



Abuse Deterrent Formulations of Opioids: Effectiveness and Value

Response to Public Comment

June 28, 2017

Prepared for:



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1	Who?	Section	Comments on ADF Draft	ICER Response
2	Collegium	Overall	it is important and vital to note that it is premature to take a definitive position on the cost consequences of ADFs. Given the very limited data used in the report, data based almost entirely on the impact of only one medication on the problems of abuse, using a very specific ADF approach in a public health arena that is undergoing constant change. There is potentially tremendous impact on abuse suggested even in the report with the problems outlined below, but where cost is concerned we strongly urge against a rush to judgment that could lead to stakeholders becoming dismissive of the enterprise and stop it from gaining traction and utilization to realize a public health benefit.	An economic analysis is essential for supporting decision-making. Uncertainties in evidence and data are taken in account by making informed assumptions and sensitivity analyses.
3	Collegium	Overall	Indeed, we question the overall approach of studying the value – clinical, societal or economic – of component parts of what should be a holistic program of interventions, including ADFs, urine drug testing, prescription drug monitoring programs, psychiatric evaluations, frequent office visits, and smaller supply of medication. These approaches should be delivered in a risk stratified and highly individualized fashion to people with pain, to render opioid therapy safer for the patient and those around them. Their effects are intended to be, and likely would be, synergistic. An analysis that only looks at one aspect of treatment, holds these components up to a standard of eliminating or reducing abuse on their own, which is not a contention of any ADF nor an expectation of clinicians that utilize them, and then is dismissive of their impact. Utilizing diminished assessments of their efficacy in economic analyses is an invalid approach and suggests biases meant to discredit the component approaches to opioid safety and in the end, is socially irresponsible.	We looked for evidence on ADF as part of a program of different interventions. No such evidence is available.
4	The Hospice and Palliative Nurses Association	Overall	Overall barriers to use including cost (high-copays). Additionally, the need for prior authorizations, that which requires a clinician’s time (i.e. nurses) may not be factored into the overall cost, but has an impact on productivity and patient care.	We have incorporated this comment into the section on Other Benefits and Disadvantages. We are not able to incorporate barriers such as high co-pays or cost of clinician time to request for prior authorizations into the model.

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5	The Hospice and Palliative Nurses Association	Overall	The Hospice and Palliative Nurses Association (HPNA) supports the findings of the ICER report that while ADFs have the potential to reduce the incidence of opioid abuse, the overall costs to the healthcare system will be high. Although the members of HPNA are concerned about misuse of opioids and the tragedy of deaths associated with opioid misuse, the mission of the organization is to provide excellent pain and symptom control to those with life-threatening illness. The increased cost of ADFs, to society and in the form of increased co-pays for individual patients, is of great concern in the provision of care to those with limited resources. Furthermore, incomplete evidence surrounding the benefits of ADFs strengthens concerns regarding widespread adoption of ADFs as standard of care.	Thank you for the comment.
6	The Hospice and Palliative Nurses Association	Overall	The Hospice and Palliative Nurses Association supports other interventions often cited to address the deaths associated with opioid misuse including careful opioid prescribing practices, availability of naloxone and increased access to medication assisted treatment (MAT).	Thank you for the comment.
7	Anthem	Overall	Anthem fully supports measures aimed at limiting prescription drug abuse and overprescribing. As part of this effort, we agree with those whom state that the abuse-deterrent potential of these “abuse-deterrent” formulation (ADF) opioids has yet to be proven.	Thank you for the comment.
8	Anthem	Overall	We also applaud ICER for analyzing this issue as part of the nationwide public health crisis, particularly given the significant gap between the need for substance use disorder (SUD) treatment and availability and/or accessibility within the Medicaid population must be further considered; Medicaid is a critical tool in the fight especially at the state level. However, we also agree with the questions posed by UPMC researchers and others regarding whether the premium and budget impact spent on these agents could be better used for broader improvements in other areas.	Thank you for the comment.
9	Purdue	Overall	Above all, do no harm. We urge ICER to return to the scientifically defensible economic model that followed their published process and rightly considered reductions in the abuse and diversion of prescription medicines. Both are well supported in the scientific literature. We also encourage ICER to apply their new value framework, and fulfill their promise to include broader public health considerations and societal costs in their review and model.	Diversion has always been included in a scenario analysis in the report. Societal costs have been added to the model in a separate scenario analysis for the report revision.

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10	NADDI	Overall	In short, I believe that abuse deterrent formulations of opioids (ADFs) can interrupt the “abuse trajectory” for these medications by preventing manipulating for nasal and intravenous abuse. This is true whether the drug is obtained by prescription or is diverted to an unintended user. NADDI supports expanding access to ADFs in order to reduce prescription drug abuse and diversion.	The concept of an abuse trajectory that can be interrupted through ADFs is often referred to, but little evidence is currently available to support this concept.
11	AMCP	Overall	AMCP urges ICER to develop a process for incorporating real-world evidence (RWE), patient reported outcomes (PROs), and other forms of new evidence as they become available into the catalog of evidence that informs the economic models and then updating the evidence report accordingly. Furthermore, AMCP urges ICER to consider methodology that would allow for a parallel analysis of ADFs to other preventative measures for opioid misuse as new evidence becomes available.	With its meeting on July 10-11, 2017, the FDA aims to improve postmarket studies by better leveraging existing data sources and methods to evaluate the impact of these products in the real world. We will also discuss how to improve this body of evidence at the policy round table discussion and include recommendations when we release the final report after the public meeting.
12	The Collaborative for Effective Prescription Opioid Policies (CEPOP)	Overall	In short, we believe that abuse deterrent formulations of opioids (ADFs) can interrupt the “abuse trajectory” for these medications by preventing manipulating for nasal and intravenous abuse. This is true whether the drug is obtained by prescription or is diverted to an unintended user. CEPOP supports expanding access to ADFs in order to reduce prescription drug abuse and its consequences.	The concept of an abuse trajectory that can be interrupted through ADFs is often referred to, but little evidence is currently available to support this concept.
13	The Collaborative for Effective Prescription Opioid Policies (CEPOP)	Overall	We strongly urge ICER to either suspend this project until more definitive data can be developed for the new ADF medications or, at a minimum, to reconsider incorporating a fair assessment of the broader societal benefit of these technologies as was performed in Canada.	This analysis is essential for supporting decision-making that is happening on an ongoing basis. Uncertainties in evidence and data are taken in account by making informed assumptions and sensitivity analyses.

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				<p>The ICER model now incorporates societal costs, including those of productivity loss and criminal justice and incarceration, derived from Birnbaum et al., 2011.</p> <p>Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. <i>Pain Med.</i> 2011;12(4):657-667.</p>
14	American Academy of Pain Medicine	Overall	We want to acknowledge the difficulty of conducting a cost analysis of Abuse Deterrent formulations (ADFs) when there is so little data available for an accurate analysis.	We took into account uncertainties in evidence and data by making informed assumptions and sensitivity analyses.
15	American Academy of Pain Medicine	Overall	We recognize a strength of the report is that it reassures those who were uncertain about the effectiveness of the technologies that ADFs have significant potential to reduce harm. To cite the report, "ADFs have the potential to substantially reduce the incidence of opioid abuse relative to non-ADF formulations among patients initially prescribed these drugs." This is an important statement, notwithstanding the fact that the purpose of the report is to putatively provide payers an analysis of the potential net cost, or savings, if ER ADFs were to replace all non ADF ER products.	Thank you for the comment.

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16	Prime Therapeutics	Overall	Prime supports the safe and effective use of opioids for those who need chronic pain management, however we do not believe there is sufficient data to support 100% conversion or mandated ADF opioid coverage at this time and are concerned about costs that might follow if ADF products become coverage mandated.	Thank you for the comment.
17	Prime Therapeutics	Overall	For a patient newly prescribed ADF opioids versus non-ADF opioids, we believe the evidence is inconclusive to demonstrate a reduced abuse risk. We do not believe action should be taken in an attempt to require non-ADF opioids be replaced by ADF opioid products until additional research has been completed.	Changes have been made in the report and to the voting questions.
18	Abuse Deterrent Coalition	Overall	<p>The initial ICER draft model, which followed their published Scoping Document and Model Analysis Plan in 2016 and early 2017, received extensive comment from the scientific community. The most relevant aspects focused on using the experience gained by the conversion of OxyContin from non-Abuse Deterrent Formulation (ADF) to its current abuse deterrent formulation. The model's results showed that ADF OxyContin prevented >7,200 cases of abuse and saved the healthcare system >\$200 million among 100,000 new ADF patients over the course of a 5-year period analyzed.</p> <p>It is profoundly disappointing that the initial systematic and collaborative effort of ICER to holistically, collaboratively and openly review the costs and benefits of ADFs in the final Scoping Document and Model Analysis Plan was undermined during the past two weeks of their review.</p> <p>For eight months, the Abuse Deterrent Coalition (ADC) and its members have worked with the Institute for Clinical and Economic Review (ICER) on their evaluation of ADF of Opioids: Effectiveness and Value.</p>	ICER strives to adopt scientifically sound methodologies in its evidence reviews. We also value the ability to hold ongoing scientific dialogue with stakeholders. However, we repeatedly told stakeholders that any preliminary assumptions and/or results were subject to both further internal and peer review. Based on the feedback we received as well as model validation exercises conducted, we felt the need to modify the model structure and change certain inputs before producing our initial draft report.

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19	Egalet	Background	We would like to make ICER aware that the drug product OXECTA, described in Table 1 was licensed to Egalet in 2015 at which time it was renamed and launched as OXAYDO® (oxycodone HCL) tablets CII; this change is not reflected in your report. The report also incorrectly identifies the aversive agent contained within OXAYDO as niacin. OXAYDO does not contain niacin, but contains the aversive excipient sodium lauryl sulfate. ¹ We would also like to remind ICER that, contrary to the statement on page 5, our product ARYMO® ER (morphine sulfate) extended-release tablets CII, has been commercially available since the end of March and has a registered trademark (ARYMO® ER vs ARYMOTM ER). We kindly request that ICER address these inaccuracies within its draft report.	Corrections have been made to the report.
20	The Hospice and Palliative Nurses Association	Topic in Context	At the current cost, abuse deterrent formulations may not be a viable option for many small hospice programs.	Thank you for your comment. Based on the results of our model, ADF opioids prevent new cases of abuse, but at an additional cost to the health system.
21	The Hospice and Palliative Nurses Association	Topic in Context	Efforts to help clinicians manage pain, (acute, chronic and pain related to serious illness) are important, including the use of opioids. We recognize that people with serious illness may have co-existing chronic pain or previous abuse issues, and that this should be considered in the overall plan for pain management.	Thank you for the comment.
22	The Hospice and Palliative Nurses Association	Topic in Context	Nurses who care for people with serious illness should receive education on the use of pain medications in different populations (culture, different pain conditions etc.) to care for our patients.	Thank you for the comment.

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23	The Hospice and Palliative Nurses Association	Topic in Context	Opioids, adjuvant pain medications, and evidenced based, non-pharmacological interventions (acupuncture for specific conditions) to treat pain are all needed, especially in the care of patients with serious illness. Safeguards to limit availability of opioids, including appropriate prescribing, disposal of medications that are not indicated should be prioritized. This will require education and system changes.	Thank you for the comment.
24	The Hospice and Palliative Nurses Association	Topic in Context	We should be careful to not stigmatize the use of opioid medications that are needed by patients with serious illness; those clinicians who care for this populations should receive education, have palliative and hospice specialty consultation available, and regulatory support to use these medications appropriately.	We agree and discuss the stigma for patients in section 2.5 (Insights Gained from Discussions with Patients and Patient Groups).

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25	Institute for Patient Access	Topic in Context	<p>The ICER report overlooks ADFs’ ability to reduce the conflict between ensuring pain patients’ access to necessary medicine and addressing the problem of opioid abuse.</p> <p>Opioid medications are highly valued by pain patients, particularly chronic pain patients. Due to the opioid addiction crisis, however, legitimate access to these medicines is becoming jeopardized. For example, the Centers for Disease Control (CDC) has issued new, more stringent prescription guidelines. While not mandatory, the guidelines discourage clinicians from prescribing opioids to patients other than pain associated with “active cancer, palliative, and end-of-life care” and then suggest that “the lowest possible effective dosage should be prescribed”.</p> <p>A 2017 survey by the Pain News Network and the International Pain Foundation found that “over 70 percent of pain patients say they are no longer prescribed opioid medication or are getting a lower dose. While reducing opioid prescriptions may have been the ultimate goal of the guidelines, it came with a heavy price: Eight out of ten patients say their pain and quality of life are worse. Many are having suicidal thoughts, and some are hoarding opioids or turning to illegal drugs for pain relief.”</p> <p>These survey results illustrate that pain patients put a high value on having effective pain management drugs available to them. Not having these drugs available can have a significant, negative impact on their quality of life. ADFs challenge the notion that treating pain and curbing addiction must be an either-or proposition. Specifically, they limit situations in which pain patients who live with a person at high risk for diversion might opt to sacrifice needed pain treatment in order to safeguard a family member who is at high risk of abuse.</p> <p>However, once again, ICER’s cost-benefit model does not consider these benefits.</p>	<p>In the report, we mention the need for access to opioids in chronic pain patients. No articles about difficulties in accessing opioids are available in the peer reviewed literature. It would be difficult to incorporate this issue into the model as suggested.</p> <p>Thank you for noting this topic, and we will make sure this is a theme on our policy roundtable</p>
26	NADDI	Topic in Context	<p>The development of abuse deterrent formulations is a scientific approach being taken to reduce illegal street activity of opioid medications. In speaking with and surveying our NADDI law enforcement members at trainings throughout the country, it appears that the rates of diversion of specific opioid medications decreased dramatically after the introduction of reformulated opiates.</p>	<p>The impact of ADFs on diversion is included as a scenario analysis in the model.</p>

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27	NADDI	Topic in Context	While the first generation of abuse deterrent formulations have reduced abuse and diversion, any advances in this technology that would further erode the street value of opioids and maintain access to the individuals who benefit from their relief would be welcomed.	Thank you for the comment. We recognize the evolution in technologies. We present the evidence as it exists currently in the literature. Our panel will vote on key questions regarding the ADFs at our public meeting in July.
28	CLAAD	Topic in Context	As ICER notes, the rise in opioid-related deaths are no longer attributable solely to prescription opioids, but also to illicit opioids, mainly heroin and illegally manufactured fentanyl. For example, between 2014 and 2015, deaths involving illegally-made fentanyl rose from 5,544 to 9,580, a 73 percent increase. Similarly, heroin-related deaths more than tripled between 2010 and 2015, with 12,989 deaths in 2015. Yet, the Draft Report only addresses how ADOs reduce abuse of prescription opioids and ignores the impact ADOs may have in reducing abuse of illicit opioids and heroin.	Evidence available on the links between ADFs and illicit drug use is included throughout the report.
29	CLAAD	Topic in Context	Misuse refers to taking a medication in a manner or dose other than prescribed. Individuals who misuse a medication do not do so with the intent to experience euphoria. For example, individuals may open a pill capsule and sprinkle its contents into their food because they have a hard time swallowing pills. They may not realize the dangers of such activity, including developing a dependence to the medication, or worse, an overdose. ADOs make it harder to manipulate a product and access its active ingredient sooner.[1] Therefore, they reduce the risk of misuse and the progression to more dangerous drugs and reinforcing routes of abuse.[2]	We searched for available evidence on the ADFs impact on progressing from misuse to abuse and spoke with experts in addiction fields. No such evidence is available.
30	Pinney Associates	Topic in Context	For now, as one author of this comment has suggested elsewhere, “prescribers should put the care of their patients first while trying to not fuel harmful use by others,” including the provision of appropriate pain relief medication, information to minimize the risks, harmful use, diversion and overdose, and referral to treatment for substance use disorder.	In the report, we focus on the evidence that evaluates the abuse-potential and real world outcomes of ADFs in comparison to non-ADFs. Considering our focus, we are unable to treat these additional issues more extensively—although we do discuss them in the report.

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31	Pinney Associates	Topic in Context	The data presented from Nelson et al. (2015) on the percent of patients prescribed an opioid who ultimately abuse an opioid suggests a rate of 0.4%, a fairly low rate. Presenting such a calculation would provide important context alongside the data that are already included.	This information has been updated in the report.
32	Pinney Associates	Topic in Context	The report presents data showing that only 7.5% of the global population had “adequate consumption” of opioid analgesics. The Adequacy of Opioid Analgesic Consumption captures availability, not use, suggesting that actual use of prescription opioids for pain relief is likely even lower than 7.5%. This is an important point to include when comparing U.S. prescribing of opioids to other countries.	All figures above 100% are considered adequate consumption. Information added that in 2010, the US had an indicator of figure of 230%. The sentence mentioning the 7.5% of global population having an adequate consumption of opioids has been deleted.
33	Pinney Associates	Topic in Context	While the 2016 Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain rapidly influenced treatment and insurance coverage, the guideline is based on fairly weak evidence and not on peer-reviewed studies. Importantly, the guideline states specifically that it is addressing treatment in primary care, but the limits in the guideline are now broadly being imposed on all prescribers by insurers, likely as a cost-saving measure, when the intended emphasis was to be in the primary care setting. This is inappropriate and quite detrimental to patients with chronic pain conditions treated outside the primary care setting.	This is an important comment. This will be discussed at the Policy Roundtable at our public meeting.

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34	Pinney Associates	Topic in Context	<p>The nuances of language are extremely important when describing the role of the FDA guidance Abuse-Deterrent Opioids — Evaluation and Labeling, which was “finalized” in 2015. As noted by FDA, the guidance provides recommendations, not requirements. It does not establish legally enforceable responsibilities but rather captures the Agency's current thinking on the topic. The guidance frames the related sections as studies “designed to evaluate the abuse-deterrent characteristics of an opioid formulation” and not as data requirements nor mandates. Further the guidance states, "in general, any development program for studying abuse-deterrent technologies should include data from all three categories of studies, there may be exceptions."</p>	<p>Adjustments were made in the wording to address this concern.</p>
35	Pinney Associates	Topic in Context	<p>We note that Category 1 studies should be conducted on the to-be-marketed formulation, and, where applicable, appropriate comparator products should be used (Table 4). Nevertheless, results of Category 1 studies have not been shown to reliably predict outcomes of Category 2 and 3 studies.</p>	<p>The following sentence has been added on page 15: Results of category 1 studies have not shown either to reliably predict outcomes of Category 2 and 3 studies.</p>

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36	Pinney Associates	Topic in Context	Regarding abuse-deterrent labeling, although some Sponsors have submitted real-world studies to support labeling, the products currently on the U.S. market only have Category 1-3 labeling (as described in Table 4 of the draft report). As noted in the draft report (pgs. 40-41), none of the nine products with abuse-deterrent labeling have Category 4 labeling (which requires post-marketing data). However, it is important to note that FDA has yet to present any criteria for what level of evidence would prove satisfactory to the Agency to approve such labeling.	The upcoming work of the FDA on improving category 4 data collection has been mentioned (FDA public meeting on July 10-11, 2017).
37	Pinney Associates	Topic in Context	Regarding Opana ER, which is described as being replaced with an abuse-deterrent formulation in 2012, we note that FDA has never approved abuse-deterrent labeling for the product. The draft report refers to safety issues with the ADF Opana ER and RoxyBond. We raise the possibility that these safety issues may not yet be fully explored and understood, and may be the result of behaviors unrelated to the formulations themselves.	The description of safety issues for Opana has been revised to clearly state that Opana uses abuse-deterrent technologies, but does not have an ADF label.
38	Pinney Associates	Topic in Context	We disagree with the importance of clinical tools to identify pain patients at higher risk of abuse. A large portion of those who abuse opioids have never received an opioid prescription, and abuse among those prescribed an opioid for pain relief may be less than 1%, as suggested in the draft report (Nelson et al., 2015). Therefore, although identifying this small group in the clinical setting may be beneficial, the vast majority of those at risk of abuse would not be detected since they are not in the clinical setting.	We have clarified our language on the absence of evidence on the effectiveness of risk tools. The information on risk of abuse in newly prescribes opioid users has also been updated.

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39	Anthem	Coverage	<p>Anthem’s current practices to curb overprescribing and assist those in need of treatment include a multi-pronged approach.</p> <p>The CDC recommends that opioids should not be the first line or only treatment for patients with chronic non-cancer pain and that clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. Anthem supports global actions to reduce opioid use, include both ADF and non-ADF formulations. To align its own pharmacy benefit management strategies with the March 2016 CDC Guideline for Prescribing Opioids for Chronic Pain, Anthem has taken the following actions:</p> <ul style="list-style-type: none"> • For short-acting opioids, initial prescriptions are now limited to 7 days and individuals can only receive 14 days’ supply in a 30 day period without additional authorization. This CDC alignment does not pertain to individuals treated palliative care setting, including those with cancer, or sickle cell disease. • Anthem has also put in place prior authorization for all long-acting opioids at initiation and continuation of therapy, and has implemented several new retroactive drug utilization review strategies to address concurrent prescribing of opioids with Suboxone, or in combination with benzodiazepines and muscle relaxants. 	<p>Thank you for describing your coverage policies. We summarize the CDC guidelines in our report and describe local initiatives to limit prescription duration and frequency.</p>
40	Analysis Group	CCE	<p>On p.32, the ICER Report states: “In one study by Rossiter et al., which was conducted over a 6 months pre- and 6 months post-reformulation period, the rate of diagnosed abuse among patients primarily on reformulated OxyContin compared with patients that were primarily on the pre-reformulated Oxycontin declined by 23% and 18% among commercially-insured patients and Medicaid patients, respectively (p<0.05).” The Rossiter et al. paper, however, examined the rates of diagnosed abuse among patients with any primary extended-release opioid treatment in the pre-reformulation period, not just OxyContin: “We examined whether rates of diagnosed abuse differed between patients whose primary ERO was reformulated ER oxycodone (in the post-reformulation period) and patients with any primary ERO (in the pre-reformulation period).”¹</p>	<p>We have revised our reporting of the Rossiter et al. study on page 34 of the report.</p>

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41	Daiichi Sankyo	CCE	<p>In the interest of including all valid, pertinent, information, we would like to suggest that you consider adding the following data to Table 9 - Pre-market Studies Evaluating the Intranasal Abuse Potential of ADFs:</p> <ul style="list-style-type: none"> • Mean Take Drug Again VAS scores (Emax): 66.4 for MorphaBond ER-crushed and 76.4 for Morphine Sulfate ER-crushed, P = 0.034. 	We have included the additional data on MorphaBond to Table 8 of the report.
42	Anthem	CCE	<p>Studies have shown that the evidence regarding the effectiveness of “abuse-deterrent” formulas in preventing occurrences of abuse cases remains open for further debate and evaluation, particularly when attempting to understand the complex interplay of these formulations with sociocultural and public health factors. For example, one case study has shown that opioid drug abuse in parts of Indiana led to a sharp rise in incidence of the HIV virus. This HIV outbreak stemmed from areas where opioid abusers changed from OxyContin, a drug that has moved to an “abuse-deterrent” formula, to Opana, an opioid painkiller that does not have an “abuse-deterrent” formula.^[1] In this case, injecting opioids caused a surge in needle sharing, leading to higher rates of HIV infection. Similarly, Hepatitis C infections have nearly tripled between 2010 and 2015, with the highest rates of new infections among young people transitioning from taking prescription pills to injecting heroin. New CDC research published in May 2017 has identified increasing injection drug use – tied to the U.S. opioid epidemic – in rural and suburban areas across the country.^[2] As this situation illustrates, “abuse-deterrent” opioids are not an isolated tool in combating prescription opioid addiction and may lead to unanticipated indirect healthcare outcomes and costs.</p>	<p>Thank you for the comment. We noted some of the safety issues that have been raised with ADF technologies after tampering for intravenous use for Opana in Section 5 of our report. However, we remain uncertain about what this means for other ADFs, particularly ADFs that use similar technologies. We believe there is insufficient evidence to assess the net health impact of ADFs to the broad population of users and abusers of opioids.</p>
43	Pinney Associates	CCE	<p>The ICER report includes a rigorous systematic review methodology with authors noting that they “...conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.” There were several items on the PRISMA checklist that do not appear to be addressed in the text of the draft guidance. More details regarding how these items were addressed, or rationale for why they were not addressed, should be added to the final ICER report:</p> <ul style="list-style-type: none"> • Item 4, Objectives: We could not locate a statement of the questions addressed using PICOS (participants, interventions, comparisons, outcomes, and study design) criteria. 	<p>The systematic review was conducted in accordance with the PRISMA guidelines. However, items 15 and 22 in the PRISMA checklist were not completed because we did not identify any study (ongoing or completed) relevant to our report on clinicaltrials.gov, therefore it was difficult to assess the cumulative evidence</p>

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			<ul style="list-style-type: none"> Item 5, Protocol Registration: We could not locate evidence that the protocol for the systematic review was registered per PRISMA guidelines (e.g., PROSPERO registration, https://www.crd.york.ac.uk/PROSPERO/) Item 10, Data Collection: We could not locate the procedures for extracting data from publications (e.g., forms, number of data extractors, efforts to obtain information from publication authors). Items 15 and 22, Risk of Bias across studies: While risk of bias was addressed within quality ratings for individual studies, it is not clear how risk of bias was assessed, if at all, across the studies. 	<p>for publication bias. We have noted this point as a footnote to the PRISMA checklist table presented on Appendix A1.</p> <p>ICER’s methods are similar to those of AHRQ and GRADE, in that we rate the quality of individual studies but use a generalized approach to evaluate the strength of evidence. We take uncertainties, inconsistencies, and potential bias into account when assigning an ICER evidence rating to the overall body of evidence.</p> <p>Items 4, 5 and 10 were completed. Item 4 - PICOS was described in the background section of the report and in Appendix E (comparative clinical effectiveness supplemental information); Item 5-protocol was not registered in PROSPERO but available at the open science frame work (https://osf.io/e3et9/), future analyses will be registered in PROSPERO consistently; Item 10- we explained the procedures for data collection in Appendix E (comparative clinical effectiveness supplemental information). A sample data</p>

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				collection form was also provided in the published protocol.
44	Pinney Associates	CCE	We disagree with the determination of a C+ for comparative clinical effectiveness of ADFs in opioid naive patients based on “likability” from human abuse potential (HAP) studies. First, HAP studies are generally conducted in recreational abusers, and thus their relevance to an opioid-naive population is uncertain. Secondly, given the broad variability in ratings of whole versus tampered drug, it seems inappropriate to give a broad C+ to the category. It seems that the products that produced 70+% reductions in drug liking would have some benefit if an opioid naive patient attempts to abuse the drug, in that a drug that produced a muted response would be less likely to lead to continued abuse of the drug (i.e., due to its lower reinforcing value).	Thank you for your comment. The evidence ratings have now been modified to distinguish between OxyContin and the other ADFs and are categorized according to patient-level and population-level evidence.
45	Pinney Associates	Controversies and Uncertainties	The draft evidence report states that, “The evidence on the impact of OxyContin reformulation shows a decrease in OxyContin-specific abuse, but also a shift in some cases toward other routes of administration, toward other prescription opioids, and toward heroin.” (This is also described in pages 41-42.) We agree this is a problem, although was to be expected and in fact was predicted. This points to the limitations of ADFs, which were designed to deter abuse of specific opioids, and so address only one part of the problem of opioid abuse. This finding serves to highlight an important public health need, which does not have an easy solution. To stop people from abusing opioids will require years of coordinated efforts to reduce demand for opioids including heroin for the purposes of abuse and reduction in the supply of heroin.	Thank you for the comment. We discuss this in our Executive Summary, Topic in Context, and Controversies and Uncertainties sections.

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46	Pinney Associates	Controversies and Uncertainties	Real-world evidence poses a different kind of challenge. With regard to patient/population-level outcomes, real-world evidence is very difficult to obtain. ICER describes the percent of opioid naïve patients who progress to non-medical use, pointing to the very small percentage who develop problems. To assess the impact of ADF versus non-ADF assignment in a randomized study would require enormous numbers of patients followed over a long period of time, and the study still may not find an impact. We found no prospective studies conducted among inception cohorts that measured real-world incidence of abuse among ADF and non-ADF users. The only study we are aware of examined tramadol and found a small but significant effect compared to hydrocodone.	Thank you for the comment. As noted in the "Controversies & Uncertainties" section, we also did not identify any prospective studies conducted in inception cohorts that measured real-world incidence of abuse among ADF and non-ADF users.
47	Pinney Associates	CCE	The draft report describes a study among Medicare patients which found that the rate of abuse increased non-significantly among continuous users of extended release (ER) oxycodone. The study did not indicate if these patients remained on the reformulated oxycodone because they had a prior history of abuse, which would have created a higher risk of subsequent abuse.	The changes reported among the Medicare population in the study was a small non-significant increase. Further details were not provided.
48	Pinney Associates	CCE	Although limited evidence from most of the time series studies suggest a decrease in Oxycontin-specific abuse and overdose following its reformulation, many of the studies also found a shift towards abuse of other prescription opioids and heroin, suggesting that a single ADF drug likely cannot affect drug abusing behaviors beyond that specific drug.	We agree. This point was discussed in the Controversies and Uncertainties section of the report.
49	Pinney Associates	CCE	It is not clear how findings from the observational study presented on page 27 contributed to the context of the findings from randomized controlled studies. More experimental (hands on) studies have been conducted by Sellers et al. (2013) and Vosburg et al. (2012).	Similar to the experimental premarket RCTs, the prospective cohort study presented on page 27 provides information on the attractiveness of ADFs. This observational study compared the perceived attractiveness of OxyContin before and after its reformulation. As stated in the study selection results section, we excluded references with non-comparative study designs; Sellers et al. (2013) was excluded

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				because it was a single-session study in which the reported endpoints were primarily descriptive in nature. Vosburg et al. (2012) was not considered because the study evaluated an intervention that was not included in the scope of our review.
50	Pinney Associates	Controversies and Uncertainties	We ask ICER to clarify the following sentence, which conflates nonmedical use with addiction. "However, none of the studies in the assessment included addiction as an outcome, so the impact of ADFs on the progression to non-medical use is unknown."	We have removed "so the impact of ADFs on the progression to non-medical use is unknown" from the sentence so it now reads: "However, none of the studies in the assessment included addiction as an outcome."
51	Prime Therapeutics	CCE	We do not believe the evidence analyzed supports a C+ grade. The evidence basis is a survey of "likeability" and makes the assumption that if you like something you will begin abusing it even if after possibly one dose. We believe more evidence should be required for ICER to support a C+ grade defined as "moderate certainty of a comparable, small, or substantial net health benefit with high certainty of at least a comparable net health benefit." Further uncertainty about the evidence is highlighted by the lack of outcome clarity, on page 43 ICER calls the outcome "Risk of Abuse and Addiction" when the last sentence on page 30 states "none of the studies included addiction as an outcome". In addition, the ICER report highlights a quote from the FDA on top of page 41 "None of the nine products approved with abuse-deterrent labeling have actually shown, to FDA's satisfaction, post marketing data that demonstrate reduced abuse in the real world." Therefore, we believe an inconclusive rating is more representative of the current data.	The evidence ratings have been modified to distinguish between OxyContin and the other ADFs.

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52	CLAAD	Other Bens	ADOs may meaningfully deter or lower the risk of illicit drug use.[1] The most common transition pathway from oral opioid abuse to heroin use is: (1) starting with oral ingestion of pills; (2) moving to crushing and insufflation of pills; (3) moving to insufflation of heroin; and finally, (4) injecting prescription medication and heroin.[2] ADOs are designed to make a product more difficult to manipulate or reduce the attractiveness or drug-like qualities of the medication through methods such as physical or chemical barriers, agonist/antagonist combinations, aversion, and delivery systems.[3] Therefore, they can potentially reduce the progression to illicit drugs.[4] ICER's Final Report should include the impact ADOs have in reducing illicit use.	The concept of an abuse trajectory that can be interrupted through ADFs is often referred to, but little evidence is currently available to support this concept.
53	The Collaborative for Effective Prescription Opioid Policies (CEPOP)	Controversies and Uncertainties	1) First, because many of the more advanced ADFs are new to market, the ICER analysis relies largely on the impact of a primitive ADF technology to power the value equation. We believe that the more recently approved and future ADF technologies will yield substantially higher benefits over time unless they are thwarted by a premature analysis that encourages health plans to create barriers to access.	Our analysis is appropriately based on currently available evidence. This current evidence will be presented for deliberation at our public meeting on July 20. Our panel will consider the available evidence, the gaps in evidence, the contextual considerations, and other benefits and disadvantages of ADFs relative to non-ADFs.

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54	Collegium	Model	<p>Costs associated with diversion should not have been removed from the model. Per SAMHSA, nearly 70% of all the opioids used from non-medical purposes are obtained from family or friends. That means that 70% of all the opioids utilized for non-medical purposes were diverted before being ultimately abused. It is for this reason that the FDA Guidance on Abuse Deterrent Opioids states that supportive information for Category 4 post marketing studies may include the impact of an ADF on diversion events. By excluding diversion from the model, ICER has eliminated a key potential benefit of ADFs. In the model as it stands now, even a modest decrease in diversion would help to render ADFs cost neutral.</p>	<p>Diversion is included in the model under a scenario analysis. We reviewed the SAMHSA data as well as other data sources but were unable to arrive at a robust estimate for diversion with ADFs and non-ADFs. We test the economic impact of diversion using ADF and non-ADF opioids and ascertain the relative reduction in diversion required by ADF opioids compared to non-ADF opioids to achieve cost-neutrality. Based on the graph presented for this scenario, stakeholders can identify additional healthcare costs associated with varying percentages of diversion in both cohorts.</p>
55	Collegium	Model	<p>The model presently looks at cases of abuse that are emergent on long acting opioids (LAOs) with and without abuse-deterrent technology. Multiple streams of data and clinical observation suggest that abuse is evident before LAOs are introduced. Starting a patient who is thereby at high risk of worsening abuse on LAOs with abuse-deterrent technology is a risk stratified approach that would bring even more potential cost avoidance and value. Such patients are typically not given ADFs in isolation at these key points in their care. Instead a whole program of clinical interventions is usually started and studying them in isolation is highly artificial as we point out below.</p>	<p>Our attention in the model is focused on long-acting opioids because that is where abuse-deterrent technology has been focused. When sufficient evidence has accumulated on immediate-release ADFs (there is only one FDA-approved form), we may consider a separate analysis.</p>

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56	Abuse Deterrent Coalition	Model	<p>While the systematic review shows substantial evidence of reduced abuse, overdose, death and diversion with the introduction of ADFs, the ICER document seems to misinterpret data on drug switching and route of abuse to draw negative inferences and conclusions.</p> <p>The hurriedly crafted model (only suggested as an outcome as recently as April 17, 2017) and released today was created by ICER without the benefit of a scoping document, analysis plan, public participation or scientific review. The most egregious change: the model removes the benefits of reducing diversion. This is equivalent to saying that a vaccine only benefits the individual being inoculated, and fails to acknowledge the benefits of the prevention of the spreading of the disease to others.</p>	<p>We reviewed several data sources but were unable to arrive at a robust estimate for diversion with ADFs and non-ADFs, in particular because the health-system costs of diversion can extend beyond the opioid in question (i.e., to other opioids or heroin), and these effects are quite challenging to quantify. Diversion has been included in the model under a scenario analysis. We test the economic impact of diversion using ADF and non-ADF opioids and ascertain the relative reduction in diversion required by ADF opioids compared to non--ADF opioids to achieve cost-neutrality. Based on the graph presented for this scenario, stakeholders can identify additional healthcare costs associated with varying percentages of diversion in both cohorts.</p>
57	Abuse Deterrent Coalition	Model	<p>The lack of consideration of the benefits of reduced drug diversion from this newly crafted analysis, a key benefit of ADF, caused the model to reach a conclusion inconsistent with the published literature that ADFs are not cost effective. The model improperly reduces the benefit of abuse avoidance in its analysis by 25%, a number without scientific basis. It uses a market basket analysis of ADFs and non-ADFs, even though there are not ADFs for all molecules (the FDA has even directly stated that it's not appropriate to equate different ADF technologies). These errors and many others could</p>	<p>The change in intervention from using a specific ADF and its non-ADF counterpart to a market-basket approach was made in order to answer our primary questions around the effectiveness of ADFs in preventing abuse relative to non-ADFs with current</p>

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			<p>have been avoided if ICER had followed its own characteristic process of garnering community and scientific input.</p>	<p>widespread use. In an earlier iteration of the model, we adopted a hypothetical non-ADF that isn't available in the current market, and hence does not help stakeholders in appreciating the true benefits of ADFs relative to non-ADFs.</p> <p>The model now uses the 2.818% estimate for the rate of abuse with ADF opioids as cited in the original publication.</p>
58	Abuse Deterrent Coalition	Model	<p>The inclusion of a new state-based model added to the document has not been shared for broad review or comment. Presented with so few details, the model cannot be evaluated, except to observe that the assumption of a wholesale conversion of the entire non-ADF market to ADFs is simply not medically feasible. For example, drugs such as the fentanyl patch do not currently have ADF equivalents, and in that example patients would simply not be switched to a different molecule and route of administration.</p>	<p>Several states have passed laws to require mandatory substitution to ADFs. In an additional twenty states, legislation has been filed. We ran this analysis as a case study to understand the budget impact of switching all ER opioid prescriptions in one state to ADFs.</p>
59	Abuse Deterrent Coalition	Model	<p>In the end, the model violates many of ICER's stated and published principles for this analysis:</p> <ol style="list-style-type: none"> 1. Reducing diversion as an expected benefit of abuse deterrence is removed from the evaluation; 2. Societal costs/benefits are not included despite the availability of published literature; and 3. Confusingly, heroin "switching" is included in the new draft, despite ICER previously stating this is inappropriate in an incident patient model. 	<p>Diversion has been included in the model under a scenario analysis, as discussed previously.</p> <p>In the final report, we have included a modified societal perspective as a scenario analysis. In keeping with ICER's guidelines for economic modeling, our basecase reports cost and health outcomes only from a health system</p>

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				<p>perspective. Our modified societal perspective includes the costs of lost productivity, and criminal justice and incarceration. The inputs for the modified societal perspective were sourced from Birnbaum et al., 2011:</p> <p>Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. Pain Med. 2011;12(4):657-667.</p> <p>Finally, evidence available on the links between ADFs and illicit drug use is included throughout the report. This is a key area of uncertainty that will be addressed at our public meeting in July.</p>
60	Analysis Group	Model	<p>On p.50, the ICER Report states: “For the new user cohort, we included the incidence of abuse for ADF and non-ADF opioids as reported by Rossiter et al. for a commercially insured population.” Note, however, that rates of abuse presented in the Rossiter et al. paper did not account for previous diagnoses, and are therefore better interpreted as prevalence rates, not incidence rates: “The rate of diagnosed abuse was calculated as the percentage of all eligible continuous ERO users with an opioid abuse diagnosis during the relevant 6-month period.”²</p>	<p>The language in the report has now been modified to say “rate of diagnosed abuse.” We have included this as a limitation in our model.</p>
61	Analysis Group	Model	<p>On p.51, the ICER Report states: “Estimates of healthcare resource utilization included annual mean numbers</p>	<p>We have replaced the health care resource utilization</p>

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			<p>of hospitalization days, emergency visits, outpatient visits, rehabilitation facility days, and other visits such as skilled nursing facility visits, sourced from a commercial claims study by Rice et al. (Table 17) that included opioid users from January 2006 to March 2012.” (emphasis added)</p> <p>The Rice et al. paper estimated the excess costs associated with opioid abuse in a commercially insured population.³ However, the study did not require evidence of opioid use at any point. The two patient cohorts consisted of: (a) patients diagnosed with abuse or dependence; and (b) a control cohort of patients with no evidence of opioid abuse or dependence in their claims data history.⁴ In fact, in a subsequent paper using the same data, Shei et al.⁵ showed that approximately 20% of the abuser cohort did not have an opioid prescription prior to their first abuse diagnosis. The authors further discuss that this estimate can be viewed as a lower bound estimate of opioid diversion.</p>	<p>estimates sourced from Rice et al., 2014 with more recent estimates based on a claims analysis done by the Health Policy Commission. The new estimates are restricted to those who have prescriptions for ER opioids.</p>
62	Analysis Group	Model	<p>On p.51 of the ICER Report, Table 17 lists the “[i]ncidence of ADF ER opioid abuse (Oxycontin®)” as 2.542%, with a note stating that this figure was “[c]alculated from point estimate of 2.818% reported in the analysis, by removing the assumption of a 25% decrease in efficacy to account for potential switching to other opioids.”</p> <p>Setting aside the issue of incidence vs. prevalence noted in point (2) above, this adjustment appears to be inappropriate. Table 1 of the Rossiter et al. paper lists the rates of abuse before (3.6%) and after (2.8%) reformulation of OxyContin and calculates a relative reduction of 22.7% in the rate of abuse.⁶ These rates are the actual observed rates in the data, and no adjustment to them is needed. The paper then continues to conduct a modeling exercise, in which the relative reduction is assumed to be only 75% of the observed 22.7%, to account for possible substitution to other abusable opioids among the prevalent cohort. That adjustment, however (which is further examined in a sensitivity analysis), was only implemented in the context of the modeling exercise, and has no bearing on the rates reported in Table 1.</p>	<p>The model now uses the 2.818% estimate for the rate of abuse with ADF opioids.</p>

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63	Analysis Group	Model	<p>On p.52 of the ICER Report, Table 18 report cost inputs for the model. Related to point (3) above, please note that the costs associated with “regular use” are actually associated with the non-abuser cohort in the Rice et al. paper, for which use of prescription opioids was not required. Similarly, the costs listed for “abuse” are those for the abuser cohort, which was selected irrespective of opioid use. It is unclear whether it is appropriate to use these costs in the context of opioid users.</p>	<p>We have replaced the health care resource utilization estimates sourced from Rice et al., 2014 with more recent estimates based on a claims analysis done by the Health Policy Commission. The new estimates are restricted to those who have prescriptions for ER opioids</p>
64	Anthem	Model	<p>The ICER Model compares a hypothetical population of chronic pain patients who were newly prescribed either extended-release (ER) ADF opioids or ER non-ADF opioids. Administering a long-acting ADF opioid to an opioid-naïve patient goes against clinical prescribing guidance from the Centers for Disease Control and Prevention (CDC) and public health agencies. CDC recommends that when opioids are prescribed, physicians should prescribe immediate-release opioids rather than extended-release/long-acting (ER/LA) opioids. Beginning with the lowest effective dose, clinicians reduce risks of opioid use disorder and overdose. Given that the Model conflicts with these enacted guidelines and best clinical practice recommendations, the validity and interpretability of ICER’s conclusion remains uncertain.</p>	<p>The target population in our model is chronic pain patients and our target interventions only include ER opioids and not IR opioids. We understand that pain patients can initially be prescribed IR opioids before they move on to ER opioids. We have modified the language in our report to now reflect chronic pain patients new to extended-release opioids.</p>
65	Anthem	Model	<p>The Cost-Benefit Analysis does not account for cases of opioid abuse that may result from inappropriate initial opioid prescribing. The conclusion suggests approval of ER ADF opioids while illustrating significant increased costs and ambiguous rates of improvements in patient related outcomes, without considering diversion and other indirect costs. Long-term affordability must continue to remain at the forefront when analyzing the use of finite healthcare resources. These cost figures estimated by ICER in aggregate and the state specific examples (see table 21, 27 and 28) may be drastically different if even one or two unaccounted abuse cases persist. Although indirect societal consequences are difficult to quantify, “real-world” implications may invalidate the nominal estimates of benefit derived</p>	<p>We reviewed the SAMHSA data as well as other data sources but were unable to arrive at a robust estimate for diversion with ADFs and non-ADF. Diversion has been included in the model under a scenario analysis. We test the economic impact of diversion using ADF and non-ADF opioids and ascertain the relative reduction in diversion</p>

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			<p>from the ICER's model. Cost calculations should include overprescribing, subsequent abuse and addiction resulting from overprescribing and the cost of other health care resources for treating potential other related conditions which may stem from initial overprescribing practices.</p>	<p>required by ADF opioids compared to non--ADF opioids to achieve cost-neutrality. Based on the graph presented for this scenario, stakeholders can identify additional healthcare costs associated with varying percentages of diversion in both cohorts.</p> <p>In the final report, we have included a modified societal perspective as a scenario analysis. In keeping with ICER's guidelines for economic modeling, our basecase reports cost and health outcomes only from a health system perspective. Our modified societal perspective includes the costs of lost productivity, and criminal justice and incarceration. The inputs for the modified societal perspective were sourced from Birnbaum et al., 2011:</p> <p>Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. <i>Pain Med.</i> 2011;12(4):657-667.</p>

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66	Anthem	Model	<p>The cost-benefit analysis excludes patients suffering from pain related to cancer, especially in palliative and end-of-life circumstances. The status accorded to ADF preparations by ICER’s cost-benefit analysis supports these preparations in the management of chronic pain, which includes treatment of cancer pain; however, this consideration is not fully supported by clinical literature, nor is this fully clarified in the analysis.</p>	<p>Cancer patients may require higher doses of opioids, and may also require IR opioids. Our target population focuses on chronic pain patients requiring ER opioids. Including cancer patients will skew the costs and resource utilization thus not presenting an accurate picture of costs and resource utilization associated with chronic pain alone.</p>
67	Institute for Patient Access	Model	<p>Currently, effectiveness data for ADFs is available only for OxyContin. Instead of using an OxyContin model, however, the ICER report uses a “market basket” ADF model to estimate costs and benefits. It is unclear whether assumptions based on OxyContin studies apply to a market basket of ADFs.</p> <p>Similarly, it is unclear how the results from a model based on a market basket ADF can be applied to any specific ADF drug. For example, the ICER model estimates the cost of opioid drugs using the weighted average cost of the drug in each category (ADF versus non-ADF drugs). The estimate for an ADF opioid is \$11.60 for 90 mg per day. The report then concludes that the weighted average cost needs to decline by 39 percent, to \$7.04 for 90 mg per day, to achieve cost neutrality.</p> <p>Claiming that the weighted average cost of an ADF opioid should be 39 percent lower is not the same as saying that the cost of any specific ADF opioid should be 39 percent lower. Yet this detail could be overlooked, leading health plans to misapply the recommended price reduction in determining their ADF opioids coverage policies.</p>	<p>We haven’t seen any effectiveness data on other ADFs in the published literature. IMS data (on file) shows that the market share of OxyContin among ADFs is currently over 90%. We therefore assumed for this model that ADF effectiveness can be represented by data from OxyContin's effectiveness. However, our cost-neutrality scenario tests what the effectiveness of the market-basket of ADFs should be in order to achieve cost-neutrality. We have added a statement in the report to clarify that the discount required by ADFs to achieve cost-neutrality need not necessarily extend to every ADF on the market.</p>

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68	Institute for Patient Access	Model	<p>There are also specific questions regarding how the ICER report applies empirical results to the cost benefit model. The ICER report uses the results from one oxycodone study (Rossiter et al., 2014), but ignores the results from 14 U.S.-based studies (16 overall) that was also reviewed in the report. These other studies, summarized in Table 11 of the ICER report, found, on average, that abuse deterrent OxyContin reduced the incidence of abuse in the U.S. by approximately 41 percent. This abuse reduction impact is significantly larger than the abuse reduction assumptions used in the ICER model (approximately 30 percent).</p> <p>To the extent that health plans use ICER data to shape and justify their coverage policies, these figures could have the effect of reducing patients' access to ADF opioids. In light of these concerns, ICER should reconsider the cost-benefit model and assumptions used in the report.</p>	<p>The population in the Rossiter study closely matches that included in the ICER model and claims data were used to identify rates of diagnosed abuse. Other studies included for review have significant variability in data sources, population characteristics, and methods of measuring abuse. Owing to these variations, combining estimates of reduction in abuse across these studies was not considered a valid approach to deriving effectiveness of ADFs in reducing the rate of abuse.</p>

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69	Institute for Patient Access	Model	<p>2. ICER’s baseline analysis ignores ADFs’ ability to curb opioid diversion.</p> <p>The ICER report focuses on the abuse and misuse of opioids by patients who are prescribed the medication; however, a large part of the opioid crisis is caused by diversion. The CDC has estimated that “between 25% and 74% of overdose decedents” did not have “a prescription for at least one of the drugs that contributed to their death.” The ICER report itself has noted that “about 50% of people who misused prescription opioids got them from a friend or relative for free”.</p> <p>Studies cited in the ICER report itself found that ADFs can significantly reduce diversion. Severtson et al. (2013) found that OxyContin diversion fell 53 percent in the period immediately following the introduction of the ADF version. By five years after the introduction Severtson et al. (2016) found that diversion fell by 89 percent. In the other diversion study reviewed by ICER, Coplan et al. (2016), diversion rates declined by 66 percent.</p> <p>By reducing diversion, ADFs could also reduce the costs that diversion generates. To ignore these savings, therefore is to ignore one of ADFs’ foremost potential benefits – significantly understating abuse-deterrent opioids’ overall value.</p> <p>While the model limitations section explains that ADFs impact on diversion is not considered, the exclusion bears pointing out again. Ignoring a crucial potential benefit of ADFs can only result in an assessment that underestimates the therapies’ value to patients, their families and communities, and public health.</p>	<p>We reviewed the SAMHSA data as well as other data sources but were unable to arrive at a robust estimate for diversion with ADFs and non-ADFs. Diversion has been included in the model under a scenario analysis. We test the economic impact of diversion using ADF and non-ADF opioids and ascertain the relative reduction in diversion required by ADF opioids compared to non-ADF opioids to achieve cost-neutrality. Based on the graph presented for this scenario, stakeholders can identify additional healthcare costs associated with varying percentages of diversion in both cohorts.</p>

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70	Institute for Patient Access	Model	<p>3. ICER’s cost model omits expected savings that ADFs generate with respect to the social costs of the opioid addiction crisis.</p> <p>As exemplified by the analytic framework described in Figure 1, and in the model limitations sections, ICER recognizes that the opioid crisis imposes costs on society beyond the health care costs associated with patient abuse and misuse. These additional problems include increased criminal activity, increased criminal justice costs, reduced workplace productivity, and adverse impacts on education outcomes.</p> <p>These costs are substantial.</p> <p>The oft-cited study by Birnbaum (2011) estimated the total costs of opioid abuse were \$55.7 billion in 2008, which comprised criminal justice costs (\$5.1 billion), workplace costs (\$25.6 billion), and health care costs (\$25.0 billion). An updated study in 2016 by the National Center for Injury Prevention and Control estimated that these costs have grown to \$78.5 billion, with only one-third associated with increased health care expenses.</p>	<p>In the final report, we have included a modified societal perspective as a scenario analysis. In keeping with ICER's guidelines for economic modeling, our basecase reports cost and health outcomes only from a health system perspective. Our modified societal perspective includes the costs of lost productivity, and criminal justice and incarceration. The inputs for the modified societal perspective were sourced from Birnbaum et al., 2011:</p> <p>Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. <i>Pain Med.</i> 2011;12(4):657-667.</p>

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71	Purdue	Model	After seeing the economic model results that were based on 8 months of scientific feedback and collaboration, ICER changed the basic model structure in the final 2 weeks before the ADF opioid draft report release, attributing those changes to anonymous “feedback.”	ICER strives to adopt scientifically sound methodologies in its evidence reviews. We also value the ability to hold ongoing scientific dialogue with stakeholders. However, we repeatedly told stakeholders that any preliminary assumptions and/or results were subject to both further internal and peer review. Based on the feedback we received as well as model validation exercises conducted, we felt the need to modify the model structure and change certain inputs before producing our initial draft report.
72	Purdue	Model	ICER removed reductions in diversion of prescription medicines as a model input, despite overwhelming scientific feedback that it is a key benefit of ADFs. The rationales provided by ICER for removing diversion from the model do not stand up to scientific scrutiny.	We reviewed several data sources but were unable to arrive at a robust estimate for diversion with ADFs and non-ADFs, in particular because the health-system costs of diversion can extend beyond the opioid in question (i.e., to other opioids or heroin), and these effects are quite challenging to quantify. Diversion has been included in the model under a scenario analysis. We test the economic impact of diversion using ADF and non-ADF opioids and ascertain the relative reduction in diversion required by ADF

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				<p>opioids compared to non--ADF opioids to achieve cost-neutrality. Based on the graph presented for this scenario, stakeholders can identify additional healthcare costs associated with varying percentages of diversion in both cohorts.</p>
73	Purdue	Model	<p>ICER changed the cost-benefit evaluation from an OxyContin-specific model to a “market basket” model. The OxyContin-specific model was previously justified because nearly all published ADF real world literature measured changes in abuse and diversion that occurred after OxyContin reformulation. This market basket approach is indefensible.</p>	<p>The change in intervention from using a specific ADF and its non-ADF counterpart to a market-basket approach was made in order to answer our primary questions around the effectiveness of ADFs in preventing abuse relative to non-ADFs with current widespread use. In an earlier iteration of the model, we adopted a hypothetical non-ADF that isn’t available in the current market, and hence does not help stakeholders in appreciating the true benefits of ADFs relative to non-ADFs.</p>
74	Purdue	Model	<p>ICER extrapolated the real-world benefits associated with OxyContin to all ADFs, counter to previous ICER statements and those of the FDA that there is no evidence that substantially different technologies (eg, crush resistant polymers versus naloxone combinations) will have the same effects on real world outcomes.</p>	<p>OxyContin is the only ADF with real-world effectiveness data available, and it also commands >90% of the market share among ADFs. We did vary the level of effectiveness in a sensitivity analysis, and found that even if ADFs completely eliminated abuse in the 100,000</p>

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				patient cohort, their use would cost approximately \$113 million over five years relative to non-ADFs (Figure 8). We do note as a limitation that current data are limited to OxyContin.
75	Purdue	Model	ICER was aware that increasing the difference in ADF/non-ADF pricing would reverse the model conclusion. Their market basket pricing method, which was not elucidated in the report, maximized this difference. Applying market basket prices to OxyContin-specific benefits violates accepted modeling norms.	The market-basket price was derived from real world evidence on utilization and costs and has been described in the report.
76	Purdue	Model	The ICER evaluation is modeled from a payer perspective. Payers do not make formulary decisions nor negotiate rebates for market baskets; they do so for individual drugs. As such, the model is not relevant to real-world payer decision making.	When effectiveness (in preventing abuse) data becomes available for ADFs other than OxyContin, payers can adopt this model to assess value of the new drugs when making formulary decisions.
77	Purdue	Model	On April 10th, the ICER team confirmed that their economic model, which followed the publicly available Scoping Document, Model Analysis Plan and Preliminary Results, found that the reformulation of OxyContin prevented >7,200 cases of abuse and saved commercial payers >\$200 million over 5 years. ICER subsequently changed this model, disregarding their published process for garnering scientific input. Those changes allowed ICER to reach what seems to be a predetermined conclusion by its Chief Scientific Officer, that ADFs are not cost effective.*	ICER strives to adopt scientifically sound methodologies in its evidence reviews. We also value the ability to hold ongoing scientific dialogue with stakeholders. However, we repeatedly told stakeholders that any preliminary assumptions and/or results were subject to both further internal and peer review. Based on the feedback we received as well as model validation exercises conducted, we felt the need to modify the model structure and change

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				certain inputs before producing our initial draft report.
78	Egalet	Model	<p>Egalet believes that one of the major limitations of the ICER model is that it only addresses the economic impact of abuse-deterrent formulations (ADF) of opioids on the “intended” population (patients prescribed opioids) and fails to consider the potential impact on people who abuse prescription opioids without a prescription, or the “unintended population”.</p> <p>Epidemiologic data point to the fact that opioids and the dynamic of diversion are inextricably linked and one cannot evaluate the impact of opioids without including the impact of diversion in the equation. Although your report states that diversion was not evaluated in the primary analysis due to “lack of data on effects of ADF use on drug-switching behavior among abusers obtaining through diversion” the exclusion of some diversion consideration in the primary analysis results in a model that only reflects part of the value of ADF opioids and handicaps the economic analysis. ADF opioids are designed to make the products more difficult to abuse and/or less liked; this would potentially decrease their street value and make these products less appealing for diversion.</p>	<p>We reviewed the SAMHSA data as well as other data sources but were unable to arrive at a robust estimate for diversion with ADFs and non-ADF. Diversion has been included in the model under a scenario analysis. We test the economic impact of diversion using ADF and non-ADF opioids and ascertain the relative reduction in diversion required by ADF opioids compared to non--ADF opioids to achieve cost-neutrality. Based on the graph presented for this scenario, stakeholders can identify additional healthcare costs associated with varying percentages of diversion in both cohorts.</p>
79	Egalet	Model	<p>ICER utilized a fixed value for effectiveness in deterring abuse across all ADF opioids and routes of abuse. Utilizing a single effectiveness value for abuse-deterrence across all ADF opioids regardless of route of abuse considerations calls into question the output of the cost-benefit model.</p>	<p>In the absence of robust data on effectiveness (in preventing abuse) for all ADFs, and with Oxycontin's current market share, ICER felt it was reasonable to adopt Oxycontin's effectiveness for all ADFs. We did not identify robust evidence on effectiveness estimates for different routes of abuse. We did vary the level of effectiveness in a sensitivity</p>

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				analysis, and found that even if ADFs completely eliminated abuse in the 100,000 patient cohort, their use would cost approximately \$113 million over five years relative to non-ADFs (Figure 8).
80	Egalet	Model	Also, ICER has chosen to base its cost-benefit model on a hypothetical cohort of only opioid-naïve patients with chronic non-malignant pain. The use of this limited cohort impacts the generalizability of the model. The population of chronic pain patients at risk for abuse and contributing to abuse is broader and includes patients who have been previously treated. ICER also states “We did not include cancer patients in the model, as there may be different considerations when determining appropriate pain management for these patients (e.g., focus on immediate-release rather than ER opioids).” The clinical data and rationale to support this statement are unclear. The National Comprehensive Cancer Network ⁴ , American Society for Clinical Oncology ⁵ , and European Society of Medical Oncology ⁶ guidelines for the management of chronic pain indicate that, in appropriate patients, clinicians should prescribe extended-release opioids for the management of chronic pain with the use of immediate-release opioids for the alleviation of breakthrough pain. Patients prescribed an opioid for chronic malignant pain conditions such as cancer represent another significant population at risk for opioid misuse, abuse, and diversion. Excluding the entire population of cancer patients from the model limits the interpretability of the model results.	Cancer patients may require higher doses of opioids, and may also require IR opioids. Our target population focuses on chronic pain patients requiring ER opioids. Including cancer patients will skew the costs and resource utilization thus not presenting an accurate picture of costs and resource utilization associated with chronic pain alone.
81	Egalet	Model	The conclusions drawn from the results of the cost-benefit model do not acknowledge the broad implications and dynamics of an evolving opioid landscape. For example, it is expected that approval of new ADF opioids, the passage of new federal and state legislation, and changes in prescription habits will impact the cost-effectiveness of ADF opioids. Acknowledging this in your cost-benefit summary will help contextualize the results.	This has been acknowledged in the revised report.

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82	NADDI	Model	<p>Because many of the more advanced ADFs are new to market, the ICER analysis relies largely on the impact of one ADF technology to power the value equation. I believe that the more recently approved and future ADF technologies will yield substantially higher benefits over time unless they are thwarted by a premature analysis that encourages health plans to create barriers to access.</p>	<p>In the absence of robust data on effectiveness (in preventing abuse) for all ADFs, and with Oxycontin's current market share, ICER felt it was reasonable to adopt Oxycontin's effectiveness for all ADFs. We did not identify robust evidence on effectiveness estimates for different routes of abuse. We did vary the level of effectiveness in a sensitivity analysis, and found that even if ADFs completely eliminated abuse in the 100,000 patient cohort, it would cost approximately \$113 million over five years relative to non-ADFs (Figure 8).</p>

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83	NADDI	Model	<p>The ICER decision to marginalize societal benefits from ADFs in reducing harms arising from prescription opioid diversion ignores this enormous dimension of the epidemic. A recent study^[1] published by the Canadian Health Policy Institute estimates that if all prescription opioids in Canada were abuse deterrent formulations, non-medical use of these drugs would be discouraged and would reduce associated societal costs by an estimated range of savings between \$140 million and \$4 billion annually. This benefit of ADFs must be included in evaluating their potential.</p>	<p>In the final report, we have included a modified societal perspective as a scenario analysis in keeping with ICER's guidelines for economic modeling, wherein our basecase will report cost and health outcomes only from a health system perspective and societal perspective will be included as a scenario analysis. Our modified societal perspective includes the costs of lost productivity, and criminal justice and incarceration. The inputs for the modified societal perspective were sourced from Birnbaum et al., 2011:</p> <p>Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. <i>Pain Med.</i> 2011;12(4):657-667.</p>
84	AMCP	Model	<p>AMCP believes economic models should be made available to managed care pharmacists and other health care providers to download, audit, and test the model by modifying the assumptions of the model based on their perspectives and their covered populations.</p>	<p>As noted in ICER's value framework update for 2017-2019, we are actively pursuing approaches to increase model transparency and allow for some level of end-user deliverable. The detailed explanation in the ICER report on the model structure, inputs, and</p>

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				assumptions is already provided so that any stakeholder wishing to replicate the model can do so.
85	AMCP	Model	In addition, AMCP urges ICER to consider a process by which stakeholders could be given an opportunity to test and validate the economic models when in draft format and provide feedback on how they can be improved prior to finalization. With this approach, the economic models are more likely to reflect current real-world conditions.	Thank you for your recommendation. We will follow up on this process request separately from this review.
86	AMCP	Model	AMCP recommends that ICER consider a free licensing process that would allow ICER to evaluate the qualifications of the requestor prior to releasing the economic model, similar to the approach used by the National Institute for Health and Care Excellence (NICE). Many managed care pharmacists have considerable expertise in pharmacoeconomics and therefore, AMCP recommends that ICER work with AMCP and other stakeholders to develop the list of criteria to use in selecting eligible recipients of the economic models and the creation of a process to minimize barriers to access.	Thank you for your recommendation. We will follow up on this process request separately from this review.

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87	CLAAD	Model	<p>ICER should include data and analysis on how ADOs reduce diversion and misuse of opioid medications in its Final Report.^[1] Diversion refers to the transfer of a legally obtained controlled substance from the individual for whom it was prescribed to another person for illicit use. As ICER notes, diversion of opioids may represent the true cost to the health system. Yet, ICER does not consider the reduction in diversion in its analysis. ADOs reduce the risk of diversion because they are harder to abuse and, therefore, have a lower street value. Available data on reformulated ER oxycodone shows a reduction in diversion by almost 90 percent.^[2]</p>	<p>We reviewed the SAMHSA data as well as other data sources but were unable to arrive at a robust estimate for diversion with ADFs and non-ADFs. Diversion has been included in the model under a scenario analysis. We test the economic impact of diversion using ADF and non-ADF opioids and ascertain the relative reduction in diversion required by ADF opioids compared to non-ADF opioids to achieve cost-neutrality. Based on the graph presented for this scenario, stakeholders can identify additional healthcare costs associated with varying percentages of diversion in both cohorts.</p>

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88	CLAAD	Model	<p data-bbox="669 191 1587 542">Societal Costs</p> <p data-bbox="669 264 1587 542">The Draft Report does not account for the societal benefits of ADOs in its cost-benefit analysis, citing a lack of data. Reducing opioid abuse in the U.S. can have a significant impact on society as a whole, including reducing lost worker productivity; the transmission of serious infectious diseases, such as HIV and hepatitis C; criminal activity; and fatal overdoses. For example, illicit drug use, which has increased with the opioid overdose epidemic, currently costs the country an estimated \$193 billion a year in public health, crime, and lost productivity expenses.</p> <p data-bbox="669 586 1587 899">CLAAD requests that ICER review several recent studies that demonstrate the societal benefits of ADOs. According to a 2014 study of reformulated extended release (ER) oxycodone, estimated societal cost savings totaled \$476 million in the workplace, including \$209 million in reductions in lost earnings from premature deaths, \$181 million in lost wages and employment, \$34 million in excess medically related absenteeism costs, \$15 million in reductions in excess disability costs, and \$38 million in presenteeism costs. The study also estimated an additional \$96 million in cost savings to the criminal justice system.</p> <p data-bbox="669 943 1587 1107">A 2017 report by the Canadian Health Policy Institute (CHPI) estimates that if all prescription opioids in Canada were ADOs, societal costs would be decreased by \$140 million to \$4 billion annually. Likewise, a 2013 U.S. study found ADO use in the U.S. can save third-party payers up to \$1.6 billion per year. Such data is vital to a quality a cost-benefit analysis of ADOs.</p>	<p data-bbox="1608 191 2001 829">In the final report, we have included a modified societal perspective as a scenario analysis in keeping with ICER's guidelines for economic modeling, wherein our basecase will report cost and health outcomes only from a health system perspective and societal perspective will be included as a scenario analysis. Our modified societal perspective includes the costs of lost productivity, and criminal justice and incarceration. The inputs for the modified societal perspective were sourced from Birnbaum et al., 2011:</p> <p data-bbox="1608 873 2001 1107">Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. <i>Pain Med.</i> 2011;12(4):657-667.</p>

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89	The Collaborative for Effective Prescription Opioid Policies (CEPOP)	Model	2) Second, the ICER decision to marginalize societal benefits from ADFs in reducing harms arising from prescription opioid diversion ignores this enormous dimension of the epidemic. A recent study published by the Canadian Health Policy Institute estimates that if all prescription opioids in Canada were abuse deterrent formulations, non-medical use of these drugs would be discouraged and would reduce associated societal costs by an estimated range of savings between \$140 million and \$4 billion annually. This benefit of ADFs must be included in evaluating their potential.	<p>In the final report, we have included a modified societal perspective as a scenario analysis in keeping with ICER's guidelines for economic modeling, wherein our basecase will report cost and health outcomes only from a health system perspective and societal perspective will be included as a scenario analysis. Our modified societal perspective includes the costs of lost productivity, and criminal justice and incarceration. The inputs for the modified societal perspective were sourced from Birnbaum et al., 2011:</p> <p>Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. <i>Pain Med.</i> 2011;12(4):657-667.</p>
90	Pinney Associates	Model	Table 15. Key Assumptions. This table includes assumptions that are not supported by studies, which is problematic as it results in costs that can be inflated. For example, the assumption that the rate of discontinuation of abuse in both cohorts is the same is hard to understand.	We found no published evidence on the rate of ceasing to abuse in general, nor any information on rates that differ for ADFs and non-ADFs. After consulting with clinical experts and stakeholders, we concluded that a 10% 'cessation of abuse' assumption was reasonable. In the absence

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				<p>of any differential data, we felt it reasonable to apply the same assumption to both cohorts. We varied this assumption in a one-way sensitivity analysis, and since its impact on the results isn't significant, we think that assigning different rates of ceasing to abuse to each cohort, unless drastically different, will not impact the model results significantly.</p>
91	Pinney Associates	Model	<p>Although admittedly not health economists, we struggled with the underlying assumptions of the Scenario beginning on page 57. A significant concern is the model is the focus on overdose deaths and does not account for abuse among those using diverted drug, which results in significant medical costs. For those who abuse prescription opioids, the most abused drugs are immediate release (IR) opioids that do not have ADF properties. Examining ADFs exclusively through a financial lens will point to increased costs, but we suggest that this is true for most advances in healthcare. As a society, we must answer the question: How much is it worth to prevent someone from dying from a drug overdose? Harm reduction has costs. The key question is -- are the individual and public health benefits worth the extra costs?</p>	<p>The scenario on diversion accounts for abuse among those who have received the opioids through non-prescription routes. This scenario also attributes costs to diverted abuse. Since we do not know what this diversion estimate currently is in the real-world, nor can we reliably estimate the countervailing effects of reduced diversion of prescription opioids and increased use of other opioids, the scenario assumes different percentages of risk of diversion for ADF and non-ADF opioids.</p>

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92	American Academy of Pain Medicine	Model	the study fails to consider the societal cost, not just the insurance cost: loss of productivity, death, crime, law enforcement, and incarceration of both the patient and non-patient populations. The cost of Neonatal Abstinence Syndrome and foster care for children whose parents died of overdoses should also have been included, although this is difficult data to obtain. The purpose of evaluating ADF technology must be broader than just a financial tradeoff for payers.	<p>In the final report, we have included a modified societal perspective as a scenario analysis in keeping with ICER's guidelines for economic modeling, wherein our basecase will report cost and health outcomes only from a health system perspective and societal perspective will be included as a scenario analysis. Our modified societal perspective includes the costs of lost productivity, and criminal justice and incarceration. The inputs for the modified societal perspective were sourced from Birnbaum et al., 2011:</p> <p>Birnbaum HG, White AG, Schiller M, Waldman T, Cleveland JM, Roland CL. Societal costs of prescription opioid abuse, dependence, and misuse in the United States. <i>Pain Med.</i> 2011;12(4):657-667.</p>
93	American Academy of Pain Medicine	Model	Another concern is that the study only projects the impact for people who are initiated on opioids. Since there is an increasing number of people denied access to opioids, whether reasonably or not, many of these patients are seeking drugs on the street (https://www.ncbi.nlm.nih.gov/pubmed/28514234). It would seem that much of the benefit of ADFs is for the population currently using opioids but not prescribed opioids, as well as for new initiates.	In order to address this, we have included a scenario analysis on diversion in the report. However, we do not have any reliable estimates of patients switching to other opioids or heroin to abuse when unable to abuse ADFs.

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94	American Academy of Pain Medicine	Model	<p>ADFs are meant to help protect a population for which the drugs are not intended (those who are not patients). Therefore, the fact that it doesn't include the impact of diversion on cost and public health is a major omission in the report's methodology. It renders the results incomplete and biased against the potential benefits of ADFs and their ability to reduce harm for society. If the Institute elects not to include the impact of diversion in the primary conclusion, there should be a secondary conclusion that includes all of the factors listed above with the caveats needed to qualify the analysis.</p>	<p>We have included the impact of diversion in the model as a scenario analysis. The scenario on diversion accounts for abuse among those who have received the opioids through non-prescription routes. This scenario also attributes resource utilization costs to diverted abuse. Since we do not know what this diversion estimates currently is in the real-world, the scenario assumes different percentages of risk of diversion for ADF and non-ADF opioids.</p>
95	American Academy of Pain Medicine	Model	<p>The following is an excerpt from the Morning Consult that summarizes a legitimate concern about the current draft of the report. "The ICER report claims that abuse-deterrent opioids — designed to deprive users of a high when cooked or snorted — provide neither financial nor societal benefits, despite the fact they (ICER) were provided data demonstrating that over five years using abuse-deterrent OxyContin prevented 4,300 cases of abuses, avoided 12,000 abuse years and saved \$300 million in medical costs for \$387 million in drug costs. ICER confirmed those results, but tossed them aside." https://morningconsult.com/opinions/icer-perpetuates-opioid-crisis/</p>	<p>ICER strives to adopt scientifically sound methodologies in its evidence review, and has stated during the preliminary results presentation that these results are subject to change if validation of the results does not meet ICER's scientific standards. Based on the feedback we received as well as model validation exercises conducted, we felt the need to modify the model structure and change certain inputs in order to adhere to ICER's core principles of producing scientifically sound research.</p>

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96	American Academy of Pain Medicine	Model	Below is an excerpt from the second article (from Forbes) that further questions the methodology used in drafting the report. “An article under review in the Journal of Managed Care and Specialty Pharmacy that was validated by ICER replicates ICER’s original methodology, and found that OxyContin ADF significantly reduced the number of opioid abusers, and reduced medical expenditures, on net, by \$208 million over 5 years.” https://www.forbes.com/sites/econostats/2017/05/11/empower-patients-not-icer/2/#6b1170072d47	This is untrue. ICER neither validated the submitted journal article nor the model replication. ICER only reviewed the preliminary results presented by the authors of this article.
97	Prime Therapeutics	Model	We agree with the ICER analysis methods and applaud them for including drug costs. Other analyses of abuse deterrent drugs and their influence on abuse do not factor in the drug cost which is substantial.	Thank you for your comment.
98	Prime Therapeutics	Model	We recognize that a QALY analysis was not used in the ADF report, however we understand this was not feasible due to a lack of data. We agree with using a net cost impact method and believe the findings add to the understanding of ADF opioids value. No other research has compiled a complete review of the opioid abuse landscape with ADF compared to non ADF opioids in a non-biased, transparent manor using all costs, including drug costs. It is important for readers to see that ADF opioid drug costs can overwhelm all other costs. In light of this, we feel the report could have firmer conclusions around the impact of costs and the lack of evidence in this space. For example, we suggest adding the report conclusion the data reported in Table 21, on page 54. For example, a sentence in the report conclusion could be added, such as, “The incremental costs per overdose death prevented are nearly \$1 billion when using ADF opioids compared to non-ADF opioids.” Even when the effectiveness of the ADF opioids is 100% for preventing abuse the incremental cost remains high at almost \$99 million.	We have now modified language in our report to include cost per incremental outcomes in the summary as per your suggestion.
99	Prime Therapeutics	Model	Was abuse defined similarly in the cost-benefit model as the comparative clinical effectiveness assessment? We believe abuse in the clinical effectiveness assessment used each of the included studies methods for defining abuse. Were these methods translated for your abuse definition in the cost-benefit model? On page 50, a statement refers to ICD9 codes used, however the code does not appear in the document? Please add the codes to the document.	ICD-9 codes for abuse are available in the appendix

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100	Prime Therapeutics	Model	The tornado diagram on page 56 could benefit from the addition of a legend for the orange and blue colors and a more clear description of the parameters. Also, the foot note under page 24 is not clear to us, "The incidence of abuse was varied such that the percentage difference in incidence between ADF and non-ADF opioids was kept constant and the same as that seen in the base case."	This has been addressed in the final report.
101	Prime Therapeutics	Model	The model structure on page 46 reports the patients modeled are non-cancer chronic pain patients with a new extended-release (ER) opioid prescription. In addition, the summary statement says again that ADFs have the potential to substantially reduce opioid abuse among patients initially prescribed these drugs for therapeutic purposes. We are unclear if this means the patients are new to all opioid therapy including short acting opioids or if they are only new to ER opioids? Does new and initially prescribed mean they were not on any opioids prior to receiving high dose chronic ER opioid therapy? If it is the former, we believe a statement should be included to acknowledge this should not be considered usual care for treatment of chronic non-cancer pain. Based on the CDC guidelines for prescribing opioids for chronic non-cancer pain, when starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.	This has been modified in the final report.
102	Prime Therapeutics	Model	Patients included in the ICER model are assumed to use opioids at an average daily 90mg morphine milligram equivalence (MME). A 90mg MME is a high dose. Again, based on the CDC guidelines, when opioids are started, clinicians should prescribe the lowest effective dosage. Therefore, our understanding is the ICER model is from a point of high dose opioid chronic use which is a unique set of patients.	We received manufacturer feedback on a trend in decreasing per day dose of opioids, with a 70mg per day dose of OxyContin as of January 2016. In alignment with this trend, we assumed a 60mg per day dose of OxyContin, which translates to 90mg MME. The 90mg MME was also referenced from a CDC report that mentioned that doses higher than this would need additional vigilance by the health care provider.

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103	Prime Therapeutics	Model	Page 46 model structure – “We did not include cancer patients in the model, as there may be different considerations when determining appropriate pain management for these patients (e.g., focus on immediate release rather than ER opioids).” We suggest using an alternative example here because it does not make sense to say that cancer patients would require a focus on IR opioids. Please consider changing to something about cancer patients needing higher doses.	This has been modified in the final report.
104	Prime Therapeutics	Model	Table 15 key assumptions – Please clarify the difference between the 3rd and 8th key assumption. They both seem to say the same thing – Effects on heroin or other opioids use that might result from opioid abusers receiving an ADF opioid were not included compared to cohort model dose not account for switches to other prescription opioids or use of illicit opioids such as heroin. The focus of both assumptions seems to be that the model is in patients with new opioid prescriptions.	This has been modified in the report.
105	Prime Therapeutics	Model	The methods on page 60 make reference to the cohort model which we believe should be cited as Figure 6 not Figure X. The state-specific model uses the same general model structure as the cohort model (Figure X).	This has been modified in the report.