PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Experience and response to a randomised controlled trial of extended-release injectable buprenorphine versus sublingual tablet buprenorphine and oral liquid methadone for opioid use disorder: protocol for a mixed-methods evaluation
AUTHORS	Lowry, Natalie; Cowden, Fiona; Day, Edward; Gilvarry, Eilish; Johnstone, Stacey; Murray, Robbie; Kelleher, Mike; Mitcheson, Luke; Marsden, John

VERSION 1 – REVIEW

REVIEWER	Saxon, Andrew J. University of Washington
REVIEW RETURNED	19-Aug-2022

GENERAL COMMENTS	This manuscript describes the protocol for a mixed-methods study that will use quantitative data from the parent study which compares extended-release buprenorphine treatment for opioid use disorder to sublingual daily administration of buprenorphine and per os daily administration of methadone. Qualitative data will come from participant interviews that are conveyed in this protocol description. The work described is important and is likely to add considerably to our knowledge of how best to treat opioid use disorder. Unfortunately, the writing itself is somewhat ragged, making it challenging for the reader to parse. Some specific examples are provided below, but they are not exhaustive. The entire manuscript, which reads more like draft, would benefit from very careful proofreading and rewriting. Also unfortunate is the fact that the researchers did not capitalize on the opportunity to interview the population which could provide the most salient information about how to improve opioid use disorder treatment—those who dropped out of care. The failure to do so should be listed as a limitation of this protocol, and it might even be wise to add a limitation section to the manuscript in the event that the authors perceive and want to convey other limitations of the protocol. Some other specific suggestions are delineated below. Page 3: For purposes of reducing stigma, it would be better to avoid the terminology “opioid substitution” and instead use “medication for opioid use disorder.”

	Page 4, lines 10-15: Methadone pharmacology is somewhat mischaracterized here. As written currently, a reader could construe that being treated with methadone increases overdose risk, whereas it actually decreases it. However, it is also the case that methadone alone can cause an overdose in vulnerable individuals, whereas the manuscript implies that it would cause an overdose only when combined with other opioids. Page 5, lines 24-26: This sentence has a missing word and a misspelling. Page 5, line 27: The word “patients” needs an apostrophe. Page 6, lines 8-10: Please rewrite this confusing sentence. Page 6, lines 13-15: The word “populations” also needs an apostrophe. This sentence confusingly uses both present and past tenses. Verb tenses should be aligned. Page 6, line 21: Why would one believe that remission would perpetuate negative quality of life? Page 6, lines 49-52: This confusing sentence also needs a rewrite. Page 6: lines 39-41 are quite redundant with lines 55-59. Redundancy should be removed. Page 6, line 28 says sample sizes will be 20-40, yet page 7, line 18 indicates that evaluation 1 will have 60 participants. Page 12, lines 8-12 contain another poorly constructed sentence which needs to be rewritten.

REVIEWER	D'Onofrio, Gail Yale University School of Medicine, Emergency Medicine
REVIEW RETURNED	02-Sep-2022

GENERAL COMMENTS	This is an ambitious and well thought out trial strengthened by its mixed methods approach. I applaud the collaboration with patient and public representatives. My only comments are to consider that in addition to primary outcomes of abstinence days, the most meaningful outcomes are noted in Dr. Ling's Treatment Effectiveness Assessment (TEA) that incorporates not only the substance use but overall health, lifestyle, (relationships, employment etc) and community. Since some portion extends to 18 months, these factors would beneficial as they really are the endpoints. A minor suggestions is to avoid the terms substitution with opioid agonists as this can be quite stigmatizing.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

1. The entire manuscript, which reads more like draft, would benefit from very careful proofreading and rewriting.

RESPONSE: Proof reading and overall editing has been made to the document.

2. Also unfortunate is the fact that the researchers did not capitalize on the opportunity to interview the population which could provide the most salient information about how to improve opioid use disorder treatment—those who dropped out of care. The failure to do so should be listed as a limitation of this protocol, and it might even be wise to add a limitation section to the manuscript in the event that the authors perceive and want to convey other limitations of the protocol.

RESPONSE: This has been added as a limitation to the project, in the 'strengths and limitations' section. The participants that have consented to continue treatment (at the 24-week end point), will all be asked to interview at 12-24 months irrespective of whether they are currently in treatment or discontinued.

3. Page 3: For purposes of reducing stigma, it would be better to avoid the terminology "opioid substitution" and instead use "medication for opioid use disorder."

RESPONSE: terminology has been amended to "medications for opioid use disorder".

4. Page 4, lines 10-15: Methadone pharmacology is somewhat mischaracterized here. As written currently, a reader could construe that being treated with methadone increases overdose risk, whereas it actually decreases it. However, it is also the case that methadone alone can cause an overdose in vulnerable individuals, whereas the manuscript implies that it would cause an overdose only when combined with other opioids.

RESPONSE: These sections have been removed from the manuscript as overdose is not a focal point of the evaluations.

5. Page 5, lines 24-26: This sentence has a missing word and a misspelling.

RESPONSE: This section has been revised "The present study will contribute to this emergent literature and will capture of a wider range of measures, over longer follow-up period. This study will also utilize a mixed methods design to synergize qualitative and quantitative data."

6. Page 5, line 27: The word "patients" needs an apostrophe.

RESPONSE: This has been amended.

7. Page 6, lines 8-10: Please rewrite this confusing sentence.

RESPONSE: This sentence has been amended to "An approach underpinned by theory is also important because this provides structure to the comparison of populations and different health related domains, and in this context will help to integrate findings within the wider literature on OUD treatment and health service evaluation (22)."

8. Page 6, lines 13-15: The word “populations” also needs an apostrophe. This sentence confusingly uses both present and past tenses. Verb tenses should be aligned.

RESPONSE: This section has been removed.

9. Page 6, line 21: Why would one believe that remission would perpetuate negative quality of life?

RESPONSE: This section has been removed.

10. Page 6, lines 49-52: This confusing sentence also needs a rewrite.

RESPONSE: reworded to the following: “Patient and public involvement representatives will be consulted throughout the EXPO trial on research design, procedures, and reporting of findings. They will be members of the trial steering committee and the data management committee.”

11. Page 6: lines 39-41 are quite redundant with lines 55-59. Redundancy should be removed.

RESPONSE: This has been removed.

12. Page 6, line 28 says sample sizes will be 20-40, yet page 7, line 18 indicates that evaluation 1 will have 60 participants.

RESPONSE: This reference has main more specific (15-30 participants), we have also clarified that the target recruitments is 15 per centre or treatment arm depending on the evaluation, due to the nature of the analysis, we are analysing the centres/arms separately and then comparing.

13. Page 12, lines 8-12 contain another poorly constructed sentence which needs to be rewritten.

RESPONSE: Reworded to the following: “Difference between treatment groups and groups of ‘engaged’ and ‘non-engaged’ participants will be mapped onto constructs of the behavioural model for health service use model, during the conceptualisation stage.”

Reviewer #2

1. Addition to primary outcomes of abstinence days, the most meaningful outcomes are noted in Dr. Ling's Treatment Effectiveness Assessment (TEA) that incorporates not only the substance use but overall health, lifestyle, (relationships, employment etc) and community. Since some portion extends to 18 months, these factors would beneficial as they really are the endpoints.

RESPONSE: As data collection has already begun, we are unable to add this measure. These domains will be covered by the measures set out in evaluation 2.

2. A minor suggestions is to avoid the terms substitution with opioid agonists as this can be quite stigmatizing.

RESPONSE: the wording has

VERSION 2 – REVIEW

REVIEWER	Saxon, Andrew J. University of Washington
REVIEW RETURNED	29-Sep-2022

GENERAL COMMENTS	This manuscript which describes the protocol for a mixed-methods study that will use quantitative data from the parent study which compares extended-release buprenorphine treatment for opioid use disorder to sublingual daily administration of buprenorphine and per os daily administration of methadone and qualitative data from participant interviews has been extensively revised in accord with reviewers suggestions. There remain a few minor wording errors that can be readily corrected. Beyond that no additional recommendations for improvement are offered at this time..