Comparative Effectiveness Review Disposition of Comments Report

Research Review Title:
Management of Suspected Opioid Overdose With Naloxone by Emergency Medical Services Personnel

Draft review available for public comment from March 16, 2017 to April 13, 2017.

Research Review Citation: Chou R, Korthuis PT, McCarty D, Coffin P, Griffin J, Davis-O'Reilly C, Grusing S, Daya M. Management of Suspected Opioid Overdose With Naloxone by Emergency Medical Services Personnel. Comparative Effectiveness Review No. 193. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 17(18)-EHC025-EF. Rockville, MD: Agency for Healthcare Research and Quality; November 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm. DOI: https://doi.org/10.23970/AHRQEPCCER193.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General Comments	I found the report clinically meaningful and timely. There is a lot of buzz around opioid treatment and this report put the known and unknown in perspective.	Thank you for the comment.
Peer Reviewer #1	General Comments	The key questions were well stated and covered the range of questions being asked by policy makers.	Thank you for the comment.
Peer Reviewer #2	General Comments	This report exhaustively and comprehensively sought answers to difficult and not very well studied, yet important questions regarding naloxone by EMS. Although applicable data were scant and of low quality, this is a strength of the methodology and specificity of the questions, and definitions of the populations. Most importantly, this report, once published, serves as the first step to designing, funding, implementing, and publishing rigorous, high-quality studies to better answer these key questions.	Thank you for the comment.
Peer Reviewer #3	General Comments	This report provides a valuable systematic review of the current published literature on naloxone treatment by Emergency Medical Services (EMS) and similar personnel. The focus of the review is the out-of-hospital setting, though emergency department studies were included due to limited other literature available. This is a very important area of investigation and this review will be a welcomed addition to current knowledge as a synthesis of the available literature on the questions addressed here.	Thank you for the comment.

Source: https://effectivehealthcare.ahrq.gov/topics/emt-naloxon/systematic-review
Published Online: November 27, 2017

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General Comments	The population and audience are explicitly defined with an exception: Page ES-5, lines 13-15 – Studies conducted in the ED settings were included as a modification in protocol for Key Question 1 and 1a. Presumably, the population was modified as well, as EMS personnel would not be the ones administering naloxone in the ED, yet this is not explicitly stated. Consider including this within the population section (Page ES-4, lines 8-14).	We revised the Populations section of the PICOTs to be clear that for KQ's 1 and 1a we also included studies of patients treated in ED settings by ED personnel
Peer Reviewer #3	General Comments	Page ES-5, line 15 – It appears this should mention Key Question 1 and 1a (1a missing).	Added Key Question 1a here as suggested.
Peer Reviewer #3	General Comments	Page ES-5, line 16 – It appears this should mention Key Question 1 and 1a (1 missing within parenthesis). [Note the above comments should also be considered for the respective section of the main body of the text]	Added Key Question 1 here as suggested. We made the same changes in the main report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General Comments	Management of Suspected Opioid Overdose with Naloxone by Emergency Medical Services Personnel. General Comments: Thank you for the opportunity to review the AHRQ Comparative Effectiveness Review of naloxone in the EMS setting. This is an extremely important topic, and indeed deserves the attention given. The report is clinically meaningful. The target population and audience are clear. The key questions are appropriate and explicitly stated. My overall impression is very favorable, and I believe the authors' followed then methodology well, and treated the available evidence very fairly. This is a well crafted document, my congratulations to the authors.	Thank you for the comment.
Peer Reviewer #5	General Comments	The report seeks to answer asks clinically relevant and important questions. Results have potential to be very clinically meaningful. Both the target population and target audience are explicitly defined. The key questions are explicated stated, and are questions that are being asked in many realms including EMS/pre-hospital, community organizations/CBOs, governmental agencies, and the greater public health sphere.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General Comments	Yes. Although the report does not reach strong conclusions, that is because the authors correctly excluded irrelevant and low-quality studies from the review. The key questions are appropriate and well stated.	Thank you for the comment.
TEP Reviewer #1	General Comments	Overall, I found this systematic review to be very well done. The methods appear sound and the limitations are well presented. Although they result in a relatively small number of studies being included, the inclusion/exclusion criteria seem reasonable. I commend the authors for using only studies conducted in the out-of-hospital context, as I believe that reports from the inpatient context are not applicable to the research questions. I also support the conclusions, which are largely that insufficient evidence exists to say much about most of the key questions. I do have some specific comments, noted below.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General Comments	ES-1, line 40: There is no evidence of which I'm aware that "Early intervention by EMS personnel is critical to prevent deaths and other complications of opioid overdose" and I would suggest that this sentence be struck or clarified. Nearly every state now permits laypeople to access naloxone, and there are tens of thousands of reports of lay overdose reversal. This strongly suggests that, while EMS response is optimal, it is not "critical." Numerous studies have now demonstrated that the people already "on the scene" of an overdose – the friends, family members, and associates of the person overdosing - are both willing and able to administer naloxone and other emergency care, such as rescue breathing.	The sentence in question does not compare the effectiveness of EMS management of overdose versus layperson management of overdose, as the reviewer suggests. It just notes that when responding to opioid overdoses, timely intervention by EMS personnel when responding to opioid overdoses is critical. We revised this sentence so that is clearer.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General Comments	ES-4, line 26: It is not correct to say of the 2mg/2ml IN “Dose not currently FDA approved”. The FDA does not approve dosing except in cases such as devices that provide a preset dose. Further, in my opinion this table is confusing as presented. I would suggest separating the two intranasal methods of administration (Narcan, the single-dose intranasal device (4mg/.1ml and 2mg/.1ml)), and the improvised intranasal device (2mg/2ml)). I would then note that the 2mg/2ml formulation is not approved for the IN *route* of administration (naloxone injection is approved only for IV, IM, and SC), although I might also note in the text that off-label use is both common and apparently effective. In any event, it is not correct to say that the 2mg/2ml “dose” is not FDA approved.	We revised the table as suggested. We also revised the text (“Field treatment of suspected opioid overdose with naloxone”) to note that off-label administration of IN naloxone in a less concentrated formulation using an improvised nasal device is also common.

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TEP Reviewer #1	General Comments	ES-10, line 27: I would temper the claim that "persons who refuse transport or are assessed as not requiring transport are likely to differ substantially from persons who are transported" perhaps by replacing "are likely to" with "may." I assume the thrust of the question is whether there's a benefit to transporting patients who are alert and oriented and capable of refusing consent to transport – that is, among similarly situated patients. In my experience as an EMS provider such transport decisions often had as much to do with agency policy, responder beliefs, call volume etc. as patient presentation.	We think the statement is accurate as written. The section in question is addressing issues related to applicability for Key Question 4. We cite a study that found that patients who are not transported are much more likely to have a GCS score of 14 or 15 than those who are transported, indicating significant differences in patient characteristics such as level of consciousness (this Key Question is not restricted to persons who are alert and oriented, as suggested by the reviewer). This is important for applicability because the studies on outcomes of transport versus non-transport provided inadequate details regarding patient characteristics, making it difficult to interpret results.

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TEP Reviewer #1	General Comments	ES-10: The Discussion and Applicability sections accurately state the low strength of evidence and limited conclusions that can be drawn from existing published data.	Thank you for the comment.
TEP Reviewer #1	General Comments	ES-11, line 10: I don't believe it's true that opioid overdoses "disproportionately impact younger persons." Both rates and raw numbers of opioid OD decedents are higher among those 25-54 than those <24 years of age. Would that 25 is "young," but the fact is that middle-aged Americans are at higher risk of opioid overdose than children, teenagers, and young adults.	We deleted "disproportionately impact younger persons" and replaced with text noting the potentially devastating consequences of opioid overdose.
TEP Reviewer #1	General Comments	Page 2, line 16: As noted in comments to the executive summary, I would modify the sentence claiming that EMS response is "critical to prevent death and other complications of opioid overdose." The Alcorn article cited in support of this statement in fact supports the opposite conclusion – that laypeople can and do reverse overdose with naloxone. If there is published evidence that EMS providers are more effective at reversing opioid overdose than trained laypeople I have not seen it.	The sentence in question does not compare the effectiveness of EMS management of overdose versus layperson management of overdose, as the reviewer suggests. It just notes that when responding to opioid overdoses, early intervention by EMS personnel when responding to opioid overdoses is critical. We revised this sentence so that is clearer.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General Comments	Page 2, line 32: I'm not sure it's true that administration of naloxone is the standard of care for EMS personnel, and the cited article doesn't support the statement. As the report notes a few sentences on, that is true for ALS but often not for BLS (although that's rapidly changing).	We revised to state, "Management of opioid overdoses by EMS Personnel includes airway management and continuous assessment of oxygenation and ventilation, along with administration of naloxone."
TEP Reviewer #1	General Comments	Page 2, line 14: It's also possible that this increase is just noise or due to increased BLS administration, protocol change, or some other variable. This is addressed well on page 25, line 6 and I would graft that more nuanced discussion here.	We were unable to determine what part of the report this comment refers to—neither of the page/line numbers appears to correspond to the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General Comments	Page 24, line 6: As noted in the comments to the executive summary, I don't think the evidence supports the claim, made several times in the draft report, that patients not transported are "likely to bet (sic) at lower risk of opioid overdose-related complications than persons who are not transported." The study mentioned to support this statement is from Finland, and as the authors note, in that study "it was unclear why patients were not transported." In the United States, patients are generally transported unless they're capable of signing the appropriate refusal form – that is, if they're alert, oriented, and not in obvious need of further care. It may be the case that those overdose patients who are AxO and refuse are different than those who are AxO and don't, but the Boyd study does not support that claim. My guess as someone with experience as an EMS provider is that, on average, there is probably not much difference between the two.	We think the statement is accurate as presented. The section in question is addressing issues related to applicability for Key Question 4. We cite a study that found that non-transported patients are much more likely to have a GCS score of 14 or 15 than those transported, indicating significant differences in patient characteristics (this Key Question was not restricted to persons who are alert and oriented, as suggested by the reviewer). As noted in the Implications for Clinical and Policy Decisionmaking section, studies were not designed to compare benefit and harms of transport versus non-transport in patients with similar characteristics. The Boyd study cited by the reviewer does not report characteristics of persons transported versus those not transported.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	General Comments	Continued from above: It's even possible that the trend might run the other way: an ambulance crew might more readily acquiesce to an alert and oriented homeless person with opioid use disorder and multiple previous overdoses refusing transport after a heroin overdose than, for example, a middle class person who had overdosed on prescription analgesics. But in any event I think this claim is not supported by the evidence and should be removed.	We think this comment reinforces the point in the sentence that people who are transported are likely to differ from those who are not transported.
TEP Reviewer #1	General Comments	Further, I would note that, in general, alert and oriented patients have a legal right to refuse further care. Any policy that requires or recommends the transport of conscious patients against their will should be very, very carefully thought out, both from a standpoint of liability for the EMS agency as well as the potential risk of decreasing calls for 911 assistance (a person who is transported against his or her will may be wary of calling 911 the next time they witness an overdose). I would recommend that the authors of this report not wade into those ethical/medical/legal waters, as there is really no need to do so here.	This report does not make policy recommendations. It notes that factors that may impact transport decisions include medico-legal considerations.

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TEP Reviewer #1	General Comments	Page 26, line 44: Another barrier to IV administration is that in every jurisdiction of which I'm aware, BLS providers are not permitted to initiate IV therapy, essentially limiting BLS administration to the IN or IM routes.	We added this sentence: "In addition, Basic Life Support EMS providers are generally not permitted to initiate IV therapy, limiting such personnel to naloxone administration via the IN or IM routes."

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TEP Reviewer #1	General Comments	Page 27, line 22: There is some evidence that even trained EMS providers often provide substandard positive pressure ventilation (PPV), but is it true that they don't have access to oxygen saturation monitoring? Surely all personnel from EMT on up have access to at least a device to measure pulse O2. It also seems to me that the list of pros/cons regarding a patient achieving full consciousness should include that negative pressure ventilation (that is, the patient breathing on their own) is in almost all cases more likely to provide a necessary level of oxygen than manual PPV. Naloxone titration, particularly via the IM or IN route, is an inexact science, and it can be quite difficult to properly ventilate a patient in the back of a moving ambulance. In my mind those two facts argue for erring on the side of over-antagonism (within reason) as opposed to under-antagonism. This isn't a clinical setting; it's not always easy in the pre-hospital world to find that Goldilocks zone where the patient is capable of adequate respirations and maintaining their airway and yet isn't fully conscious.	We revised as follows: "EMS personnel vary with regard to their ability to provide ventilatory support, and may not have uniform access to tools to assess for adequate ventilation." There are more advanced tools than pulse oximetry to assess ventilation. We also added the sentence: "In addition, negative pressure ventilation (i.e., patients breathing on their own) is more likely to achieve adequate oxygenation than manual positive pressure ventilation."

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TEP Reviewer #1	General Comments	Page 27, line 52: Naloxone is absolutely not available over the counter in any states. States have not and can not make it OTC – only the FDA can. See Davis et al, Legal Changes to Increase Access to Naloxone for Opioid Overdose Reversal in the United States. Drug and Alcohol Dependence 2015.	We revised to be clearer that in many states naloxone is available without an individual patient prescription, through standing orders or collaborative practice agreements with prescribers. We also added the reference to Davis et al.
TEP Reviewer #2	General Comments	Report is clinically meaningful, but may well just demonstrate the need for additional work to be done in this area. The most important consideration is that all trials can not be performed as randomized and controlled; from time to time we will have to recognize that the best strength of evidence on a clinical question will need to be expert consensus. With naloxone and opioid overdose, it is not possible to conduct true randomized trials because the population is so varied and all clinically pertinent variables can not be accounted for. Perhaps this is the most important conclusion that can come from this paper.	Thank you for the comment. We included observational studies addressing the Key Questions.
TEP Reviewer #3	General Comments	The research questions are appropriate. The key questions are clear. The manuscript is a systematic review and does quite well at that. Unfortunately the paucity of evidence given the methods severely limits the potential for the document to be clinically meaningful.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	General Comments	Yes	Thank you for the comment.
TEP Reviewer #5	General Comments	This is a good review of the literature and my enthusiasm is only slightly muted by the fact that there simply is not enough evidence to answer the questions set out as the goal. Still I do have a few comments on conclusions drawn by the authors, including a missing endpoint or two.	Thank you for the comment. We responded to specific comments from this reviewer.
TEP Reviewer #6	General Comments	The topic is important but the dearth of actual data leaves it as premature. The end result is a less than compelling finding for the use any particular dose or delivery method. The key questions are thorough, clearly stated, and well though out.	Thank you for the comment. The lack of evidence is an important limitation highlighted in the Discussion. The Research Recommendations section describes future research priorities that could help fill in the gaps.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, Paul Roszko Naval Medical Center Portsmouth	General Comments	There needs to be a discussion on the need to update the National EMS Scope of Practice model to reflect IN / IM naloxone administration by EMRs and EMTs, and a consideration of this being a technique taught by the NREMT for those levels of certification. There is a need to take cost of new devices and formulations into account, as well as a need to take the cost of provider training into account. From a public health perspective, if it can be shown a first responder, EMR, and EMT can safely administer naloxone and treat most opioid overdoses, the return on investment (i.e. cost to train personnel) is higher than it would be for paramedics. Further, if a less expensive formulation of naloxone is found to be as efficacious as a more expensive (e.g. IN vs IM auto-injectors) then this should be accounted for as States set their protocols and standards for treatment. There is a need to account for the fact that the drugs available on the street tend to vary from year to year and have recently focused on high potency, inexpensive synthetic opioids and thus data from even 5 years ago may have limited applicability to current recommendations. This is relevant in the discussion of which initial dose should be given to patients. Patients tend to not be aware of taking higher potency synthetic opiates and there are case reports of patients requiring multiple high doses of naloxone to successfully reverse their overdose.Continues below.	As described in the Results and Discussion, there was insufficient evidence to determine effects of EMS personnel training on comparative benefits and harms of naloxone dosing and routes of administration. Making policy recommendations changes regarding the National EMS Scope of Practice is outside the scope of this review. We mention costs of formulation as one of the factors that may influence policy decisions; we also mention the prevalence of overdoses associated with high potency opioids or the proportion of patients requiring multiple doses as considerations.

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Public Reviewer #2, Paul Roszko Naval Medical Center Portsmouth	General Comments	Continues from above: 0.4 mg may be too low of a dose at this day and age, but there is no current data to support that suspicion. Mandatory reporting to the State Depart of Health for any patients seen and treated at an Emergency Department could helpful in gathering outcome data on patients who are treated and transported via EMS. How many self present vs are transported? How many receive additional treatment in the ED or are admitted to the hospital? Do the ones who require additional treatment have higher rates of use of synthetic opiates (e.g. fentanyl) versus those who are discharged after simple observation? How many are given referrals for outpatient community treatment? How many will return with another overdose and what time frame does this happen within? Future EMS protocols should look at if patients treated with naloxone by an EMR or EMT-B require EMT-A or paramedic level response? Do all patients require a provider who can provide IV access and other advanced airway management techniques? Or could these patients be successfully managed by EMTs once the diagnosis of opiate overdose is confirmed?	Thank you for the comment. The evidence on dose comparisons is addressed in the report. The Future Research Needs section discusses the use of EMS registry data. The importance of assessing effects of level of training and type of opioid involved in the overdose are discussed as well.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #5, Daniel Sledge, Williamson County EMS/ Mobile Outreach	General Comments	--On transporting pts: I think a lot of these folks will want to refuse EMS transport. Many people who inject drugs are uninsured, and may also lean more toward overly self-sufficient--(don't want to accept help or burden others; don't want an ER bill and bigger EMS bill). Something to maybe look at is what type of opioid the pt OD'd on (long-acting or short-acting) and whether there was a re-overdose (either in the filed or the ER setting). Pts who OD on long-acting opioids (Oxycontin, methodone, Demerol, etc.) should be very strongly encouraged to go to the ER (even POV) for observation and probable re-dosing of Narcan. Also, the risk of adverse event will also have to do w/ the pt's overall health otherwise (wound infxns, uncontrolled HTN or DM, PNA, TB). Also if the pt is adamantly refusing transport, consider the social environment the pt will be left in--will someone be there to watch the pt in case of re-OD and give more Narcan. Will that person keep the pt from using more opioids right away (since the pt will be dope-sick, but the last hing you want is for them to pile on more oipoids while the Narcan is still in board--it'll be a big re-OD when the Narcan wears off). --On doses and routes: it's interesting to see more products come out w/ higher doses--which makes sense in the case of fentanyl (and derivatives) ODs. Continues below.	As described in the results, there was very limited information in studies of transport versus non-transport regarding patient characteristics including the type of opioid involved in the overdose, co-morbidities, and other factors. Evidence on dose comparisons is addressed as a Key Question.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #5, Daniel Sledge, Williamson County EMS/ Mobile Outreach	General Comments	Continued from above: But these higher doses might be overshooting the runway for other non-fentanyl ODs (heroin, Percs, hydrocodone). This could result in exposing lay rescuers to more acts of violence from OD pts in the throes of withdrawal. But then again, these are tough to titrate--as opposed to IV Narcan, where it is very easy to titrate to the pt's respiratory drive. That's how we give it on the trucks, although I've seen docs and other medics slam it in a more punitive fashion--which is NOT why Narcan should be given (but that's a whole different rant). But there's no way to tell where the sweet spot is for designing a dose-specific product. A dose that's exceedingly high will send all pts into acute w/d (which is better then not breathing), but a dose too small may not reverse the OD enough. So, maybe a good method now is the kits w/ 2 doses--where you give the 2nd dose if they don't respond to the 1st). I love the user-friendliness of the Amphastar prefilled syringe w/ the MAD adapter (even though it's more of a DIY, not FDA approved that I know of method). The IN method takes the needle out of the equation--which reduces needle-stick injuries, and in PWID the incidence of HIV and HCV is higher than in the general population. Also--super nerdy--but the plural of appendix is appendices.	Thank you for the comment and contextual information. AHRQ format uses the appendixes label rather than appendices.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4, Alan Goldberg ADAPT Pharma	General Comments	I write on behalf of Adapt Pharma, the manufacturer of Narcan® Nasal Spray, the first and only Food and Drug Administration (FDA) approved nasal formulation of naloxone. The following comments are in response to the request for comment regarding the Comparative Effectiveness Review, “Management of Suspected Opioid Overdose with Naloxone by Emergency Medical Services Personnel.” We did request the opportunity to contribute in email correspondence between our Chief Operating Officer, Eunan Maguire and Amanda Borsky dated September 7 & 9 2016, but this request was rejected and we were advised to participate in the public comment period.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4, Alan Goldberg ADAPT Pharma	General Comments	I am deeply concerned that the draft report excludes key data because of the timeframe limitation and that the conclusions you draw pertaining to nasal administration of naloxone appear to be in respect of non-FDA approved improvised kits that have never been FDA approved. The FDA-approved nasal formulation, which was approved on the basis of an FDA-reviewed comparison to the intramuscular formulation, is now the most pharmacy-dispensed naloxone product. By excluding the FDA-approved nasal formulation and presenting only older data on unapproved nasal formulations, the article risks presenting a misleading picture of the options available for treatment, and worse, risks skewing the treatment decision on the basis of data which is no longer applicable or even relevant to the most widely-available treatment options, with potentially serious consequences for patients in need of emergency treatment. The data highlighted below, I believe, help address your questions and I strongly urge that you consider these data for incorporation into your findings so that the decision to prescribe this potentially life-saving treatment can be made on the basis of complete, up-to-date information on the available options and their relative merits.	As described in the Methods, we included the FDA-approved nasal formulation. However, no studies of the FDA-approved nasal formulation met inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4, Alan Goldberg ADAPT Pharma	General Comments	Background Narcan® Nasal Spray 4mg was approved under priority review by FDA in November 2015 and launched in February 2016, while Narcan Nasal Spray 2mg was FDA approved in January 2017. Narcan Nasal Spray 4mg has been widely adopted and is now the most dispensed naloxone at retail pharmacies, according to IMS Health prescription data (February 2017). Narcan® Nasal Spray is approved as a 4mg/0.1ml and a 2mg/0.1ml concentration.	Thank you for the comment.
Public Reviewer #4, Alan Goldberg ADAPT Pharma	General Comments	Pharmacokinetic and Human Use Data Comparative pharmacokinetic data of Narcan® Nasal Spray (2 mg - 8 mg) and naloxone 0.4 mg administered by intramuscular (IM) injection, was in fact published by Krieter et al in October 2016 [1]. As is widely known, dose and onset are key considerations in attempting to treat a known or suspected opioid overdose. This study showed that administration of IN naloxone formulations of from 2 to 8mg “results in PK parameters that either equal or exceed those observed following the IM dose of naloxone (0.4mg) that is approved for the treatment of opioid overdose.” Onset was not significantly different between the IM and Narcan® Nasal Spray product. In this publication, results from human use factor studies were also presented, which supported the use of the product in the community setting where the vast majority of opioid overdose deaths occur, according to the CDC Wonder Database.	Thank you for the comment. The studies discussed here (pharmacokinetic studies and human use factor studies) do not meet inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4, Alan Goldberg ADAPT Pharma	General Comments	The Krieter publication [1] states “A single dose of 4 mg naloxone was selected as the final formulation for Narcan® Nasal Spray because it delivers approximately the same amount of drug as 2 mg IM, the highest recommended initial dose for treating suspected opioid overdose. In addition to the simplicity associated with a single administration, the 4-mg IN dose increases the potential for a reversal of opioid overdose compared to either improvised IN devices or the approved autoinjector that delivers 0.4 mg of naloxone. This is especially relevant because of the dramatic rise in the abuse of high-potency opioids such as fentanyl that require higher concentrations of naloxone to treat overdose.”	This study does not compare clinical outcomes of different naloxone doses/formulations and does not meet inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4, Alan Goldberg ADAPT Pharma	General Comments	Post-market experience Furthermore, a retrospective analysis of in-market performance of Narcan® Nasal Spray was presented in March 2017 as a late breaking poster (LB001) at the American Academy of Pain Medicine (AAPM) in Orlando, Florida. (Use of Naloxone Nasal Spray in the Community Setting: a Survey of Use by Community Organizations) [2]. This poster highlighted 'real world' survey data indicating that: • Narcan® Nasal Spray was successful at reversing the effects of opioid overdose in most reported cases "of 245 cases with outcomes reported, 98.8% (242/245) were reported to be successful". [2] • The majority of events observed for the reversal cases were consistent with other naloxone formulations (opioid withdrawal) [2]. • The data was based on responsive reporting from eight law enforcement or community-based organizations of 152 contacted.	This study does not compare routes or doses of naloxone and does not meet inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4, Alan Goldberg ADAPT Pharma	General Comments	Incorrect EMS price Finally, it is stated that the price for the new 4mg/0.1ml intranasal device costs $150 which is inaccurate. As Qualifying Group Purchasers, the Narcan® Nasal Spray 4mg price offered to EMS (the target of your report) is in fact $37.50 per dose of 4mg.0.1ml or $75 per carton of 2 devices. This pricing represents a 40% discount off the Wholesale Acquisition Cost (WAC) of $125 per carton. [3]	The pricing information cited in the report is from a New England Journal of Medicine article by Gupta et al (N Engl J Med 2016;375:2213-15), which was obtained from Medi-Span Price Rx.
Public Reviewer #4, Alan Goldberg ADAPT Pharma	General Comments	We respectfully urge you to consider inclusion of these highly pertinent data and the impact on your conclusions. It is critical, in our view, that accurate and timely data be presented so that communities, including EMS, can make appropriate product decisions. The urgency is further heightened by the rapid emergence of highly potent synthetic opioids, such as illicitly manufactured fentanyl, which appear to require stronger naloxone doses.	The data cited by the reviewer do not meet the pre-specified inclusion criteria for this review.
Public Reviewer #4, Alan Goldberg ADAPT Pharma	General Comments	We are available to discuss at your convenience. Kind regards, Alan Goldberg, RPh Senior Director, Product Safety and Medical Services	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4, Alan Goldberg ADAPT Pharma	General Comments	[1] Krieter P, Chiang N, Gyaw S, et al. Pharmacokinetic Properties and Human Use Characteristics of an FDA-Approved Intranasal Naloxone Product for the Treatment of Opioid Overdose. J Clin Pharmacol. 2016 Oct;56(10):1243-53. [2] George Avetian, DO, FCPP, avetiang@co.delaware.pa.us1; Phillip Fiuty, N/A2; Pratibha Hebbar, PhD3; (1) Delaware County Government, Intercommunity Health; (2) Santa Fe Mountain Center; (3) Synchrony Medical Communications Use of Naloxone Nasal Spray in the Community Setting: A Survey of Use by Community Organizations. Late Breaking Poster (LB001) presented at American Academy of Pain Medicine in Orlando Florida. Available at: http://www.painmed.org/2017scientific-abstracts/late-breaking/#abstractlb001 [3] Adapt Pharma. Available at: https://www.narcan.com/affordability	These citations have been reviewed and do not meet inclusion criteria because they are pharmacokinetic studies or do not address any of the key questions.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6, Keith Wages National Association of State EMS Officials	General Comments	Thank you for the opportunity to review and provide comment on the draft report titled "Management of Suspected Opioid Overdose with Naloxone by Emergency Medical Services Personnel". The National Association of State EMS Officials (NASEMSO) deeply appreciates the time and resources that the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality has dedicated to one of the important challenges inherent within our nation's opioid crisis.	Thank you for the comment.
Public Reviewer #6, Keith Wages National Association of State EMS Officials	General Comments	The draft report contains several references to the National EMS Scope of Practice Model, a document published by the National Highway Transportation Safety Administration in 2007. The report notes that naloxone administration is not within the national EMS scope of practice for emergency medical responders (EMRs) or emergency medical technicians (EMTs). It also notes that the National EMS Scope of Practice Model was published prior to the availability of newer formulations of naloxone and newer evidence of the benefits of field use of naloxone.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6, Keith Wages National Association of State EMS Officials	General Comments	The National EMS Scope of Practice Model contains a section titled “The Role of State Government”. Within this section, it states, “Each State has the statutory authority and responsibility to regulate EMS within its borders, and to determine the scope of practice of State-licensed EMS personnel. The National EMS Scope of Practice Model is a consensus-based document that was developed to improve the consistency of EMS personnel licensure levels and nomenclature among States; it does not have any regulatory authority.” Due to evidence-based research paired with advancements in medicine, medical technology, and EMS provider capabilities, states have independently amended their respective EMS scopes of practice for multiple psychomotor skills with the goal of improved patient care and safety.	We revised the Introduction to note that states can independently determine its EMS scope of practice.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6, Keith Wages National Association of State EMS Officials	General Comments	Regardless of the omission of naloxone administration by EMRs and EMTs, the majority of States have already taken the initiative to expand their respective EMS scopes of practice to allow this avenue of patient care. A survey of states conducted by NASEMSO in May 2016 demonstrated that 80% of states permitted EMTs to administer naloxone. If adding states that were in the process of implementing change and were successful, the proportion would increase to 92%. In addition, within the 25 of 41 states that license the Emergency Medical Responder/First Responder level, 61% permit administration of naloxone (5 states were pursuing implementation, which would raise the level to 73%). While an amendment in the National EMS Scope of Practice Model to add naloxone administration to the EMR and EMT provider levels is contemplated, the overall impact to patient care may be minimal in light of the number of EMRs and EMTs who are already administering naloxone.	The Introduction notes that all jurisdictions permit paramedics and 48 permit intermediate/advanced EMT's to administer naloxone, and fewer permit BLS EMS personnel to administer naloxone, based on a recent review of state regulations by Davis et al. These data appear consistent with the data cited by the reviewer; we did not find a published version of the NASEMSO survey mentioned in the reviewer comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6, Keith Wages National Association of State EMS Officials	General Comments	We agree that there is insufficient research or evidence to support a recommended dosing regimen for naloxone although the notation that the intranasal route of administration was associated with increased likelihood of rescue naloxone use compared to the intramuscular route is helpful. The initiation of intravenous access is traditionally outside of the scope of practice for an EMR or EMT, and any comparative research between the intranasal and intramuscular routes may impact their patient care protocols. The increased incidence of high potency opioids involved in an overdose will make the determination of a recommended naloxone dose for EMS personnel extremely difficult for several reasons. The dose of an opioid taken by a patient can rarely be determined nor is there an avenue to differentiate between high potency opioid versus one of lower potency in the out-of-hospital setting.	Thank you for the comment.
Public Reviewer #6, Keith Wages National Association of State EMS Officials	General Comments	The demographics of the opioid crisis vary widely among regions of our nation. In regions where there is a higher incidence of high potency opioid overdose, smaller or incremental naloxone dosing may actually be detrimental to a patient or be an impediment to adequate airway management by EMS providers .[1]	Thank you for the comment. This comment underscores the reason for evaluating comparative benefits and harms of different doses of naloxone.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6, Keith Wages National Association of State EMS Officials	General Comments	It is commendable that your organization acknowledges the need for additional research to address the four key questions explored in your draft report. Specific to the second key question, there is an unexplored topic regarding the comparative benefit and harms of titration of naloxone administered by EMS personnel until the patient resumes sufficient spontaneous respiratory effort versus until the patient regains consciousness that may positively impact EMRs and EMTs. Adequate airway management is imperative in the treatment of all patients. While the use of pulse oximetry is an important adjunct, multiple studies have demonstrated that oxygenation is not equivalent to adequate ventilation which can be assessed with digital capnometry or waveform capnography.	Thank you for the comment. The methods used to evaluate adequate ventilation during management of suspected opioid overdose was outside the scope of this report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6, Keith Wages National Association of State EMS Officials	General Comments	Digital capnometers are relatively inexpensive (currently less expensive that a 2 mg dose of naloxone). These devices, potentially in combination with pulse oximeters, may be useful to EMTs and EMRs in the decision-making process of if naloxone should be administered and, if so, the dose and frequency that should be provided to the patient. Digital capnometry may be a useful tool in ongoing patient monitoring, particularly during longer patient transport times, for those EMS systems that elect a goal of reversing respiratory depression in lieu of a fully conscious state. The 2007 National EMS Scope of Practice Model document includes capnography solely at the Paramedic level. Additional research on this topic may add support to the addition of capnometry and/or capnography to the other levels of EMS personnel to the national EMS scope of practice if enhanced patient care, assessment, and safety is demonstrated.	Assessing the optimal methods for assessing ventilation during management of suspected opioid overdose was beyond the scope of this report.
Public Reviewer #6, Keith Wages National Association of State EMS Officials	General Comments	Thanks again for the opportunity to provide input to this draft report. If you have any questions or concerns, please do not hesitate to contact Executive Director Dia Gainor at dia@nasemso.org. Best regards, R. Keith Wages President cc: Carol Cunningham, MD, FAAEM, FAEMS Kenneth Williams, MD, FACEP, FAEMS	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6, Keith Wages National Association of State EMS Officials	General Comments	[1]Burns G, et al., Could chest wall rigidity be a factor in rapid death from illicit fentanyl abuse?, Clinical Toxicology 54: 420-423, No. 5, 27 May 2016	This study was reviewed and does not meet inclusion criteria because it does not address any of the key questions.
TEP Reviewer #11	General Comments	Update 3 to Three and 4 to four in the abstract in the front matter and ES file	We changed to three and four.
TEP Reviewer #11	General Comments	Comment in abstract conclusions on dose after "highly concentrated": Also approved as 2 mg/0.1ml	We added the 2 mg/0.1 mL formulation (already mentioned in the text)
TEP Reviewer #11	General Comments	Comment in background section of front matter and ES file: Evzio, the approved autoinjector is also appropriate for use by persons with limited or no healthcare training	We revised to be clearer that both the auto-injector and IN formulations are designed for ease of administration even by persons with limited or no healthcare training.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #11	General Comments	Comment in Research Recommendations section of front matter and ES file: This may raise ethical issues as these products have not been approved and it is unclear if they have met FDA's pharmacokinetic standard for approval.	We think that the reviewer is referring to the sentence calling for future research on alternative routes of administration, such as mask nebulization, sublingually, or buccally. We deleted this from the ES as we do not feel this is a key future research need that needs to be highlighted. The main report discusses these routes in more detail and potential drawbacks. As with all new formulations/products, research would be expected to follow standards.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #7, David J. Withers	General Comments	I am a former emergency physician (17 years, with a lot of that in EMS) and a current practicing addictionist (17 years) and former addiction medicine fellowship founder/director. I can appreciate the difficulty of this project. EMS varies widely in training/proficiency/experience. E.D. docs too for that matter. It seems that any naloxone is better than no naloxone. It seems that i.v. naloxone wakes patients up faster than IN or IM. It seems that more is better, if it means the difference between life or death. Yes, narcotic overdose patients can be combative, unhappy, vomiting after naloxone. Titrating naloxone is best done by the more seasoned personnel. I have no idea how to tease these intricacies out of existing literature. In general I am fine with this project and conclusions. I would have to say that it is difficult to capture the stress and drama from the individual cases and the devil would be in the details not easily accessed in the reviews. (patients that were moribund, anoxic, hysterical, fighting etc.-each EMS call is a bit different)	Thank you for the comment.
Public Reviewer #7, David J. Withers	General Comments	I do think that opioid overdose reversal will be a moving target owing to the increasing amount of fentanyl and carfentanyl showing up as “heroin”. Things will further change as the prescription drug monitoring programs come into greater force-prescription drugs are getting harder to come by and folks shift to “heroin” which may be street fentanyl analogues.	Thank you for the comment. The issue of illicit fentanyl and fentanyl analogues and how they may impact dosing is discussed in the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #7, David J. Withers	General Comments	I was surprised by the low mortality among those given naloxone who refused transport/further care. Surprised because of the comparatively short half life of naloxone.	Thank you for the comment.
Public Reviewer #8, Shawn A. Ryan	General Comments	Overall well researched (tough to do on this topic) and well written paper. It is very important to remember given the focus of the topic, that many non-academic people may be reading the article. As is often the case with situations like that, many people only read the executive summary and/or conclusions/discussion. Please take extra care with those sections as small details may get misconstrued. Ex: Given a reported 160,000 doses administered in 2014, how many actual EMS injuries were reported due to dose specific issues. Meaning, it should be clearly discussed that with the high potency opioids in our country today, that low dose naloxone is likely not appropriate given the high risk of death/disability vs the low risk of injury to the person giving the medication (needs to be defined clearly; 6/261 = aggression/violence/assault) in this abstract: American Academy of Pain Medicine (AAPM) 2017 Annual Meeting. Late Breaking Poster # LB001). Especially depending on whether the administrator is a medical professional or not (ie capable of understanding risk/benefit, titration, etc). Although I understand the potential theoretical risks of higher dosing, this article is attempting to focus on the evidence and shouldn't propagate theories of potential risk when the most significant issue is saving a life from high potency opioids.	The background section states "Naloxone may precipitate withdrawal symptoms.[13] While uncomfortable, withdrawal symptoms are generally not serious or life-threatening and generally short-lived; the half-life of naloxone is about 30 minutes. Post withdrawal agitation following naloxone administration may put the person giving the naloxone at increased risk for injury.[14,15]" We believe these statements are accurate. One of the purposes of the report is to report comparative harms of different routes and doses of naloxone. The issue of illicit fentanyl and how it may affect dosing is discussed in several places in the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8, Shawn A. Ryan	General Comments	Linkage to treatment also needs to be discussed briefly in regards to naloxone being only a step towards recovery.	Linkage to care as a potential benefit of hospital transport is one of the listed outcomes for Key Question #4. However, as detailed in the Results, no studies evaluated this outcome.
Public Reviewer #1, Joi Kelly	General Comments	The following is based upon rural health settings within the Commonwealth of Virginia and are not representative of all rural areas but depicts typical circumstances when it comes to Emergency Medical Personnel responses and response times within this geographical area.	This comment provides background for subsequent comments, which we responded to separately.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1, Joi Kelly	General Comments	It appears that the document was prepared by the "Agency for Healthcare Research and Quality" a division of the Department of Health & Human Services, however does not disclose the investigator(s) names, preparer name, and/or contract no., however it can be considered that there was some sort of research but location of such research was not disclosed. The document goes on to indicate that "None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report." Further indicating the report is "based on research conducted by an Evidence-based Practice center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD, with the finding and views being that of the author and not necessarily the view of AHRQ."	Per AHRQ processes, the investigators and specific EPC conducting the review are redacted during the peer review phase but will be reported when the final report is published. The report adhered to AHRQ conflict of interest policies

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1, Joi Kelly	General Comments	The author indicated on numerous cases in the report that the use of Naloxone in the field of treatment of Suspected Opioid Overdose is based on the appropriate level of training by the EMS personnel who is permitted to administer such drug as Naloxone. Healthcare has an array of professionals and not all professionals are trained the same or trained at all. The report further indicates that the potential modifiers of interventions is "Based on training and background of the person administering the Naloxone." This is an agreeable statement and I have indicated on numerous times in such discussions that "training" is important and just because Naloxone is not deemed or have been indicated to be a drug that will not cause harm if it's not an opioid crisis, does not mean its still suppose to be in the hands of any and everyone. Trained personnel can assess the need for certain drugs just from the signs and symptoms of the emergent individuals conditions. I have further indicated that Naloxone is not a cure all medications. CPR is the key when respirations, pulse, and heartbeats cease as well as identifying unresponsive individuals.	Thank you for the comment. The report attempted to assess the effects of level of training of EMS personnel on findings but found insufficient evidence to address this.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1, Joi Kelly	General Comments	In theory, where it has been represented in public that Naloxone has no harmful effects, the report indicated that "Naloxone may precipitate withdrawal symptoms." However, not life-threatening and generally short-lived but also posing a risk for the administering person, placing them at increased risk for injury." The benefits may be worth the risks if the individual is successfully revived. Although 911 is the first contact indicated after noticing an unresponsive person, which places EMS personnel and police officers on the scene as first responders, those individuals training is not often equivalent to that of a Medical Doctor or Registered Nurse. Medical Training has always been the cornerstone of medically managing medical conditions and should not be overlooked. In rural health area(s), EMS personnel are often volunteers. The response times are not necessarily what they are in the city and the truth of the matter is that often times, individuals have to transport affected individuals in personal vehicles to meet ambulance services. Continues below.	Thank you for the comment. The report summarizes the evidence on benefits and harms; the discussion of harms includes serious harms when such data are available. As described in the Results, data on harms was very limited. We found insufficient evidence to determine how level of training impacts estimates of comparative effectiveness/harms.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1, Joi Kelly	General Comments	Continued from above: These are not altered results, these are "reality", pure "evidence-based". Police officers are not sufficiently trained to handle IV administration products and it would only be acceptable for them to use nasal Narcan (intranasal). In hospital settings, only Registered Nurses are allowed to push IV medications. Therefore, while formulary administrations are addressed, there is no significant data indicating "life-sustaining" evidence from an incident as opposed to mortality. There are other drugs that can aide in resuscitation other than Naloxone. However, this report does describe such efforts and further excludes "Naloxone in combination with other medications. Training is essential and training is important as well as having the knowledge of the medications that are being used, the possible side effects, the proper technique or "antidote" for a given adverse medication and the co-existing treatments necessary to sustain an individual.	The Discussion notes that BLS EMS personnel cannot administer IV medications and are therefore limited to IN or IM administration. In-hospital use of naloxone is outside the scope of this review, as are use of medications other than naloxone.
Public Reviewer #3, Steven Linder Department of Veterans Affairs	General Comments	There is a paucity of evidence surrounding the attitudes of those professional first responders most often responsible for directly dealing with opioid overdose sufferers. While there has been a strong effort in some urban areas to equip professional first responders with naloxone, standardized training for this population is largely unavailable.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3, Steven Linder Department of Veterans Affairs	General Comments	Public comments on Twitter regarding naloxone were collected for a period of 3 consecutive months. The occupations of individuals who posted tweets were identified through Twitter profiles or hashtags.	Thank you for the comments. This information does not appear to meet inclusion criteria.
Public Reviewer #3, Steven Linder Department of Veterans Affairs	General Comments	Primary themes included burnout, education and training, information seeking, news updates, optimism, policy and economics, stigma, and treatment. The highest levels of burnout, fatigue, and stigma regarding naloxone and opioid overdose were among nurses, EMTs, other health care providers, and physicians.	This study does not address the Key Questions for this review.
Public Reviewer #3, Steven Linder Department of Veterans Affairs	General Comments	Social media platforms, such as Twitter, is a means for a general outreach expanding overdose response education inexpensively to time pressed providers. Twitter is a social media platform that promotes concise information sharing in a peer to peer format, which may make professional educational materials more readily accessible and acceptable. Professional first responder tweets that mention naloxone use problems as well as potential solutions can help guide EMS administrators & physicians towards consensus over a overdose reversal protocol.	Thank you for the comment. The Twitter study does not meet inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3, Steven Linder Department of Veterans Affairs	General Comments	Without social media facilitated discussion OEND programs risk becoming disconnected and fragmented. Providers in states with high rates of opioid overdose should consider using social media to engage public dialog in crafting appropriate OEND programs that both reduce overdose mortality while minimizing law enforcement frustrations.	Thank you for the comment. Use of social media was outside the scope of this report.
Public Reviewer #3, Steven Linder Department of Veterans Affairs	General Comments	Bielenberg J, Haug NA, Linder SH, Lembke A. Assessment of Provider Attitudes towards #Naloxone on Twitter. Subst Abus 2016:35-41. Muquit L, Krasner MA, Bielenberg J, Linder SH, Haug NA. Naloxone and Opioid Overdose Education on Twitter: Facilitating Community Engagement. Collaborative Perspectives on Addiction 2016 - San Diego CA March 19 2016 Krasner S, Muquit, LS, Linder, S H., & Haug, N. A. (2016, October). Dissemination of Opioid Overdose Education, Naloxone Training and News on Twitter. Poster presented at the Addiction Health Services Research Conference, Seattle, WA.	These studies do not meet inclusion criteria.
Peer Reviewer #1	Introduction	Introduction was appropriate. Short and Sweet. It got to the point without a lot of fluff.	Thank you for the comment.
Peer Reviewer #1	Introduction	The intent of the report was clearly stated.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Introduction	The introduction uses all relevant data available at the time of synthesis to demonstrate the extraordinary burden opioid overdose response places on EMS personnel. The current armamentarium of naloxone formulations are adequately described, as well.	Thank you for the comment.
Peer Reviewer #3	Introduction	The introductory sections are well written and convey the importance of the work.	Thank you for the comment.
Peer Reviewer #3	Introduction	The introductory sections (and a few other places in the report) raise the question of whether EMS personnel with different levels of training should be permitted to administer naloxone. This is a very important question, yet was not addressed by any of the Key Questions of this review. The authors could provide a better description of how their findings (at least indirectly) inform this question, such as the lack of evidence of adverse events occurring from naloxone administration in standard doses.	As described in the methods, we evaluated the training and background of the person administering naloxone as a potential modifier of treatment effects. The "Subgroup effects" section in the Results for the Key Questions notes that few studies specified the level of training of EMS naloxone administrators and there was insufficient evidence to determine how level of EMS training affected findings.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Introduction	Similarly, Figure 1 identifies "injury to naloxone administrator" as an important harm outcome being evaluated, but is glossed over later in the report. Presumably, this is because none was found in published literature, a finding that is important and can inform those who make decisions regarding EMS personnel scope of practice and regulators who may allow use of naloxone by all lay persons.	The Discussion notes that studies were not designed to assess risk of serious injuries such as needle stick, and that no cases of serious injuries were reported in the RCTs or observational studies.
Peer Reviewer #3	Introduction	Page 4 – the final paragraph should include mention of addition of ED sites and ED personnel to the search strategy for Key Questions 1 and 1a.	Revised as suggested.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Introduction	1 27 Note that the paper by Sutter, et al makes the point that extremely high doses of naloxone are required by individuals taking large doses of fentanyl. This is also related to the issue that we don't know the optimal dosing of naloxone in the "fentanyl" or "ultra-potent" synthetic era.	The Sutter paper is cited in the Introduction when discussing fentanyl-related overdoses. We revised the Introduction to be clearer about issues related to fentanyl: "Of recent concern is whether current dosing guidelines are sufficient for reversing overdose related to highly potent synthetic opioids (e.g., fentanyl and fentanyl analogues)." We also added a sentence to the Research Recommendations section: "Of particular interest is whether overdoses related to illicit fentanyl or fentanyl analogues require higher doses of naloxone."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Introduction	2 8 As before the duration of action may be out to 80 minutes. I strongly agree with the statement that the risks of withdrawal are mild.	We revised the sentence to delete the discussion of naloxone half-life and added a sentence: "The duration of action of naloxone is 20 to 90 minutes, or shorter than many opioids." The source of the 20 to 90 minutes range is a recent NEJM article on treatment of opioid overdose.
Peer Reviewer #4	Introduction	2 29 Again, as scope of practice has not been updated since 2007, EMS providers have more knowledge than laypersons. They are great candidates to administer naloxone at all levels.	Thank you for the comment.
Peer Reviewer #4	Introduction	2 44 All true regarding the recommended starting doses of naloxone. AHA document is a consensus statement, and is not based on hard data. Again, in the ultra-potent synthetic era, those low doses have no place in the EMS setting, and are questionable in the ED setting).(04 mg).	The Introduction notes the concern about dosing given the increase in overdoses related to fentanyl. The purpose of the review is in part to determine appropriate dosing given the changing epidemiology of the opioids involved in overdose episodes.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Introduction	3 7 While the FDA approval process is very important, it is also notable that there is a large experience with the successful and safe use of off-label formulations in the prehospital setting.	We agree that there is clinical experience suggesting effectiveness of off-label IN naloxone; however, there are also concerns about its use. We added a sentence to the Introduction: "Despite clinical experience suggesting effectiveness of such off-label IN administration, potential concerns include inadequately characterized pharmacokinetics, low bioavailability, high rates of administration errors, and inadequate dosing for overdoses due to potent opioids."
Peer Reviewer #5	Introduction	The introduction clearly outlines the scope of the problem and why the topic is important for study and review. It also raises appropriate questions regarding the need to assess for the most appropriate initial and repeat naloxone dosing to achieve reversal of respiratory depression without the negative effect of inducing opiate withdrawal symptoms, as well as addressing the need for transport to a health care facility vs release on scene.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Introduction	ES-1 Second paragraph/Second sentence: - Early intervention is critical. Early EMS intervention is not. Hence the success of the community access naloxone programs.	We revised this sentence to be clearer that we are referring to timely interventions when EMS personnel respond to suspected opioid overdoses.
TEP Reviewer #2	Introduction	- Figure one - good representation of the questions and the answers sought.	Thank you for the comment.
TEP Reviewer #2	Introduction	Would suggest "administrator of naloxone" rather than "naloxone administrator" in the text.	Revised as suggested.
TEP Reviewer #3	Introduction	This was clear. I have attached a paper that may have been helpful in the overview of dosing- Connors review of dosing. But my notes further down suggest that some of the information under Findings in Relationship.... may be more appropriate in this section	We had identified this study which reviewed IV naloxone dosing recommendations in the update search; it does not meet inclusion criteria but we added a sentence in the Background describing the range in IV dosing recommendations.
TEP Reviewer #4	Introduction	yes	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Introduction	In both the Executive Summary (page ES-1, line 19-21) and the Introduction (page 1, line 33) the suggestion is made that most heroin users started with opioids prescribed for them. In fact although there is considerable evidence that heroin addicts started by abusing prescription drugs there is little evidence that these prescription opioids were actually prescribed for them (and not diverted). I am not certain that this point is relevant to this report in any event and I would delete it.	Deleted as suggested.
TEP Reviewer #5	Introduction	I would also delete the sentence on page 1, line 34 containing "serious adverse health consequences" or clarify what is meant. The magnitude of the problem stands quite well without these two sentences.	We revised to note hypoxic brain injury, aspiration, and seizures as potential serious adverse health consequences of nonfatal opioid overdoses.
TEP Reviewer #5	Introduction	Also of the editorial variety in the sentence on page 2, line 6 "incidence" may be more accurate than "rates".	We think it is appropriate to either use the term “rate” or incidence of withdrawal following administration of naloxone.
TEP Reviewer #5	Introduction	On page 3, the sentence on lines 14-17 the increase in repeated naloxone doses could also be due to variable endpoints for "reversal" with regard to time and degree (e.g., increased ventilation rate versus less sedation).	We are not sure how variable endpoints for reversal would result in increased use of multiple naloxone doses, or data to suggest that this is the case. We did not make revisions in response to this comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Introduction	Also on page 3, line 23 "upper airway obstruction" should replace "hypoxic injury" as unconsciousness does not routinely cause the latter without the former.	Revised as suggested
TEP Reviewer #5	Introduction	Finally on page 3, lines 25-30 the sentence enumerating the advantages of transport to hospital apart from death prevention should include " alerting prescribers if the offending opioids were prescribed".	Revised as suggested.
TEP Reviewer #6	Introduction	Comprehensive yet succinct review of why this topic is important.	Thank you for the comment.
TEP Reviewer #11	Introduction	Evzio, the approved autoinjector is also appropriate for use by persons with limited or no healthcare training	We revised to be clearer that both the auto-injector and the FDA-approved IN formulations can be used by persons with limited or no healthcare training.
Public Reviewer #7, David J. Withers	Introduction	Well written and I would not change it.	Thank you for the comment.
Public Reviewer #8, Shawn A. Ryan	Introduction	Key Question #4 needs to discuss availability of linkage to treatment when transported. Although it is currently poor in the US EDs, if they are not transported, the linkage to appropriate treatment is nearly 0%.	Linkage to care as a potential benefit of hospital transport is one of the listed outcomes for Key Question #4; however, as detailed in the Results, no studies evaluated this outcome.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8, Shawn A. Ryan	Introduction	Consider timing of administration in patient population with difficult IV access. With anoxic brain injury occurring 4-5 minutes from initial respiratory arrest, it should be discussed that delay to administration is a real issue.	We revised the "Implications for Clinical and Policy Decisionmaking" section to note that attaining IV access can be difficult and result in delays in administration.
Peer Reviewer #1	Methods	The inclusion and exclusion appear to justifiable, yet it was a bit challenging to follow what they we rein reference to as there are two sets of criteria listed. document flow issue? Search criteria was explicitly stated and appeared logical.	We are not sure what the reviewer is referring to in terms of "two sets of criteria listed". The Inclusion/Exclusion criteria section of the Methods describes one set of inclusion and exclusion criteria; as described some criteria varied for different Key Questions.
Peer Reviewer #1	Methods	I did not find the definitions and diagnostic criteria clearly stated.	The inclusion criteria are described in detail in the methods using the PICOTS approach. We are not sure what other "definitions and diagnostic criteria" the reviewer is referring to.
Peer Reviewer #1	Methods	Do not know enough about statistical methods to comment on this. Yet the descriptions of the methodologies made sense to me.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Methods	The rigor of these search and study selection methods and adherence to comparative effectiveness assessment guidelines cannot be overstated.	Thank you for the comment.
Peer Reviewer #3	Methods	The methods used in this systematic review are appropriate, justifiable, and generally appropriately described. Consider the following:	Thank you for the comment. See responses to specific comments from this reviewer.
Peer Reviewer #3	Methods	Page ES 5, lines 33-34 – Were the two investigators who reviewed the abstracts the same ones that reviewed the full-text articles? Minor point, but for clarity, consider stating "the same two investigators…" if appropriate.	No, they were not necessarily the same two investigators. Full text and abstract review were split among the investigators so there are not two specific investigators to list.
Peer Reviewer #3	Methods	Page ES-5, line 35 – "Discrepancies were resolved by discussion and consensus". Contrast this with the main report methods section (page 7, lines 16-17), that identifies use of "…a third investigator to resolve disagreements if necessary." This should be stated in the Executive Summary as well.	The Executive Summary is meant to be briefer so some details about the Methods (such as using a third investigator to resolve discrepancies) were omitted.
Peer Reviewer #3	Methods	Page 10, line 22 – "PICOTs" = "PICOTS".	Typo corrected.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	Inclusion and exclusion are good. I appreciate the grading of evidence in terms of risk of bias. This is accurate and appropriate. Search strategies were logical and appropriate. Definitions and outcome measures were clear and very clinically applicable. Methodology appropriate, and not doing a meta-analysis is appropriate.	Thank you for the comment.
Peer Reviewer #5	Methods	Inclusion and exclusion criteria are appropriate and justifiable. The methods are appropriate, well defined and clear. The statistical methods are also appropriate.	Thank you for the comment.
TEP Reviewer #1	Methods	The inclusion and exclusion criteria are reasonable. The search strategy makes sense and seems to have turned up all of the studies I would expect.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Methods	Literature search strategy:. Settings and study designs allowed inclusion of studies without controlled designs as they are rare in the EMS world and comment on the lack of evidence this creates. While I don't disagree; this is a key component of the issue that exist with the paper - there will not be better evidence. While not a key question, it probably should have been, "what is the outcome sought"? Some authors seek consciousness to a GCS of 15 and some allow somnolence and some to adequate respiratory rate or effort. This is sometimes not even clear in the papers and there is limited consensus as to the goal between the folks from emergency medicine and the folks from harm reduction.	As described in the Inclusion and Exclusion Criteria section of the Methods, we amended the protocol to included uncontrolled longitudinal studies for Keyu Question 4 of patients who were successfully treated for suspected opioid overdose with naloxone in the field and not transported to a healthcare faicility due to the lack of controlled studies addressing. The Results and Discussion note the limitations of this type of evidence. The Results describe the definition of "response/reversal" to the extent reported in the studies. We added a sentence to the "Limitations of the Evidence Base" section to note that "Studies varied in how an adequate response to naloxone was defined, or did not define adequate response."

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Methods	The steps are described explicitly. The criteria are justified but given the paucity of data I wish that they had been expanded. I can't comment sufficiently on the statistical methods	Thank you for the comment.
TEP Reviewer #4	Methods	Yes	Thank you for the comment.
TEP Reviewer #5	Methods	Methods were generally good despite minimal database to draw from without extensive bias. I would have liked to have what the reviewers mean by "statistical adjustment" which was referred to several times as a useful hedge against bias.	Statistical adjustment is a standard technique used to control for potential confounders, typically in observational studies. As this is a standard method for reducing confounding/bias in observational studies we did not feel that it warranted explanatory text.
TEP Reviewer #5	Methods	Editorially on page 9, line 11 "duration" should be clarified ("time to effect", "time of effect", "time to administration", etc) and on page 10, line 7 "will not" should probably be "did not". Similarly on page 11, line 24 "will be" should probably be "were".	We revised page 9 line 11 to clarify that we were referring to timing of initial and repeat dosing. Other edits made as suggested.
TEP Reviewer #6	Methods	Appropriate search strategy used to address key questions	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #7, David J. Withers	Methods	I thought that the literature search was fairly exhaustive. The sheer volume of articles picked up by the search was impressive. I think restricting the language to English may have missed a few but I see no other practical way to do the search. Seasoned researchers read each one for applicability/suitability for inclusion	Thank you for the comment. As noted in the "Limitations of the systematic review process" section of the Discussion, we excluded English language studies, but also did not identify any foreign language studies that appeared to meet inclusion criteria in our literature searches or in references lists.
Public Reviewer #8, Shawn A. Ryan	Methods	Good methodology when dealing with a complicated mostly community based question and paucity of evidence.	Thank you for the comment.
Peer Reviewer #1	Results	Amount of detail in the results were appropriate. results as presented should be able to be understood by all levels of EMS providers.	Thank you for the comment.
Peer Reviewer #1	Results	Key messages were clear.	Thank you for the comment.
Peer Reviewer #1	Results	Consider adding a table that includes data in key findings section. Numbers get lost in the narrative.	The key findings, including strength of evidence ratings, are summarized in Appendix F. Each section of the Results has key findings summarized; findings are further summarized in the Discussion and Conclusions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	Not aware of any missed studies.	Thank you for the comment.
Peer Reviewer #2	Results	The key characteristics of the studies are summarized in an easily comparable format. I appreciated the section on excluded studies and reason why excluded, but I feel the report could be more clear if there were more specific definitions/examples of the exclusion criteria for these studies, instead of "wrong outcome" for example, list that studies outcome and the desired outcome needed for inclusion in the analysis.	The outcomes were specified in the PICOTS section of the Methods. We did not track the outcomes evaluated in excluded studies.
Peer Reviewer #3	Results	The results as reported appear an appropriate summary and interpretation of prior work. However, findings of prior studies are repeated at least 5 times each in different sections of the report (between Executive Summary and Main Report) making the entire report needlessly lengthy and wordy. This includes description of the same results in various discussion sections provided. Consider modifying the report to avoid needless repetition of findings. Ideally there should be one description of findings (results section) and one discussion of said findings.	The Executive Summary is meant to be a standalone document; therefore results are presented there as well as in the Main report. Because some readers focus on the Discussion section, we also include descriptions of the results to the extent needed to provide context to the Discussion.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	Page ES-8, lines 28-31 – Recommend providing some details of the findings of the two cohort studies comparing IN vs IV naloxone. In spite of the expressed limitations of these studies, given the lack of additional literature, a description of their core findings would seem appropriate here. Same comment for the respective section in the main report (page 13, lines 45-48).	We think that the details of the cohort studies, which were generally of low quality, are presented adequately in the Key Points presented in the ES. The results of the cohort studies are described in detail in the Results section of the main report as well as in the summary table and evidence table.
Peer Reviewer #3	Results	Page ES-8, line 37 – "difference doses" = "different doses".	Typo corrected.
Peer Reviewer #3	Results	Consider adding reference/citations in the Key Points sections to be clear about what study is being summarized.	The Key Points are intended to summarize the main findings without references; the references are included in the text detailing the results.
Peer Reviewer #4	Results	Detail: Good Characteristics: Well summarized Key messages are explicit and clinically applicable. Tables with summaries of the studies are good. Inclusion of appropriate studies good.	Thank you for the comment.
Peer Reviewer #4	Results	13 15 Very clearly presented.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	16 1 Tables very clear. Good presentation of bias level up front.	Thank you for the comment.
Peer Reviewer #4	Results	21 43 The discussion of to transport or not transport is excellent. In particular framing it that "100% of patients who were not transported had a GCS of 14-15 compared to about 50% of patients who were transported to the ED." This is very important. Also important are the limitations in follow-up. Not necessary to include but for your reference is this recent paper that questions the duration of observation time in the ED after a heroin OD. They do not acknowledge the issues of selection bias of those transported to the ED as being a different population adequately. Using highly biased evidence to change practice in another setting is risky. Michael W. Willman, David B. Liss, Evan S. Schwarz & Michael E. Mullins (2016): Do heroin overdose patients require observation after receiving naloxone Clinical Toxicology, DOI: 10.1080/15563650.2016.1253846	Thank you for the comment. We identified the Willman article cited by the reviewer. It is a review article and therefore did not meet inclusion criteria. We reviewed the references in the article for potential inclusion and identified no additional studies that met inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Results	The results section clearly presents the data found in their review of studies, and also points out that there is not good evidence available to actually address the key questions. The characteristics of the studies are clearly described. The key messages for me are clear in that the review points out that there is very limited data to base broad policy decisions upon. The figures, tables and appendices are adequate and descriptive.	Thank you for the comment.
TEP Reviewer #2	Results	I was surprised at the lack of inclusion of an on-going field trial comparing the 0.4/1 and the 2/2 intranasal formulations. This non-corporate sponsored trial is likely the best comparison that will be available of these naloxone formulations and was readily available to the authors. The trial information was provided at the recent FDA meetings and was also provided to the authors directly.	The reviewer sent an abstract of this study. However, we verified with the reviewer that this study has not yet been published (either as an abstract or full study) and is ongoing. Therefore, it does not meet criteria for inclusion in the report. We added a sentence to the Research Recommendations Section noting that this field study is ongoing, with a brief description of its design.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	The studies are completely described and the tables appropriate. I have attached another study that might have been useful in answering Key question 4- Rudolph. And I believe that Michael Dailey's abstract comparing the 2mg/2cc IN to the 4mg/0.1cc was available but the researchers chose not to use it. It is small numbers but it has been very useful The Key Points for Q1 on page 13 are too detailed to digest quickly, much can be left in the synthesis.	The Rudolph study assessed patients who were not transported to a hospital following treatment for opioid overdose, but was excluded because opioid overdose was treated by physicians, not EMS personnel. The Dailey study has not yet been published (either as an abstract or full study) and is ongoing. Therefore, it does not meet criteria for inclusion in the report. We added a sentence to the Research Recommendations Section noting that this field study is ongoing, with a brief description of its design.
TEP Reviewer #4	Results	Good detail	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	Results were clearly documented, illustrated and described in the text generally. I would have liked to hear anything about N/V and particularly aspiration. Presumably this adverse response to overdose or naloxone reversal was either not stated in the literature reviewed or not thought to be important although is clearly a risk for morbidity from opioid overdose - likely rivaling apnea for causing hypoxia in these patients.	We revised the Results to be clearer that there were not differences in rates of nausea and vomiting in the RCT's. There were also no differences in serious adverse events, which would presumably include aspiration.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	In the description of the RCTs on page 14, line 33-52 little was made of the difference between the 8 minute endpoint at the beginning of the paragraph and the 10 minute endpoint at the end. Clearly the more concentrated naloxone was thought to be more important and yet the difference between rescue naloxone in the IM groups (13% vs 4.5%) is clearly not explained by IN naloxone concentration.	The reviewer appears to be referring to the outcomes evaluated in two different trials (spontaneous respirations at 8 minutes in one trial and "adequate response" within 10 minutes in the other) and comparing rates of rescue naloxone use across trials. We don't think it is possible to make inferences based on these differences given that they are based on cross-trial comparisons, other factors also differed across the studies, and there were only two studies. Rather, we focused on the within-study findings from individual trials and then discussed how those findings differed.
TEP Reviewer #5	Results	I was also disappointed to not see any Glasgow scores in the study at the end of the paragraph and assume that this was an oversight by the original authors and not the reviewers.	The second trial of IN vs. IM naloxone did not report outcomes defined by Glasgow scores. The proportion of patients responding to naloxone based on GCS scores is reported form the first trial.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	Again, in discussing Key Question 1A on page 19, lines 24-29 no mention is made of nausea, vomiting or aspiration unfortunately.	We revised the results for KQ 1 (where the main results of the trials were presented) to clarify that there were no differences in rates of nausea or vomiting. There were also no differences in serious adverse events, presumably including aspiration.
TEP Reviewer #5	Results	Similarly, in detailing the review related to Key Question 3 on page 20, lines 51-56 no aspiration concerns were mentioned and the importance of airway skills likely important in determining best time intervals for repeating naloxone was only hinted at.	No studies met inclusion criteria for Key Question 3, therefore no outcomes (including aspiration) could be reported.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	Research is limited on this topic so it would have been useful to broaden the scope of studies reviewed.	As described in the Methods, we included RCTs as well as cohort and case-control studies for all Key Questions. For Key Question 4, we also expanded inclusion criteria to include longitudinal studies of patients treated for opioid overdose who were not transported to a hospital. Further, we expanded inclusion beyond administration of naloxone in field settings by EMS personnel to include studies of naloxone administered in field settings by first responders and laypersons, and studies conducted in ED settings. Despite broadening the criteria to address the Key Questions, evidence was still very limited.
Peer Reviewer #1	Discussion/ Conclusion	Discussion section clearly stated major findings.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion/ Conclusion	I was impressed with the future research section. It clearly suggested types of studies that should be conducted to answer the questions past studies did not address. This section also identified some of the challenges facing future studies.	Thank you for the comment.
Peer Reviewer #2	Discussion/ Conclusion	Yes, the implication are clearly stated, and the included studies' information in the tables is helpful.	Thank you for the comment.
Peer Reviewer #2	Discussion/ Conclusion	The future research section is an adequate blueprint for future studies; it could be improved with more graphical descriptions instead of just text.	Thank you for the comment. We revised the future research needs section to include bullet points for improved readability.
Peer Reviewer #3	Discussion/ Conclusion	The discussion points are appropriate. As with the results section, there is substantial repetition of the various points that are made and repetition of study findings, in some cases almost verbatim. See additional comments below under Clarity and Usability.	The Executive Summary is meant to be a standalone document; therefore results are presented there as well as in the Main report. Because some readers focus on the Discussion section, we also include descriptions of the results to the extent needed to provide context to the Discussion.
Peer Reviewer #3	Discussion/ Conclusion	Page ES-9, line 54 – “due serious” = “due to serious”.	Typo corrected.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Discussion/ Conclusion	Page ES-10, lines 8-11 – "There was also insufficient evidence to determine how the type or training of EMS personnel administering naloxone impacted comparisons involving different routes of administration or doses of naloxone." As mentioned above, it is unclear how or if this question was directly addressed by the project's methodology. A comparison of administration by different provider types was not a Key Question and it is unclear in the methods how the authors aimed to answer this question directly. Was it an a priori question being answered, or a concept considered after review of the literature? If the authors aimed to answer this question directly, some description of their approach should be included in the methods section (even if only being looked at indirectly but with forethought).	As described in the methods, we evaluated the training and background of the person administering naloxone as a potential modifier of treatment effects. The "Subgroup effects" section in the Results for the Key Questions notes that few studies specified the level of training of EMS naloxone administrators and there was insufficient evidence to determine how level of EMS training affected findings.
Peer Reviewer #3	Discussion/ Conclusion	Page ES-10, lines 48-49 – The detail that in the Iranian trial a high proportion of overdoses was due to opium (versus other opioids used in the US) is an important point that should be included in the results section (consider mentioning within ES-8, lines 19-28).	The ES is meant to summarize key findings. The detail about the proportion of overdoses related to use of opium is discussed in the Results of the Main report.
Peer Reviewer #3	Discussion/ Conclusion	ES-12, line 15 – Concentration of IM naloxone should be included here for completeness.	The concentration of IM naloxone is not thought to be critical for effectiveness as for IN naloxone, so we do not think providing this detail is necessary.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Discussion/ Conclusion	Page 24, line 55-56 – Consider changing "requiring repeat doses" to "receiving repeat doses" for the reasons described later in this paragraph. Same for Page 29, line 34.	Revised as suggested.
Peer Reviewer #3	Discussion/ Conclusion	Page 28, lines 26-38 – This entire paragraph seems repetitive of content from prior section.	The reviewer is referring to the "Limitations of the Evidence Base" section. The limitations are alluded to in other parts of the report but summarized in this section as per the standard AHRQ EPC report template. We did try to summarize the Limitations succinctly in a single paragraph.
Peer Reviewer #3	Discussion/ Conclusion	Page 29, line 7 – Consider mentioning need for future research not only on ability of different provider levels to use naloxone, but on use by lay persons as well.	The Research Recommendations section notes that studies of naloxone administration by non-EMS first responders and laypersons could also be informative.
Peer Reviewer #4	Discussion/ Conclusion	24 8 "bet" should be "be"	Typo corrected.
Peer Reviewer #4	Discussion/ Conclusion	24 54 This is a very important observation in the EMS registry, and should be followed in the future to inform our handling of the ultra-potent opioids.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Discussion/ Conclusion	25 16 I don't know the answer to this, but for the Pharma cited studies, is it worth noting when they are industry-sponsored, or have not gone through independent peer review? I don't know if there is a procedure for this. For example "one study presented at the FDA meeting found that survival rates were very similar following IN admin of one, two, or >3 doses of IN naloxone 93-95%.." The effect of naloxone vs, or with the airway adjuncts makes this difficult to interpret.	The reviewer is referring to studies presented at the FDA meeting. We added the following to the end of this section: "Unpublished data presented at the FDA meeting have not undergone independent peer review. In addition, some studies were funded by industry." None of these studies met inclusion criteria and are mentioned only to provide some context to the Discussion. We also added information to the Results regarding whether included studies were industry-funded.
Peer Reviewer #4	Discussion/ Conclusion	26 10 Again, This is a very important point.	Thank you for the comment.
Peer Reviewer #4	Discussion/ Conclusion	26 16 Implications for Clinical and Policy Decision making section is very good.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Discussion/ Conclusion	27 47 A point that could be highlighted.	The point the reviewer is referring to is that evidence on use of naloxone by laypersons could inform use of naloxone by EMS personnel. This is noted again in the Research Recommendations section, and we planned to include studies of naloxone delivered by laypersons (none met inclusion criteria).
Peer Reviewer #4	Discussion/ Conclusion	27 52 You could also include that in an increasing number of states, that Pharmacists can do the prescribing and training themselves such as in Illinois even though it is not OTC.	Prescribing and training related to naloxone is outside the scope of this review.
Peer Reviewer #4	Discussion/ Conclusion	28 24 No attempt at meta-analysis: Kudos.	Thank you for the comment.
Peer Reviewer #4	Discussion/ Conclusion	21 41 Cost is a very important factor, and the off label products have been shown with safe and effective use. The EMS community should keep this in mind.	Thank you for the comment. Cost is noted as one of the factors that might influence decisions regarding dose and route of administration in the "Implications for Clinical and Policy Decisionmaking" section.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Discussion/ Conclusion	Although the results section is clear that the strength of evidence is insufficient to answer any of the key questions, there is important information to be gained from this relative lack of evidence. The key messages for me are clear. There is not good evidence to support increasing the minimum standard dose of naloxone for a suspected or confirmed opioid overdose from the FDA threshold dose of 0.4 mg IM as it currently stands, or to definitively state that increased dosing is necessary.	Thank you for the comment.
Peer Reviewer #5	Discussion/ Conclusion	The authors are also clear that there is not evidence to support titrating reversals only to reverse the respiratory depression but not to return a patient to full consciousness so that they are capable of being released on scene. The lack of evidence is also reported clearly regarding the safety of releasing opiate overdose patients after they have had a successful reversal.	Thank you for the comment.
Peer Reviewer #5	Discussion/ Conclusion	The future research needs section lays out the clear needs to move forward with new research, especially with research that will address the key questions this study sought to answer.	Thank you for the comment.
TEP Reviewer #1	Discussion/ Conclusion	The implications of the results are well stated. The authors correctly note the limitations of the study, which are mainly due to the paucity and relatively low quality of the underlying research.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/ Conclusion	Odd that throughout the paper the IM auto injector is mentioned as the "recently FDA approved" device and the 4mg in 0.1ml IN device does not get similar treatment. Indeed, the Evzio auto injector was marketed prior to the approval of the Adapt device.	This is not accurate. We describe both the FDA-approved IM and IN formulations as “recently” approved (see Abstract/Limitations, page 27 paragraph 1, p 28 paragraph 3)

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/ Conclusion	Long commentary on the "evidence was insufficient" however the reality would be that the reasons the evidence was insufficient included questions that will not be able to be answered. Opioid overdose victims do not fill a single demographic and will not be able to be accessed in a standardized manner with well structured variables readily available for review - type and dose of opioid, prior opioid overdose, concomitant psychiatric disease and other confounders will not be able to be included in any study design, but more importantly, will not be able to be included in a plan of treatment either. This is an esoteric series of questions with limited clinical relevance for EMS naloxone dosing as the EMS dosing will not be based upon any factors other than the findings of suspected opioid overdose.	Thank you for the comment. The Key Questions were determined with input from NHTSA, other federal partners, technical experts, and the public. Questions related to comparative effectiveness of different doses and routes of administration, as well as transport vs. non-transport, can be addressed in trials and appropriately designed observational studies. Although evaluating effets of some potential modifiers of treatment effects such as type and dose of opioid involved in the overdose may be challenging, but could be examined in appropriately designed studies.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion/ Conclusion	The papers discussing the non-transport are interesting as well. Clearly this is a growing practice in EMS, but the newer trends in oral opioid use as well as high potency synthetic opioids bring questions for previously studied practice. The said, the population described, the opioid user, is unlikely to ever participate in a trial for longitudinal outcomes unless it can be done in a relatively blinded fashion. Scandinavian studies with their robust systems of longitudinal data collection may allow for this - US studies will not be likely. Suggest Gjersing & Bretteville-Jensen article in Addiction (DOI: 10.1111/add.13026) as a reference.	We did not restrict inclusion of studies to trials—in fact for this key question we specifically broadened inclusion criteria to include uncontrolled studies of non-transport as well as controlled studies. The Gjersing study does not meet inclusion criteria, it compared mortality risk following an overdose episode vs. outside an overdose episode; it did not compare outcomes of transport vs. non-transport.
TEP Reviewer #2	Discussion/ Conclusion	The conclusion does not allow for EMS care as it suggests that naloxone 2mg / 1 ml be used IN which is not a formulation in regular clinical practice in the US. I this a typo and should have been 2mg/2ml?	The 2 mg/1 mL formulation was used in the randomized trials, so is the only IN formulation that randomized trial evidence is available for.
TEP Reviewer #3	Discussion/ Conclusion	The limitations are clear. Unfortunately the limitations are such that it is hard to draw new policy decisions from it. The major findings are only clear in the abstract and the conclusion.	Thank you for the comment. We agree that there are important limitations in the literature that we attempted to highlight in the Abstract and Conclusion.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Discussion/ Conclusion	Much of the discussion is noting the lack of studies which is well noted throughout the document. Perhaps it could be shortened to discuss the existing evidence and a list made of the unanswerable questions?	The Key Findings and Strength of Evidence section of the Discussion summarizes the main conclusions, as well as some of the limitations in the literature. There are separate sections that discuss Applicability issues as well as Limitations of the Evidence Base in more detail.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Discussion/ Conclusion	Pg 24 Findings in Relationship to what is already known: It is not clear what has been added, this section adds new information, primarily about the FDA meeting. Perhaps this belongs in the introduction?	The purpose of this section is to provide some context to our findings and how they may be consistent with or differ from existing knowledge in this area. This section often contrasts our findings with preexisting systematic reviews, but in this case there are no systematic reviews on dose or route of naloxone administration. We elected instead to focus on how other types of evidence (e.g., pharmacokinetic studies, EMS registry studies, survey data) that did not meet inclusion criteria but may provide some useful contextual or background information; much of the information was drawn from a recent FDA meeting and associated materials presented there.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Discussion/ Conclusion	Pg 25 And while the retrospective Amphastar is vague on who the NYS and NJ first responders are it could be clarified now that in NYS it was law enforcement. Law enforcement perhaps straddles the line between EMS and community as they may carry some basic ventilation equipment but often have none and may not have had up to date CPR training. (also the references 52 and 73 link to the same Amphastar document) The section on research is very helpful	We revised the discussion of the retrospective study to refer to "first responders" rather than "EMS personnel." As the materials available from the FDA meeting do not describe the first responders in more detail, we did not add further information about the first responders being law enforcement personnel.
TEP Reviewer #4	Discussion/ Conclusion	Yes	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Discussion/ Conclusion	In the discussion several mentions are made of the FDA conferences around naloxone. However no mention is made of why concentrations have been changing for both IN and IM FDA approved products. Surely there must be some data to suggest why formulation changes are being made or even why the decisions were made to so highly concentrate the IN naloxone (40X more concentrated than the studies reviewed). Is there ANY relevance in looking at past studies if the much more concentrated naloxone given IN is a game changer?	The Introduction notes that concentrated IN solutions are important given the low rate of absorption/low bioavailability of lower concentration/higher volume doses. The Introduction also describes the equivalent FDA threshold dose (0.4 mg IM naloxone) used to inform approval of new formulations. Also, as discussed in the Introduction, the FDA recently approved a higher dose auto-injector formulation, but less concentrated/lower dose IN formulation, suggesting uncertainty with regard to optimal dosing.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Discussion/ Conclusion	On page 26, in the last line vomiting and perhaps aspiration is specifically called out as a risk of naloxone but no data is given regarding comparative risk with "No naloxone".	This sentence is describing risks of withdrawal, which include agitation, vomiting, and potential aspiration. The effects of different routes of naloxone administration on risk of nausea/vomiting are discussed in the Results; no cases of serious AE's or aspiration were reported.
TEP Reviewer #5	Discussion/ Conclusion	On page 27, lines 24-28 in discussing the endpoint for naloxone titration I would encourage reviewers to remember their earlier comments regarding the common additional sedatives found in opioid overdoses (as high as 70% in some coroner studies). If patients are ventilating appropriately it seems unwise to continue to give naloxone hoping for return of consciousness as this is likely to cause more and more withdrawal (including agitation) without effect in a nonopioid sedation circumstance.	We added the following sentence: "In overdoses involving opioids plus non-opioid substances and drugs, attempting to dose naloxone to achieve full consciousness may be futile and cause more severe withdrawal and agitation."
TEP Reviewer #5	Discussion/ Conclusion	Editorially, on page ES-9, line 54 "to" should go between "due" and "serious" and and on page 25 in line 13 "may" should be followed by "be".	Typos corrected
TEP Reviewer #6	Discussion/ Conclusion	Summary of the reviewed studies is clear and appropriate.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #11	Discussion	Particularly in the early critical period after drug administration. For example, a new product may achieve similar rates (Cmax) and extent (AUC) of absorption but could have overall lower levels in the first few minutes after dosing. Therefore, to ensure an acceptable onset of action, the levels achieved with the new product need to be comparable to or greater than the approved dose in this early period.	Thank you for the comment. Details about pharmacokinetics are beyond the scope of this report. The Introduction does note that the FDA threshold for approval of new IN formulations was based on similar pharmacokinetics to a 0.4 mg IM dose.
TEP Reviewer #11	Discussion	Consider whether “route of administration” is relevant for inclusion in this list	We were unable to determine where in the Discussion this comment referred to.
TEP Reviewer #11	Discussion	From the naloxone label: In neonates, opioid withdrawal may be life-threatening if not recognized and properly treated.	Use of naloxone in neonates is outside the scope of this report.
TEP Reviewer #11	Discussion	The two doses were approved because both met the pharmacokinetic standard outlined by the Agency.	Thank you for the comment. We describe the recently approved FDA formulations in the report.
TEP Reviewer #11	Discussion	These studies may pose significant ethical challenges	The Research Recommendations section notes ethical and logistical challenges of conducting RCTs, and suggests leveraging existing EMS dat registries.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #7, David J. Withers	Discussion	I love the discussion of the prices of the various products being included, and some of them on the market that did not show up in the literature.	Thank you for the comment.
Public Reviewer #8, Shawn A. Ryan	Discussion	Given that we are seeing increased rates of IV use = harder to obtain IV access for administration, should there be more discussion about ease of use and lower needle stick rates when using IN formulation. EMS harm from needle sticks in a population with high rates of Hep C should be at least mentioned as a risk/benefit evaluation.	We revised the Implications for Clinical and Policy Decisionmaking section to note "delays in administration" as a potential drawback of IV administration of naloxone. This section already discusses concern regarding the risk of needle stick injuries and potential advantages of needleless routes of administration.
Public Reviewer #8, Shawn A. Ryan	Discussion	Potentially could put linkage to treatment discussion here.	The Results and Discussion note that it is not known whether hospital transport is associated with beneficial effects on outcomes such as linkage to treatment.
Public Reviewer #7, David J. Withers	Conclusions	I do agree with the conclusions, in general	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8, Shawn A. Ryan	Conclusions	Although it is tough to make conclusions in this body of research, the group did a good job with what is available. Especially given the difficulty of IV access in this population. It was also good that the high potency of synthetic opioids is discussed (please see below for important discussion on risk/benefit of higher dose of naloxone)	Thank you for the comment.
Peer Reviewer #1	Clarity and Usability	I found the document a nice balance, not so complicated and not too simplistic.	Thank you for the coment.
Peer Reviewer #1	Clarity and Usability	EMS professionals need to be pushed to read documents like this to understand the complexity of making evidence-based decisions.	Thank you for the comment.
Peer Reviewer #1	Clarity and Usability	I think the report manages this balance well.	Thank you for the comment.
Peer Reviewer #2	Clarity and Usability	The report is well-organized, but the length and repetitiveness of both the main report and the executive summary may limit usability and/or generate new research. The appendices are helpful, as well as the tables and figures, but sometimes the authors could be more succinct, especially in the executive summary.	We attempted to keep the Executive Summary as brief as possible (e.g., shorter Introduction, results limited to bullet points, shorter Discussion). However, because this is intended to be a standalone document, some details regarding background, methods, results, and findings are necessary.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Clarity and Usability	The conclusions ARE succinct and should drive policy, but their greater reach should be to fund research to better answer these key questions. For overdose response researchers like me, this report adds no new information, but rather confirms assumptions and literature evaluation via a systematic review.	Thank you for the comment. The Future Research Needs section is intended to help inform future research priorities.
Peer Reviewer #3	Clarity and Usability	Generally, the report is lengthier than needed to convey the limited information found in this systematic review. Aiming for a shorter report that avoids extensive repetition of the same content would substantially improve the readability, clarity, and especially the likelihood that important stakeholders will read through the report (usability). The authors should consider the ability to condense the report and avoid repetition as important as the need to provide a full description of pertinent findings.	The report was summarized in an Executive Summary as well as in an Abstract and Key Messages. We intend to submit a journal manuscript of this report for publication, to provide an even more condensed version.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Clarity and Usability	As example, the Executive Summary is 12 pages (minus references), more than 1/3 the length of the full report (30 pages) and in many ways provides the same information in almost as much detail. A condensed Executive Summary should be considered. I would suggest that not all sections of the main report are necessary for an Executive Summary. As further example, the Key Findings and Strength of Evidence section summarizes the results and the Applicability section summarizes the results again.	We attempted to keep the Executive Summary as brief as possible (e.g., shorter Introduction, results limited to bullet points, shorter Discussion). However, because this is intended to be a standalone document, some details regarding background, methods, results, and findings are necessary and sections of the Executive Summary generally parallel those in the main report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Clarity and Usability	The section on Research Recommendations could be substantially shortened for the Executive Summary. What are the most important gaps in knowledge that were identified in this literature review? This is arguably the most important contribution that this literature review will make to this topic given the limited literature found. Where should the focus of future research on this topic be (i.e. what are the top 3-5 questions that remain to be answered – the Key Questions not answered in this report or additional concepts such as ability of lay persons versus EMS personnel of different levels being able to administer naloxone)? Generally, this section could be more succinct and impactful.	We deleted the last paragraph from the Research Recommendations section in the Executive Summary on alternative routes of administration (e.g., mask nebulization, SL, buccal), which we do not feel are major priorities for the reasons described in the full report. We also revised to shorten the text in this section to make it more succinct and highlight the priorities for the various Key Questions.
Peer Reviewer #4	Clarity and Usability	This report is well organized. The main points are clear. The conclusions identify future directions for study. They could compare off label to FDA approved products to see if the more costly approved products are any different, but calling on the as yet untested FDA approved products to be tested is appropriate.	Thank you for the comment.
Peer Reviewer #4	Clarity and Usability	We must watch the efficacy of naloxone in the field closely as the context of high potency opioids being out there will change our current understanding.	Thank you for the comment. This issue is highlighted in the Introduction as well as in Research Recommendations.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Clarity and Usability	This report is structured well, reads clearly, and presents the main points clearly and thoroughly. The conclusions are relevant and describe the need for further research as well as lay out the specific areas where research is needed. There is not new information presented per se, but the summation pulls the existing base of knowledge together well and it definitely contributes to a greater understanding of the existing data.	Thank you for the comment.
TEP Reviewer #1	Clarity and Usability	The report is well presented and readily understood.	Thank you for the comment.
TEP Reviewer #2	Clarity and Usability	Considerations for future research is the most valuable section of the paper. This is a difficult issue to study, with a population generally untrusting of the public safety rescuers who would be tasked with performing the studies. Longitudinal studies will be difficult, so best practices must be openly shared. I would suggest that the conclusions add little to policy decisions and nothing to the understanding of the problem - this is not the fault of the authors, but is the nature of the literature they have at their disposal.	Thank you for the comment. The Research Recommendations section discusses ethical and logistical challenges with conducting the needed research, as well as some potential strategies.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Clarity and Usability	I am perplexed by the Executive summary which seems to be a repeat of the actual piece. A 2 page summary of the key questions and key points would be very helpful.	We attempted to keep the Executive Summary as brief as possible (e.g., shorter Introduction, results limited to bullet points, shorter Discussion). However, because this is intended to be a standalone document, some details regarding background, methods, results, and findings are necessary and sections of the Executive Summary generally parallel those in the main report.
TEP Reviewer #3	Clarity and Usability	The work also is rather repetitive on the lack of data, it was hard to tease out what was found except in the abstract and the conclusion.	The Key Findings and Strength of Evidence section of the Discussion summarizes the main conclusions, as well as some of the limitations in the literature. There are separate sections that discuss Applicability issues as well as Limitations of the Evidence Base in more detail.
TEP Reviewer #3	Clarity and Usability	The section on what research is needed is very useful.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Clarity and Usability	Well organized	Thank you for the comment.
TEP Reviewer #5	Clarity and Usability	Clear and organized. The Executive Summary may be a bit long (12 pages of text vs 30 pages in the main report).	Thank you for the comment.
TEP Reviewer #6	Clarity and Usability	Yes all key questions were addressed based on available research.	Thank you for the comment.
Public Reviewer #7, David J. Withers	References	clearly a wide enough survey, well described, references annotated appropriately.	Thank you for the comment.
Public Reviewer #7, David J. Withers	Tables	lot of information and not sure how to compress it without losing granularity.	Thank you for the comment.
Public Reviewer #7, David J. Withers	Figures	figures were pretty clear. I don't know how to make them more clear.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Executive Summary	Specific Comments: Page Line ES-1 19 This is indeed the common narrative that many individuals began with a prescription. The 80 percent may be from a prescription that they received, or may be from prescription pills that they may have used through diversion. Indeed we need to learn more to know what the current statistics are, and how many are going directly to heroin. Also useful is the relationship between gross pill counts and misuse. Not sure that this info is necessary here.	We deleted the sentence discussing the proportion of heroin users who report prescription opioids as their initial opioid of abuse; we agree with the reviewer that it is not necessary.
Peer Reviewer #4	Executive Summary	ES-1 36 While the concept of "half-life" is very important, so is the concept of pharmacodynamics, or the duration of effect. This does not always correlate cleanly with half-life. Particularly in the case of methadone, naloxone can have a more prolonged duration of withdrawal. However, in the population being discussed here with the routine EMS use, I feel this is reasonably presented. Some do cite a range of half life out to 80 min.	We agree that the duration of action may be more clinically relevant than the half-life. We revised the sentence to delete the discussion of naloxone half-life and added a sentence: "The duration of action of naloxone is 20 to 90 minutes, or shorter than many opioids." The source of the range in duration is from a recent NEJM review article on treatment of opioid overdose.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Executive Summary	ES-1 56 Good discussion on appropriate training levels for EMS personnel who are permitted to administer naloxone: It is notable, as discussed by the authors, that laypersons have been trained and have successfully used naloxone. I would argue that as this is indeed the case, that all levels of EMS personnel can be trained to administer naloxone.	Thank you for the comment.
Peer Reviewer #4	Executive Summary	ES-10 18 The discussion here about determining evidence regarding transport is excellent. This is a correct interpretation of the literature. Many are challenging practice and stating that non-transport is safe, but you correctly point out the limitation of the studies published.	Thank you for the comment.
Peer Reviewer #4	Executive Summary	ES-10 34 Agree with limitations section. One additional reference pointing out the high proportion of fentanyl in Massachusetts is good for context: Somerville NJ, O'Donnell J, Gladden RM, et al: Characteristics of fentanyl overdose-Massachusetts, 2014-2016 2014–2016. MMWR Morb Mortal Wkly Rep 2017;66:382–386. DOI: http://dx.doi.org/10.15585/mmwr.mm6614a2.	We added the suggested reference to the Introduction when discussing overdoses related to illicit fentanyl, and another article by Tomassoni et al (MMWR 2017;66:107) that also discussed an outbreak of fentanyl-related deaths.