PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative effectiveness of Buprenorphine-Naloxone versus Methadone for treatment of opioid use disorder: a population-based observational study protocol in British Columbia, Canada
AUTHORS	Piske, Micah; Thomson, Trevor; Krebs, Emanuel; Hongdilokkul, Natt; Bruneau, Julie; Greenland, Sander; Gustafson, Paul; Karim, Ehsan; McCandless, Lawrence; Maclure, Malcolm; Platt, Robert; Siebert, U; Socías, M.; Tsui, Judith; Wood, Evan; Nosyk, Bohdan

VERSION 1 – REVIEW

REVIEWER	Linda Gowing University of Australia, Adelaide
REVIEW RETURNED	18-Dec-2019

GENERAL COMMENTS	Thank you for a very well written protocol, and a study that is potentially of great value to the field. Randomised controlled trials and meta-analyses of randomised controlled trials are powerful tools for establishing the efficacy of interventions, meaning the effect of interventions under controlled trial conditions. As noted by the authors, randomised controlled trials and meta-analyses of randomised controlled trials are limited in their capacity to determine the effect of interventions under day to day conditions. The datasets available to the authors provide an exciting opportunity to assess the real-life performance of methadone and buprenorphine for the treatment of opioid dependence. Furthermore the sample size should be large enough to support the analyses proposed by the authors. The analyses proposed seem appropriate to allow for confounding and to explore the impact of different factors on the outcomes. As noted, early studies of buprenorphine used an aqueous sublingual solution, whereas standard formulations are now the buprenorphine-naloxone tablet, or in Australia the film preparation. Assessment of the effect of dose on outcomes taking account of the preparation will be an important contribution. Consideration of the type of opioid that is the primary drug is also important as we have little understanding of how different types of opioid drug influence response to treatment. If it is possible with the data, I think it would be of interest to look at prior opioid substitution treatment as a factor in therapeutic engagement. For example, are outcomes with buprenorphine different for people transferring from a period of methadone treatment, compared to those coming immediately from heroin or other unsanctioned opioid use? Are outcomes better or worse on average for episodes of treatment following previous failed episodes? The effect of adjunct psychosocial support on treatment outcome is another aspect that is difficult to assess through randomised controlled trials given that in real life the nature and intensity of psychosocial support is likely to be

	tailored to individual need and willingness to engage. The potential for insight into this aspect is another exciting dimension to this proposal. I look forward to the results with considerable anticipation.

REVIEWER	Nikolaj Kunøe Lovisenberg Diaconal Hospital, Oslo, Norway
REVIEW RETURNED	20-Dec-2019

GENERAL COMMENTS	The draft protocol will analyze a large amoung of patient data from OAT in BC, Canada, in order to estimate the comparative effectiveness of mmt vs bp-nlx tx on retention, hospitalization, and mortality over a minimum 5-year time-span. The potential benefits of such results could be made more clear to the reader via summary, examples of clinical or policy decisions facilitated by the knowledge resulting from the study. The retention outcome should specify whether intentional tapering (to transition to medication-free treatment or recovery modalities) will be included, or will be treated as a confounder or an unknown confounder in the data. The authors are concede that their registry-based dataset may miss important variables directly related to OAT medication selection, especially at the patient level. The The statistical analysis plan for this large dataset exceed this referee's expertise. I have requested the article receive a separate statistical review. A completed SPIRIT form has not been attached, but the draft appears to contain the registry study-relevant requirements listed in the form.

REVIEWER	Blair Bishop Massey University, Otago School of Medicine, and Capital Coast District Health Board Wellington New Zealand
REVIEW RETURNED	21-Jan-2020

GENERAL COMMENTS	Page 10 Lines 50-56: This strikes me as an abitary timeframe for discontimuation criteria. The researchers should acknowledge the international variability on these time frames. Auatralasian guidelines for instance recommend retitration commence after 3 missed doses of methadone and 4 missed doses of buprenorphine. Overall I see this as a valuable research protocol. My only concern is that agian the comparative measures of effectiveness are mortality and retention in treatment. Assessing other outcome measures such as employment, housing, and abstinece from opioid use following the exit from OAT would provide clinicians with a wider lens to compare the efficacy of methadone and buprenorphine

REVIEWER	Masanori Nojima The Institute of Medical Science, The University of Tokyo
REVIEW RETURNED	12-Mar-2020

GENERAL COMMENTS	The research proposal submitted by Piske et al. is outstanding in that: 1. The rationale of conducting observational studies using

large-scale real-world data is very clear, and logically states the advantages of existing meta-analyses with previous RCTs. 2. Analyzing the impact of uncontrolled confounding, the currently most powerful approaches are taken for the problem. The same applies to time-dependent confounding. 3. The selection of covariates is systematic, comprehensive, and highly objective. The identification of important conditions related to the outcomes and covariates is clearly provided in the tables. In addition, the research team is highly reliable in conducting the study, as it is comprised of sufficient number of medical, epidemiological and biostatistical experts. Please consider several minor points listed below.

1. The target disease (OUD) is not included in the title. The title alone does not tell what the treatments are for.
2. There is not much description about the study size. If the estimates of the number of enrolled patients and the average follow-up period are given in the study design section, it may be easier for readers to imagine the scale and potential of the study.
3. The specific definition of the patients those who exposed with primary exposure (methadone and buprenorphine/naloxone) in each statistical analysis seems to be not clear. For example, is it defined if either treatment is given at least once (or one day)?
4. Statistics that will finally be calculated to explain the difference in the effect of the treatments for each outcome (and calculation methods) are not clearly indicated (e.g. hazard ratio by Cox regression). It may help readers imagine how useful the research findings will be.
5. Will any treatment change and time-dependent confounding during the follow-up period not be considered in the ITT approach?
6. Will the effect modification of dosage by multiple time-varying factors be dealt with using the accelerated failure time model in PPS approach?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Linda Gowing

Institution and Country: University of Australia, Adelaide

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Thank you for a very well written protocol, and a study that is potentially of great value to the field. Randomised controlled trials and meta-analyses of randomised controlled trials are powerful tools for establishing the efficacy of interventions, meaning the effect of interventions under controlled trial conditions. As noted by the authors, randomised controlled trials and meta-analyses of randomised controlled trials are limited in their capacity to determine the effect of interventions under day to day conditions. The datasets available to the authors provide an exciting opportunity to assess the real-life performance of methadone and buprenorphine for the treatment of opioid dependence. Furthermore the sample size should be large enough to support the analyses proposed by the authors. The analyses

proposed seem appropriate to allow for confounding and to explore the impact of different factors on the outcomes. As noted, early studies of buprenorphine used an aqueous sublingual solution, whereas standard formulations are now the buprenorphine-naloxone tablet, or in Australia the film preparation. Assessment of the effect of dose on outcomes taking account of the preparation will be an important contribution. Consideration of the type of opioid that is the primary drug is also important as we have little understanding of how different types of opioid drug influence response to treatment. If it is possible with the data, I think it would be of interest to look at prior opioid substitution treatment as a factor in therapeutic engagement. For example, are outcomes with buprenorphine different for people transferring from a period of methadone treatment, compared to those coming immediately from heroin or other unsanctioned opioid use? Are outcomes better or worse on average for episodes of treatment following previous failed episodes? The effect of adjunct psychosocial support on treatment outcome is another aspect that is difficult to assess through randomised controlled trials given that in real life the nature and intensity of psychosocial support is likely to be tailored to individual need and willingness to engage. The potential for insight into this aspect is another exciting dimension to this proposal. I look forward to the results with considerable anticipation.

RESPONSE: Thank you for your comments and interest. While it is certainly likely that the different types of opioids play an important role in response to treatment, we do not have the information in our health administrative datasets required to determine a patient's 'primary drug'; however, we will use a previously-developed case finding algorithm by Janjua et al. (1) to determine injection drug use to consider as a potential confounding variable. We have now updated Table 1 accordingly.

We have indicated in Table 1 that we will consider previous receipt of Buprenorphine/naloxone or methadone as a potential confounding variable affecting retention (medication history). In addition, medication switching will also be accounted for in our sensitivity analyses for both the intention-to-treat and per-protocol analyses (as indicated in Table 2).

We've otherwise previously documented that individuals with multiple methadone treatment episodes tend to stay in treatment for progressively longer periods in later episodes compared to individuals with fewer treatment episodes (Nosyk et al. 2009) (2) and we have added this to Table 1 as a potential confounding variable.

Similarly, while we do not have a direct measure of receipt of psychosocial treatment; we have identified a proxy variable to assess receipt of behavioral therapy (Table 1).

Reviewer: 2

Reviewer Name: Nikolaj Kunøe

Institution and Country: Lovisenberg Diaconal Hospital, Oslo, Norway

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The draft protocol will analyze a large amoung of patient data from OAT in BC, Canada, in order to estimate the comparative effectiveness of mmt vs bp-nlx tx on retention, hospitalization, and mortality over a minimum 5-year time-span. The potential benefits of such results could be made more clear to the reader via summary, examples of clinical or policy decisions facilitated by the knowledge resulting from the study. The retention outcome should specify whether intentional tapering (to transition to medication-free treatment or recovery modalities) will be included, or will be treated as a confounder or an unknown confounder in the data. The authors are concede that their registry-based dataset may miss important variables directly related to OAT medication selection, especially at the patient level. The statistical analysis plan for this large dataset exceed this referee's expertise. I have requested the article receive a separate statistical review.

A completed SPIRIT form has not been attached, but the draft appears to contain the registry study-relevant requirements listed in the form.

RESPONSE: Thank you for your comments. We have clarified in the abstract's conclusion the relevant clinical and policy implications that may result from this work (Page 3, Paragraph 1):

> **"*Evidence from real-world data represents a valuable opportunity to improve personalized treatment and patient-centered guidelines for vulnerable populations and inform strategies to reduce opioid-related mortality.*"**

We do not have information on whether the taper was initiated by the client or prescriber, or whether tapering episodes are intended to transition to medication-free treatment or recovery modalities. However, we can observe dose tapering on a daily basis and can assess the impact of this decision on the comparative effectiveness of the medications. We have now included an additional sensitivity analysis for both ITT and PP analyses in which OAT episodes initiating a taper (defined as a dose reduction with no record of reversion for at least 4 weeks), will be censored on the date the taper was initiated (Table 2).

We have attached a completed SPIRIT form indicating page numbers for each item in the checklist where relevant to our study.

Reviewer: 3

Reviewer Name: Blair Bishop

Institution and Country:

Massey University, Otago School of Medicine, and Capital Coast District Health Board

Wellington

New Zealand

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Page 10 Lines 50-56: This strikes me as an abitary timeframe for discontimuation criteria. The researchers should acknowledge the international variability on these time frames. Auatralasian guidelines for instance recommend retitration commence after 3 missed doses of methadone and 4 missed doses of buprenorphine.

RESPONSE: We have accounted for this recommendation in Table 2 Section 3. Variable classification (episode discontinuation). We will consider shorter discontinuation thresholds of 3 missed doses for methadone and 4 missed doses of buprenorphine in our sensitivity analyses. We have also added a reference (Australian Government Clinical Guidelines, 2003) (3) in the rationale, in addition to our local and national clinical guidelines.

Overall I see this as a valuable research protocol. My only concern is that agian the comparative measures of effectiveness are mortality and retention in treatment. Assessing other outcome measures such as employment, housing, and abstinece from opioid use following the exit from OAT would provide clinicians with a wider lens to compare the efficacy of methadone and buprenorphine

RESPONSE: Other outcomes such as employment, housing, and abstinence are not captured within our health administrative databases. In the case of employment and housing, these are more distal outcomes that will be strongly influenced by our primary outcome. We feel many such social outcomes are influenced primarily through treatment status, supporting our choice for retention as the primary outcome in this analysis.

Reviewer: 4

Reviewer Name: Masanori Nojima

Institution and Country:

The Institute of Medical Science, The University of Tokyo

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below

The research proposal submitted by Piske et al. is outstanding in that: 1. The rationale of conducting observational studies using large-scale real-world data is very clear, and logically states the advantages of existing meta-analyses with previous RCTs. 2. Analyzing the impact of uncontrolled confounding, the currently most powerful approaches are taken for the problem. The same applies to time-dependent confounding. 3. The selection of covariates is systematic, comprehensive, and highly objective. The identification of important conditions related to the outcomes and covariates is clearly provided in the tables. In addition, the research team is highly reliable in conducting the study, as it is comprised of sufficient number of medical, epidemiological and biostatistical experts. Please consider several minor points listed below.

1. The target disease (OUD) is not included in the title. The title alone does not tell what the treatments are for.

RESPONSE: Thank you for your comment. We have updated the title to specify we are referring to treatment of opioid use disorder (Page 1):

> *"Comparative effectiveness of Buprenorphine-Naloxone versus Methadone for treatment of opioid use disorder: a population-based observational study protocol in British Columbia, Canada."*

2. There is not much description about the study size. If the estimates of the number of enrolled patients and the average follow-up period are given in the study design section, it may be easier for readers to imagine the scale and potential of the study.

RESPONSE: We have now added these details in Section 2.1 Study design (Page 10, Paragraph 1)*:*

> *"As of the most recent data update, September 30th, 2018, our study cohort (individuals initiating OAT after January 1st, 2008) consisted of 47,563 individuals with an average duration of follow-up of 60 months (from first OAT dispensation to death, administrative censorship, or the end of study follow-up period)."*

3. The specific definition of the patients those who exposed with primary exposure (methadone and buprenorphine/naloxone) in each statistical analysis seems to be not clear. For example, is it defined if either treatment is given at least once (or one day)?

RESPONSE: We have now clarified the primary exposure in Section 2.2 Outcomes (Page 10, paragraph 3):

> "*The primary exposure is a binary indicator for receipt of at least one dispensation of OAT (either methadone or buprenorphine/naloxone). Retention can then be measured at daily, weekly or monthly time intervals."*

We have also now provided further details in Section 2.2 Outcomes as follows (Page 11, paragraph 1):

> *"If a prescription was supplied for more than one day of OAT medication, we assumed that the individual received OAT for the duration of days the medication was prescribed.*

We defined continuous OAT retention as the time interval during which an individual received OAT with no breaks in days dispensed lasting longer than 5 days for methadone and no longer than 6 days for buprenorphine/naloxone. These discontinuation criteria were based on BC guidelines recommending resetting starting doses after these durations of non-compliance to ensure safety."

An exception to this rule that we would like to make note of is for hospitalizations during an OAT episode. We do not have explicit medication within inpatient settings and assume that those who started OAT (prior to their hospitalization) continued their treatment with the same OAT type while in hospital. We have now included this detail in Section 2.2 Outcomes (Page 11, paragraph 1):

"*Our data do not capture OAT receipt in inpatient settings, and therefore we assumed that those who started OAT prior to their hospitalization were retained in treatment throughout the duration of their hospitalization."*

4.   Statistics that will finally be calculated to explain the difference in the effect of the treatments for each outcome (and calculation methods) are not clearly indicated (e.g. hazard ratio by Cox regression). It may help readers imagine how useful the research findings will be.

RESPONSE: We have now clarified this in Section 2.4 Analysis plan (Page 11, paragraph 3):

"*We will report the comparative effectiveness as a relative risk in order for our results to be comparable with clinical evidence from RCTs."*

5.   Will any treatment change and time-dependent confounding during the follow-up period not be considered in the ITT approach?

RESPONSE: In the ITT approach, the covariates and the treatment will be measured at the start of each OAT episode (defined as the continuous period of dispensed OAT medication without interruptions in prescribed doses ≥5 days for methadone and no longer than 6 days for buprenorphine/naloxone as previously indicated in Section 2.2 page 11, paragraph 1).

To account for treatment change between the two types of medication within an OAT episode, we indicated in Table 2 that medication switching will be included in our proposed sensitivity analyses (Table 2, Page 26, 3. Variable classification). We have now clarified in Table 2 this will be considered in the ITT approach as well. For ITT, an OAT episode is a continuous period of one type of OAT. When a medication switch happens, the current episode is discontinued, and a new episode is initiated.

6.   Will the effect modification of dosage by multiple time-varying factors be dealt with using the accelerated failure time model in PPS approach?

RESPONSE: We have now clarified in Section 2.4.2 (Page 15, paragraph 4):

"*To address for effect modification between time-varying factors, we will follow the setup presented by Vansteelandt & Sjolander (2016)*"**(4)**

VERSION 2 – REVIEW

REVIEWER	Linda Gowing University of Adelaide Australia
REVIEW RETURNED	21-Apr-2020

GENERAL COMMENTS	The authors have appropriately addressed comments on the first version of this manuscript. This is a protocol for a complex analytical study. It will provide a valuable level of detail to complement the results of the study when they become available. It also provides a useful discussion of the limitations of RCT evidence, and an argument for use of a range of research methodologies to provide evidence to underpin informed clinical and policy decisions.

REVIEWER	Nikolaj Kunøe Lovisenberg Diaconal Hospital, Oslo, Norway
REVIEW RETURNED	04-May-2020

GENERAL COMMENTS	This protocol article has been revised since the previous version, something that has improved clarity and transparency. It has now reached a standard that is sufficient to earn my recommendation for publication.

REVIEWER	Blair Bishop Capital and Coast District Health Board, Massey University, & Otago School of Medicine
REVIEW RETURNED	05-May-2020

GENERAL COMMENTS	This is an excellent protocol aiming to address the significant gaps in comparative analysis of two largely effective medications. I would like to note to the authors a couple of things. Firstly the reasons behind the reduced likelihood of injecting of buprenorphine compared to methadone is unclear. Some authors propose this is related more to the relative stability and lower acuity of those self-selecting buprenorphine over methadone. Additionally buprenorphine is a newer medication and I note anecdotally in new Zealand Aotearoa there are increasingly more presentations of intravenous BUP/NX use. Also, ultimately, criteria to measure effectiveness needs to be broadened beyond mortality, relapse rates, and transmissible diseases to include quality of life measures and outcomes.

	Overall I think this is a fantastic protocol which will add significant value to clinical reasoning around selection of the best option of OAT for a particular client/patient

REVIEWER	Masanori Nojima The University of Tokyo
REVIEW RETURNED	07-May-2020

GENERAL COMMENTS	The author's responses are sufficient as answers to my comments, and the manuscript has been modified appropriately enough. There is no further comment.

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VERSION 2 – AUTHOR RESPONSE

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Reviewer: 1

Reviewer Name

Linda Gowing

Institution and Country

University of Adelaide
Australia

 Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
The authors have appropriately addressed comments on the first version of this manuscript. This is a protocol for a complex analytical study. It will provide a valuable level of detail to complement the results of the study when they become available. It also provides a useful discussion of the limitations of RCT evidence, and an argument for use of a range of research methodologies to provide evidence to underpin informed clinical and policy decisions.
RESPONSE: Thank you kindly for your review and your comments.

Reviewer: 2

Reviewer Name

Nikolaj Kunøe

Institution and Country

Lovisenberg Diaconal Hospital, Oslo, Norway

 Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
This protocol article has been revised since the previous version, something that has improved clarity and transparency. It has now reached a standard that is sufficient to earn my recommendation for

publication.
RESPONSE: Thank you kindly for your review and your comment.

Reviewer: 3

Reviewer Name

Blair Bishop

Institution and Country

Capital and Coast District Health Board, Massey University, & Otago School of Medicine

 Please state any competing interests or state 'None declared':
None Declared

Please leave your comments for the authors below
This is an excellent protocol aiming to address the significant gaps in comparative analysis of two largely effective medications. I would like to note to the authors a couple of things. Firstly the reasons behind the reduced likelihood of injecting of buprenorphine compared to methadone is unclear. Some authors propose this is related more to the relative stability and lower acuity of those self-selecting buprenorphine over methadone. Additionally buprenorphine is a newer medication and I note anecdotally in new Zealand Aotearoa there are increasingly more presentations of intravenous BUP/NX use.

RESPONSE: Thank you kindly for your review and for highlighting this point.

We have clarified its role in potentially decreasing risks of injection on Page 5, Paragraph 2:

> ***"Buprenorphine additionally may offer a decreased risk of injection, and therefore harms related to diversion when taken in the buprenorphine/naloxone formulation."***

Also, ultimately, criteria to measure effectiveness needs to be broadened beyond mortality, relapse rates, and transmissible diseases to include quality of life measures and outcomes.

RESPONSE: Thank you for your comment. Measuring the quality of life in people who use opioids is reportedly challenging even with existing validated quality of life instruments where limited suitability of these tools for this population has been noted (1). Within the scope of our health administrative databases, we can additionally offer to investigate psychiatric hospitalizations, emergency department visits, and incarceration as secondary outcomes.

We have revised section 2.4.4 Subgroup and Sensitivity Analysis on Page 16, paragraph 2 to account for these additions:

> ***"Secondary outcomes such as psychiatric hospitalizations, emergency department visits and incarceration may also be considered in additional sensitivity analysis."***

Overall I think this is a fantastic protocol which will add significant value to clinical reasoning around selection of the best option of OAT for a particular client/patient

Reviewer: 4

Reviewer Name

Masanori Nojima

Institution and Country

The University of Tokyo

 Please state any competing interests or state 'None declared':
None

Please leave your comments for the authors below
The author's responses are sufficient as answers to my comments, and the manuscript has been modified appropriately enough. There is no further comment.

RESPONSE: Thank you kindly for your review.

References

1.   Strada L, Vanderplasschen W, Buchholz A, Schulte B, Muller AE, Verthein U, et al. Measuring quality of life in opioid-dependent people: a systematic review of assessment instruments. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2017;26(12):3187-200.