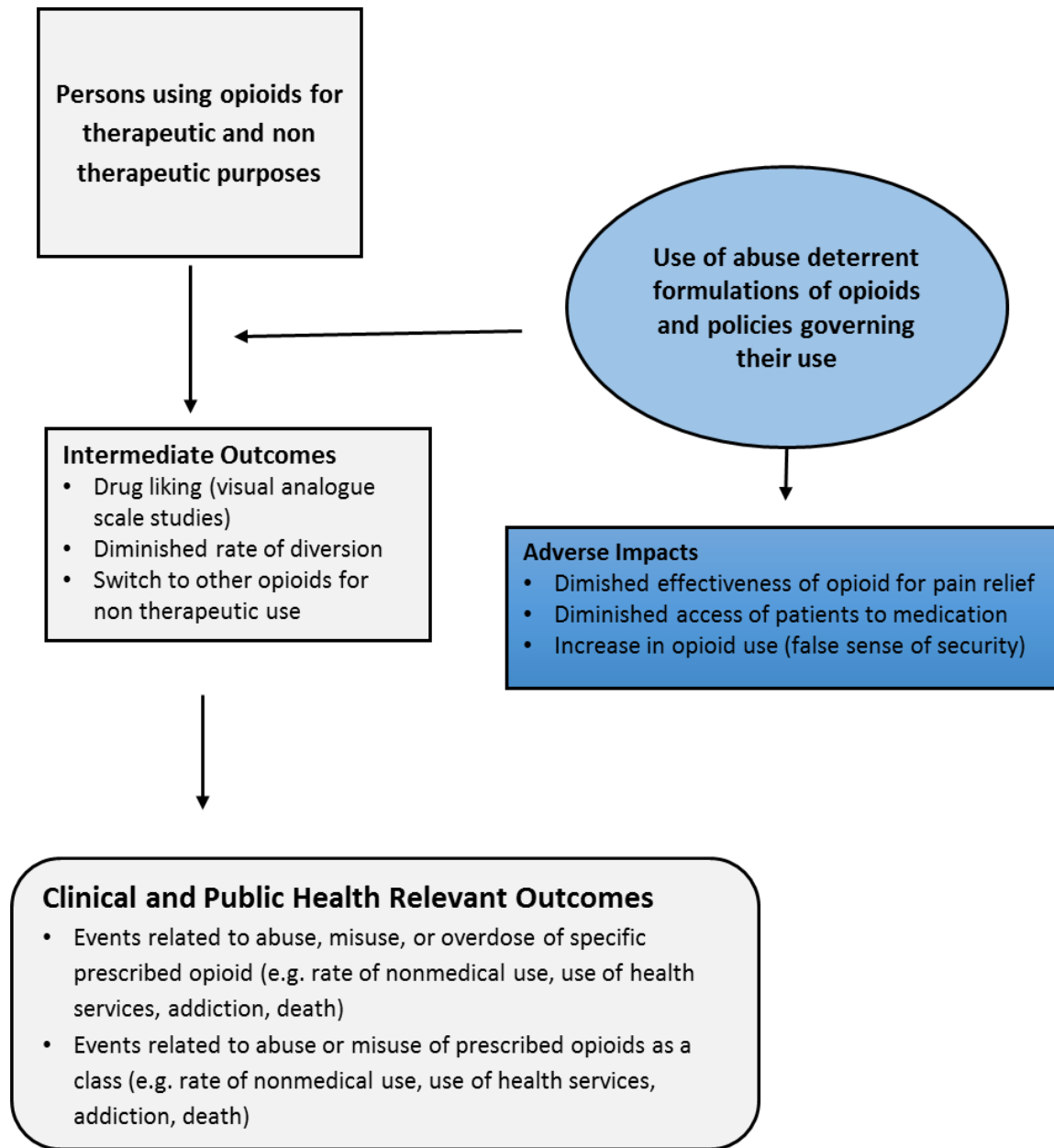
Scope of the Assessment

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. We will conduct a systematic literature review using best practices for search strategy development and article retrieval. Evidence will be culled from randomized controlled trials as well as high-quality systematic reviews; observational studies will be considered, particularly considering the difficulty of conducting randomized controlled trials for non-medical use of opioids. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see <https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/>).

Analytic Framework

The general analytic framework for the evidence review of abuse-deterrent opioids in pain management is depicted in Figure 1. As can be seen in the Figure, most outcomes studied as part of regulatory review (e.g., “drug liking”) are not generated in the pain populations of primary interest, and we therefore expect that most comparisons of clinically- and policy-relevant outcomes (e.g., abuse-related events) will be available only as part of time series studies examining periods before and after introduction of a specific ADF.

Figure 1: Analytic Framework: Abuse-deterrent Formulation of Opioids in Pain Management



Populations

The population of focus for the review will include all persons using opioids for therapeutic (as prescribed and misused) and non-therapeutic use (abuse, addiction). We will also seek evidence on several key subpopulations suggested by stakeholders, including the following:

- Patients with non-cancer chronic pain, stratified by age group where feasible

- Patients with cancer, with particular attention to cancer patients in palliative care
- Recreational drug users
- Persons addicted to opioids

Interventions

The intervention of interest will be introduction and use of abuse-deterrent formulations. Currently, six opioid products have U.S. FDA-approved abuse-deterrent labeling and another three products are expected to reach the market before the end of 2016. However only four products are currently available in the US marketplace. The abuse-deterrent formulations of opioids, approved or nearing approval, that are of interest for this review are listed below by active ingredient:

Oxycodone:

- Oxycontin® (oxycodone extended release, available on the market)
- Xtampza™ (oxycodone extended release, available on the market)
- Troxyca® ER (oxycodone + naltrexone extended release; approved, but currently not available on the market)
- Remoxy™ (oxycodone extended release [Investigational])

Hydrocodone:

- Hysingla® ER (hydrocodone extended release; available on the market)
- Vantrela™ ER (hydrocodone extended release [Investigational])

Morphine:

- Embeda® (morphine + naltrexone extended release; available on the market)
- Morphabond™ (morphine extended release; approved, but currently not available on the market)
- Arymo™ ER (morphine extended release [Investigational])

As the use of ADFs is tightly linked to several components of the policy arena, such as health insurance coverage, state legislation, and professional regulation, the review will also explore any evidence on the impact of such policies on the outcomes of interest.

Comparators

The comparators of primary interest will include non-abuse-deterrent formulations of specific opioids, both in immediate- and extended-release forms.

Outcomes

Clinical and public health relevant outcomes related to use of abuse-deterrent formulations of specific opioids are difficult to measure and to link causally to the intervention. The current FDA regulatory framework includes premarket studies of drug liking (visual analogue scale studies) comparing the ADF to comparator drugs. These randomized controlled studies do not involve patients with pain, but rather drug-experienced, recreational users. They provide some information but are unable to predict the real world potential of abuse deterrence in the broader population.³ The real world impact of ADFs depends somewhat on intermediate outcomes, such a diminished attractiveness of the ADF opioid leading to diminished rate of diversion, a diminished street value of opioid (an incentive for drug diversion) and a switch to other opioids for non-therapeutic use.

To the extent feasible, however, our review will also examine observational studies for key clinical and public health relevant outcomes related to use of abuse-deterrent formulations of specific opioids. These include events related to abuse or misuse, and will be measured both for specific opioids as well as at a class level:

- Non-therapeutic opioid use
- Dependence and/or addiction (new cases and relapse)
- Emergency department and hospital utilization
- Overdose
- Death

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, including inpatient, clinic, and office settings.

Economic Evaluation

We will review the published literature for analyses that have examined the economics of opioids in abuse-deterrent forms. This may include studies of the cost to implement and use ADFs rather than other opioids, analyses of the costs that are potentially offset through the use of ADFs (e.g., reductions in number of addictions or in downstream medical costs), and cost-effectiveness analyses. Our report will summarize what is currently known in the literature about the economic impact of ADFs or specific types of ADF, the strength and validity of that evidence, and where gaps in knowledge still exist.

Data permitting, we will also model the estimated cost-effectiveness of ADFs, using a cost per quality-adjusted life-year (QALY) or cost per life-year framework. Data needed for this evaluation will include:

- Prevalence/incidence of medical and non-medical abuse or misuse when using ADF and non-ADF opioids
- Annual/monthly numbers of prescriptions for ADF and non-ADF opioids
- Per-month cost of ADF and non-ADF opioids
- Direct and indirect health care costs of untreated and treated pain for specified conditions
- Healthcare resource utilization and costs for abuse-related episodes
- Quality of life measures for untreated pain, treated pain, and abuse-related episodes

Key to this analysis will be estimates of the effectiveness of ADFs in delaying or preventing abuse as well as other outcomes that may arise from such abuse (e.g., addiction), and the cost offsets associated with such delay/prevention. The base case analysis will take a health care perspective (i.e., will include only direct health care costs); however, in recognition of the multiple effects ADFs may have on outcomes outside of the health care system, a scenario analysis using a societal perspective will also be included, data permitting.

If sufficient data are not available for a complete cost-effectiveness analysis, we will explore the potential to conduct other types of economic modeling. This may include threshold analyses, e.g., to determine how effective ADFs would need to be in reducing abuse-related episodes to achieve specific levels of cost per QALY at current prices, or cost-consequence analysis, where estimated costs and policy consequences are tabulated separately and not combined in any formal ratio.

We will also explore the potential health system budgetary impact of ADFs over a near-term time horizon, utilizing modeled results and published or otherwise publicly-available information on incremental ADF costs, any cost offsets, and the potential population eligible for ADFs. These budgetary impact analyses will assume specific drug “uptake” rates over a 5-year period for specific populations of interest, given the availability of relevant data and the assumption of different policies being enacted. This analysis will indicate the potential budgetary impact of widespread implementation of ADF use, and allow assessment of any need for managing the cost of such interventions. More information on ICER’s methods for estimating product uptake and calculating potential budget impacts can be found at: <http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf>.

References

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