# Abuse-Deterrent Formulations of Opioids: Effectiveness and Value

***Revised Background and Scope***

**October 13, 2016**

## Stakeholder Input

This scoping document has been revised following input from chronic pain patient organizations, addiction-related community organizations, pain and addiction clinical experts, manufacturers, and payers. Their input influences our view of patient populations and outcomes of interest, as well as the optimal methods for our evidence review and simulation modeling efforts. While this document provides an overview on research methods, detailed protocols for both the evidence review and cost-effectiveness model will be posted to the ICER page on the Open Science website (https://osf.io/7awvd/) in the coming weeks. ICER looks forward to continued engagement with stakeholders throughout the entire project timeline, up to and including the public meeting on March 23, 2016. We have summarized many of the key inputs to the revised scoping document in the following paragraph.

Pain patient organizations stressed continued, affordable patient access to opioid therapy for daily function, while also recognizing the need to curb opioid misuse and addiction. Some pain patients, who needed opioid therapy to manage their pain, saw abuse deterrent opioid formulations (ADFs) as a way to access necessary medication without the stigma of needing controlled substances. All stakeholders considered ADFs as part of a multifaceted strategy to control opioid abuse and addiction and its overall impact on society. Many stakeholders mentioned the potential for positive impacts of existing ADFs on both abuse and its criminal manifestations. Several stakeholders stressed the need for incremental innovation to continuously advance ADFs so that they can better prevent misuse of opioids. The importance of assessing the value of ADFs was widely recognized as an essential step for their rational use.

## 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, and addiction.

In an effort to help tackle the public health crisis of opioid misuse, abuse, 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 of 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]

Due to the higher price of ADFs and uncertainty about their relative impact on abuse, misuse, and diversion, many insurers restrict access to ADFs in their coverage policies through prior authorization and step therapy protocols. Some patient groups are concerned that policies aimed at managing access to ADFs could lead to higher cost sharing for long-term pain medication or added barriers to therapeutic pain relief.

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. It is beyond the scope of this evidence review to compare the benefits of ADFs to other strategies to tackle the abuse of opioids, such as non-opioid pain management strategies, prescription monitoring or 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. We will not look at outcomes related to pain alleviation and tolerability, as ADFs are considered bioequivalent to their relevant non-ADF formulation.[4] Rather, we will primarily focus on evidence comparing the impact of different types of ADFs on opioid misuse and abuse. We will also evaluate the strength of any evidence linking surrogate outcome measures

accepted by the FDA to the true patient-centered and health system outcomes of interest. Finally, we will focus on whether certain types of ADFs have demonstrated more potential to reduce negative outcomes.

We will also search for real world health system evidence evaluating the impact of introducing ADFs into clinical practice. Of interest will be studies that evaluate both short- and long-term changes in rates of misuse, abuse, and diversion. If available, we will be particularly interested in reviewing studies that evaluate the impact of different formulary strategies, such as step therapy, exclusion of non-ADFs, etc., on important outcomes.

The great challenge for our evaluation will be making judgments about how to draw inferences linking evidence from focused clinical trials of ADFs among limited populations to health and economic outcomes for varying patient populations, including patients starting their first opioid prescription, those using opioids recreationally, and those addicted to opioids. Similarly, it will be difficult to extend inferences from limited clinical trials using surrogate outcome measures to real world outcomes, such as diversion and other abuse-related outcomes on society, such as economic productivity, educational loss, and the criminal justice system. Throughout our report, we will call attention to the strengths and limitations of the evidence base, and we will seek to capture broader policy relevant insights through the deliberation with stakeholders that will occur at the public meeting of the New England CEPAC.

**Scope of the Assessment**

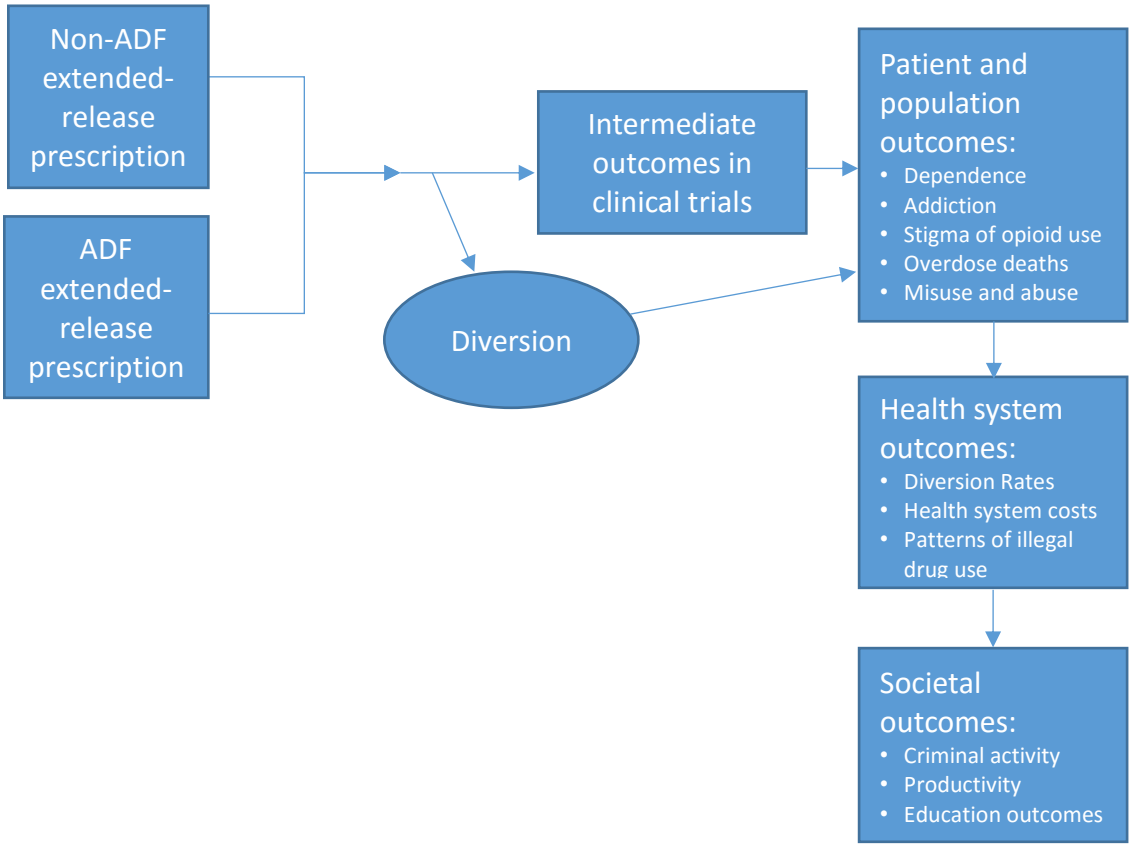
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. We will conduct a systematic literature review using best practices for search strategy development and article retrieval. Evidence 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 is depicted in Figure 1. Measurements of opioid attractiveness are studied as part of regulatory review but are not generated in pain populations. We 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**




## 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).

## Interventions

The intervention of interest will be abuse-deterrent formulations of opioids. Currently, seven opioid products have U.S. FDA-approved abuse-deterrent labeling and another two 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)
- Targiniq® ER (oxycodone + naloxone extended release; approved, but currently not available on the market)

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 describe 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 as appropriate. We will seek to compare the relative impact of the four major types of ADFs currently available on the market (physical barriers; chemical barriers; agonist/antagonist formulations and non-oral delivery systems) on surrogate outcomes. If suitable data are available, the review may include head-to-head comparisons through methods such as network meta-analysis.

Outcomes

*Patient & Population Level*: The impact of ADFs on individual patients will be assessed by evaluation of the following outcome measures, many of which are surrogate outcomes currently being used by the FDA in granting marketing approval.

*Abuse Potential Endpoints*

- Opioid attractiveness scaling (VAS measures (0-100) of drug liking, take drug again, alertness/drowsiness, high, good effects, bad effects, any effects)
- Scores from the Addiction Research Center Inventory (ACRI)
- Cue reactivity
- Tampering

*Misuse and Abuse*

- Overdose death
- Drug switching and illicit drug use
- Physical evidence of misuse/abuse (e.g., positive urine drug screens)
- Self-reported misuse, abuse and tampering

*Health System Level*: To the extent feasible, our review will also examine studies for broader system and public health relevant outcomes related to use of ADFs. These include events related to abuse or misuse, and will be measured both for specific opioids as well as at a class level.

- Health system costs
- Drug loss and diversion rates
- Patterns of illegal drug use

*Societal level*: Where evidence is available, we will also seek to capture the societal impact of ADFs, including outcomes related to the criminal justice system, worker productivity, and education.

The analysis of outcomes will be based on a systematic literature review of peer reviewed publications and on evidence in the grey literature. We do not anticipate that we will pursue any form of primary research on real world evidence, such as analyses of claims data.

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**

The primary purpose of our modeling is to compare the potential benefits of using ADFs (e.g., reduced costs associated with opioid abuse) to the costs of using ADFs (e.g., higher costs for ADFs compared to generic opioids). This analysis will attempt to determine whether the net impact of ADFs is likely to be positive (net benefit) or negative (a net cost). The model will reflect current uncertainty around specific effects of ADF utilization by varying parameter estimates over plausible ranges. This allows us to explore how effective ADFs, at current prices, need to be in reducing abuse to achieve cost neutrality or net savings.

To explore these issues, ICER plans to develop a cohort model of patients newly prescribed with an opioid medication, and to follow those patients under two scenarios – one in which they receive an ADF opioid and one in which they receive a non-ADF opioid. The model will estimate the effect of ADFs on rates of non-medical use and diversion of opioids, and the subsequent impact on health and economic outcomes, such as rates of overdose, emergency department visits and hospitalizations, and drug and overall health care costs. Comparison of the cumulative outcomes for ADF and non-ADF opioids will allow estimates of the impact of ADF utilization under various assumptions.

To the extent possible, we will compare outcomes for each of the ADF opioids listed above to the corresponding non-ADF opioid medication, using the cost for each drug. We will search for drug-specific data on rates and routes of non-medical use for ADF and non-ADF versions of each opioid; in the absence of such data, we will assume a range of plausible values based on data for similar medications. Our base case analysis will be from a health care system perspective, with a five-year time horizon. We do not plan to conduct value-based price benchmark analyses.

Many of the potential benefits of ADFs would not be included in an analysis using a health care system perspective, such as impacts on productivity and criminal justice costs. To the extent that data on the impacts are available, we will also conduct the analysis using a societal perspective to account for factors such as work productivity and criminal justice cost offsets.

We intend to use a cost-benefit framework for this model instead of a cost-effectiveness model that uses measures such as cost per quality-adjusted life-year (QALY) gained. The problem of non-medical use of opioids goes beyond effects on the individual patient's length and quality of life, in a more dramatic and extensive fashion than for most other conditions. In addition, opioids are prescribed for patients with a variety of different conditions, which would complicate the calculation of expected life-year and QALY gains or losses for a "typical" patient.

The model structure will be informed by previously published net benefit models assessing the health and economic outcomes of opioid abuse after the introduction of ADFs.[5,6] Model inputs will be based on a review of relevant published clinical, health economic and grey literature. Key model inputs 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
- Healthcare resource utilization and costs for abuse-related episodes, overdoses and deaths

To inform our model, 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, if any. 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.

We will also explore the potential impact of ADFs over a near-term time horizon at a state-wide level, utilizing modeled results and published or otherwise publicly-available information on the potential population eligible for ADFs and current rates of opioid misuse and abuse within each state in New England (given the availability of relevant data). These analyses will assume specific ADF opioid scenarios that model different policies being enacted. The scenarios to be modeled include: 1) no additional ADF utilization, 2) mandated ADF for all new ER opioid prescriptions (leaving current non-ADF prescriptions as is), 3) switching all ER opioid prescriptions (whether new or existing) to ADF, and 4) the use of screening tools to determine which patients are prescribed ADF or non-ADF opioids. This analysis will indicate the potential budgetary impact of widespread implementation of ADF use, and allow assessment of the cost of different interventions to increase ADF utilization.

## References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