PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	User-Centered Clinical Decision Support to Implement Emergency Department-Initiated Buprenorphine for Opioid Use Disorder: Protocol for the Pragmatic Group Randomized EMBED Trial
AUTHORS	Melnick, Edward; Jeffery, Molly; Dziura, James; Mao, Jodi; Hess, Erik; Platts-Mills, Timothy; Solad, Yauheni; Paek, Hyung; Martel, Shara; Patel, Mehul; Bankowski, Laura; Lu, Charles; Brandt, Cynthia; D'Onofrio, Gail

VERSION 1 – REVIEW

REVIEWER	Franchitto Nicolas Service d'Addictologie, CHU PURPAN, Toulouse, France
REVIEW RETURNED	20-Jan-2019

GENERAL COMMENTS	Thank you for giving me the opportunity to review this trial. This interesting subject is timely. Opioids use disorder is a major public health problem worldwide. Emergency departments are usually the first contact with medical and social care for these patients, underlining the need to promote such promising treatment. I have minor comments: - regarding the high prevalence of patients presenting to emergency departments (ED) with opioid use disorder, I agree that trained physicians inside the ED should initiate opioid substitution rather than referring patients to specialized team after being detoxified. Nonetheless, are the authors sure that patients are motivated enough when they are admitted to the EDs? Is vulnerability to morbidity or mortality not a barrier to start the treatment? - the CBS EMBED intervention is well designed. - one strength is the fact that non-waivered clinicians may administer a one-time dosing to alleviate ow symptoms. - authors should explain the figure 2 – indeed if COWS score is higher than 8, BUP is given inside the ED and patient is observed. Then, if a waivered provider is able to prescribe BUP, 16 mg dosing for each day is delivered to patient until appointment for ongoing treatment. This latter point is hard to understand. When the patient is discharged from ED, does he have received many pills once? Should he return every day to ED to take the 16 mg pill? Is the patient aware of the date of the next appointment when he./she is discharged?

	- regarding the DSM5 criteria, how do the trained physicians deal with comorbid substance use disorder (especially alcohol use disorder) and comorbid psychiatric condition before initiating BUP?

REVIEWER	Laura Kehoe, MD, MPH Massachusetts General Hospital
REVIEW RETURNED	18-Feb-2019

GENERAL COMMENTS	Outstanding -- really looking forward to the results! 1)Figure 3 notes bupe initiation recs for DSM V criteria >/= 3, but PDF of ED initiated bupe algorithm is for moderate- severe use disorder, which would be >/= 4 DSM V criteria 2) P 12, line 44: please define JDD 3) P13, line 43: if pt not seen for fu in the same system, what is the fu plan for those outside the system? 4) P 13, line 48- what are the predetermined intervals to send data to DCC? 5) P 13 line 54, what is considered a recent admission (days, weeks, months)? 6) P 14, line 5 - how will you control for different tox sceens, particularly as not all testing for fentanyl? 7) P 15, line 6: are repeat ED visits for all reasons, or only SUD related?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Franchitto Nicolas
Institution and Country: Service d'Addictologie
CHU PURPAN
Toulouse
France
Please state any competing interests or state ‘None declared’: none declared

Please leave your comments for the authors below
Thank you for giving me the opportunity to review this trial.
This interesting subject is timely.
Opioids use disorder is a major public health problem worldwide.
Emergency departments are usually the first contact with medical and social care for these patients, underlining the need to promote such promising treatment.

Thank you for your comments. We agree that emergency departments have a unique medical and social relationship with patient populations at risk for opioid use disorder and opioid overdose. We hope that our findings will be helpful both within and outside the United States.

I have minor comments:

- regarding the high prevalence of patients presenting to emergency departments (ED) with opioid use disorder, I agree that trained physicians inside the ED should initiate opioid substitution rather than referring patients to specialized team after being detoxified. Nonetheless, are the authors sure that

patients are motivated enough when they are admitted to the EDs? Is vulnerability to morbidity or mortality not a barrier to start the treatment?

Thank you—this is an important question for clinicians to consider as they decide on the most appropriate treatment for each patient. Please note that the clinical decision support tool being tested in this RCT is based on the ED-Initiated Buprenorphine protocol used at Yale-New Haven Hospital. That protocol has been successfully tested in an RCT and found to increase engagement in treatment at 30 days vs. referral alone or referral plus a brief intervention : D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence: A Randomized Clinical Trial. JAMA. 2015;313(16):1636–1644. doi:10.1001/jama.2015.3474).

We have found that ED visits can represent important "teachable moments" for patients with OUD, where the negative consequences of their substance use may be especially apparent to them, and they may be open to change. The senior author of this protocol has written more on this here, if you are interested: Bernstein SL, D'Onofrio G. Screening, treatment initiation, and referral for substance use disorders. Addict Sci Clin Pract. 2017 Aug 7;12(1):18. doi:10.1186/s13722-017-0083-z. PubMed PMID: 28780906; PubMed Central PMCID: PMC5545867.

Your comments as a whole are targeted at ensuring that the care patients receive is appropriate for their often-complicated needs. We agree wholeheartedly that this should be the primary concern for all involved in patient care. The clinical decision support tool is intended to support physicians in providing an intervention proven in trials to be highly efficacious, but unfortunately still not widely used in practice. An important argument in favor of the ED-Initiated Buprenorphine protocol is that patients who receive buprenorphine in the ED will not be worse off, even if they choose not to attend their follow-up appointment. As always, physicians participating in the study will use their clinical judgement to determine whether patients are safe to go home—considering whether they are a danger to themselves or others, whether their other medical problems require inpatient care, and so on—and whether patients have any contraindications to buprenorphine treatment (for example, allergy to buprenorphine or current methadone use). So assuming patients can safely receive buprenorphine, from a harm reduction standpoint, the question of their readiness to engage in treatment should not prevent them from receiving buprenorphine in the ED or a prescription. If they take buprenorphine—at least that's one day where they will not overdose on opioids and will not suffer withdrawal symptoms. And, for some, it will be the first step in remission of their OUD. If they have other substance use issues—alcohol or methamphetamine, for example, again, that's not in itself a contraindication for treating their OUD with buprenorphine. If you consider treatment for other chronic diseases, no emergency physician would refuse insulin to patients with diabetes because they weren't sure the patients would continue to use the insulin or would show up for a follow-up appointment with an endocrinologist. Nor would an emergency physician refuse insulin to patients with diabetes because they hadn't yet addressed their comorbid obesity by losing weight or because they were still using alcohol. Certainly, the physician would do everything possible to make treatment available to their patients and to warn them of the risks of drinking alcohol, but would not refuse to provide insulin. There's no doubt that this is a complicated and vulnerable patient population. Our goal in this study is to increase adoption of this this safe and effective treatment by help emergency physicians become more comfortable providing it in their routine practice.

- the CBS EMBED intervention is well designed.
- one strength is the fact that non-waivered clinicians may administer a one-time dosing to alleviate ow symptoms.

Thank you for your comments. Yes—in the United States, clinicians who are not waivered may administer buprenorphine for OUD to a patient for 3 days in the emergency department. That 3-day period allows time for patients to connect to longer term treatment.

- authors should explain the figure 2 – indeed if COWS score is higher than 8, BUP is given inside the ED and patient is observed. Then, if a waivered provider is able to prescribe BUP, 16 mg dosing for each day is delivered to patient until appointment for ongoing treatment. This latter point is hard to understand. When the patient is discharged from ED, does he have received many pills once? Should he return every day to ED to take the 16 mg pill?
Is the patient aware of the date of the next appointment when he./she is discharged?

If a waivered provider is available, the provider writes the patient a prescription for buprenorphine to be filled by the patient at the pharmacy of their choice. It is left to the prescriber to determine the number of days' supply. Trial sites will have different capabilities for directly scheduling follow-up appointments. For example, some sites will allow clinicians to directly schedule a follow-up appointment within that same system, at other sites, a social worker calls a partner MAT treatment provider to schedule an appointment. As noted in the ED-Initiated Buprenorphine protocol diagram, patients should leave the ED with a warm hand-off including a scheduled appointment within 24 to 72 hours if at all possible. The availability of that appointment will likely guide prescribers as they decide how many days to supply in the prescription.

- regarding the DSM5 criteria, how do the trained physicians deal with comorbid substance use disorder (especially alcohol use disorder) and comorbid psychiatric condition before initiating BUP?

Clinicians will continue to use their judgment in assessing and treating comorbid conditions, as they currently do. Since many patients with OUD do have other mental health conditions, treatment of the moderate to severe OUD improves the ability of the patient and his or her clinicians to treat comorbid conditions. However, as always, clinicians will need to use their best judgment to prioritize patient issues and treatments.

Reviewer: 2
Reviewer Name: Laura Kehoe, MD, MPH
Institution and Country: Massachusetts General Hospital
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
Outstanding -- really looking forward to the results!

Thank you very much for your comment—we hope that this decision support tool will help clinicians to provide high quality, humane care to their patients.

1)Figure 3 notes bupe initiation recs for DSM V criteria >/= 3, but PDF of ED initiated bupe algorithm is for moderate- severe use disorder, which would be >/= 4 DSM V criteria

Thank you for catching this typo. We have revised Figure 3 to read >/= 4 DSM V criteria

2) P 12, line 44: please define JDD

Apologies for the confusion. JDD is Dr. James D. Dziura, the senior statistician on the study. We have clarified this in the text

3) P13, line 43: if pt not seen for fu in the same system, what is the fu plan for those outside the system?

As we note above, different sites have different access to long-term buprenorphine treatment within or outside of their systems. At the time the study begins, all sites will have follow-up protocols, including the sites that provide follow-up appointments, the method for scheduling follow-up appointments, procedures in case long-term follow-up is not available within 72 hours (e.g., bridge clinics), and so on.
In terms of the study, we will not be assessing patient-level follow-up outcomes. We have clarified this in the manuscript by revising a sentence on pg 13 that indicated that we would collect information on whether the patient attended the follow-up appointment. It now reads: "Information on whether the patient attended the referred follow-up visit and whether the patient was prescribed BUP as an outpatient will be abstracted from the EHR only if available in the same EHR (e.g., if the patient is seen for follow-up within the same system). Given the waiver of informed consent, we will be unable to track patients referred out-of-system."
We consider that the protocol for initiation of buprenorphine in the ED has been tested at multiple institutions and found to be a safe and effective treatment. We will be protecting patient confidentiality by not requesting that patient-identifiable information to be transmitted outside the treatment site to the main study site and by not requiring study personnel to re-contact patients.

4) P 13, line 48- what are the predetermined intervals to send data to DCC?
We will request data be sent every two weeks and will adjust as needed. We will begin testing data transmission from each site well before the study begins to minimize problems once the intervention goes live. We have clarified this in the text (page 13)

5) P 13 line 54, what is considered a recent admission (days, weeks, months)? We capture the patient's most recent admission, if any, regardless of how long ago it was.

6) P 14, line 5 - how will you control for different tox sceens, particularly as not all testing for fentanyl?
We will not be able to control for different urine drug screen protocols at different sites. We do not anticipate that the error in this variable will substantially affect the analysis of results. However, if that is a problem, it will be controlled for in our sensitivity analyses using GLMM with site effects.

7) P 15, line 6: are repeat ED visits for all reasons, or only SUD related? We will capture all ED visits, regardless of chief complaint.

VERSION 2 – REVIEW

REVIEWER	Franchitto Nicolas Department of Addictology Medicine, University hospital of Toulouse
REVIEW RETURNED	31-Mar-2019

GENERAL COMMENTS	Authors have replied to the previous comments. The clinical decision support tool is intended to support physicians in providing an intervention proven in trials to be highly efficacious, but unfortunately still not widely used in practice: the authors are right and we hope that it will be extended. The explanations requested especially concerning fig 2 have been done.

REVIEWER	Laura Kehoe

	Massachusetts General Hospital, USA
REVIEW RETURNED	19-Mar-2019

GENERAL COMMENTS	Responses and revisions clear, and questions addressed. Thank you, and I am looking forward to this critically important study. Thank you for inviting me to review! Laura