PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Epidemiology and Management of invasive infections among people who Use drugs (EMU): protocol for a prospective, multicentre cohort study
AUTHORS	Attwood, Lucy; Bryant, Mellissa; Lee, Sue; Vujovic, Olga; Higgs, Peter; Doyle, Joseph S.; Stewardson, Andrew

VERSION 1 – REVIEW

REVIEWER	Lewer, Dan University College London, Institute of Epidemiology and Healthcare
REVIEW RETURNED	19-Dec-2022

GENERAL COMMENTS	Many thanks for sharing this study protocol with me. I think this study addresses an important research question. Generally, I would have liked a greater focus on the descriptive elements of the analysis, eg. what are the characteristics of patients and infections, what is the ratio of different treatment modalities, what is the rate of treatment completion, etc. The primary analysis will compare completion of antibiotic treatment between an inpatient and outpatient group. The key problem likely to be confounding by indication. The allocation between treatment groups will be based on the type of infection, the clinical severity, and the likelihood that the patient will complete treatment in that setting. The analysis will adjust for "active injecting drug use (within the last three months), current homelessness, predominant injecting substance (opioid versus amphetamine), and opioid replacement therapy (methadone/ suboxone/ buprenorphine.)" I am not sure these variables will control much of the confounding. Why are you not controlling for the type and severity of infection and comorbidities, for example? (Apologies if the analysis does control for these factors and I misunderstood.) It may be worth developing a causal model / DAG to guide your selection of confounders and help readers understand why you chose these variables. Are there any "natural experiments" that might provide more robust causal inference? For example are there any hospitals that prefer one treatment modality over another, or any areas where one treatment modality is simply not available? Finally, in terms of power, it sounds like the power calculation assumes equal numbers in two groups. However, the study has 4 groups and it sounds like the group sizes may not be equal. My "gut feeling" is that 73 patients per group is likely to have quite low power. The anticipated difference is large (65% vs. 85% complete) and even if this is the "true" difference you may get quite imprecise results.

REVIEWER	Traver, Edward University of Maryland School of Medicine I am involved in similar research to assess the epidemiology and clinical features of infections related to injection drug use.
REVIEW RETURNED	23-Dec-2022

GENERAL COMMENTS	Comments to Author The pages are numbered twice in different ways. I am using the page numbers on the top (X of 19) Page 6, line 40: Provide a reference to the SPIROS statement. I found papers about the process of creating the SPIROS criteria but not a clear reference document. Is a partial list of the STROBE criteria not sufficient? Page 6, Line 57: Inclusion criteria - Self report of IDU: how is that recorded? This is addressed briefly in the Study Summary, but should be expanded here. Page 7 line 35 Clarify “Victorian participants”– presumably one of the study sites? Page 7, line 41 “Participants will be identified by reviewing ID inpatients and consults”… but some sites don’t have ID service? How does that work? Page 8 Line 37 **It is not clear to me that EMU-Audit will collect discharge data to assess the primary outcome. If I correctly understand the later outcome/analysis discussion, the primary outcome will be based on Audit alone. It is not clear that the data included here (EMU-Audit: Discharge Data) includes the data or the time points that will allow for categorization in the primary outcomes.** Page 8 line 41 explain/define Code Greys Page 8 line 58 “Follow up via a private social media messaging”. What kind of service is that? Is it secure? Page 9, Line 18 Data linkage – will all participants in EMU-Cohort be linked to their EMU-Audit records? Or only at Victorian sites? How many sites are Victorian? Need some description of the number and nature of the sites. Page 9, line 55 Please define OPAT more clearly. Sometimes it is used to describe IV antibiotics through a long-term IV access device at home, at a daily outpatient infusion center, in a skilled nursing facility, and/or in residential drug-treatment facility. Page 10, line 7 How will you categorize a patient who receives 10 days of inpatient IV and 7 days of outpatient PO? Admittedly this would be an unusual

	regimen, but it would meet both the inpatient IV criteria (for >50%) and the early oral therapy (for <2 weeks of IV). Page 10, line 26 Primary outcome assessment - Are you accessing medical records for EMU-Cohort? Is this only for the Victorian participants? If not, I don't know where you describe medical record review for EMU-Cohort. - How will you assess loss to follow up? o This is answered in table 1, but could be clarified at Page 10, line 34. - How do you account for long-term suppression with oral antimicrobials? Some physicians prescribe months or years of oral antibiotics after completing a primary course (IV or po) if infected hardware is retained. You note that deaths during oral antimicrobials will be counted as mortality and failure to complete planned therapy, but this might be misapplied for someone taking oral suppressive therapy for 2 years (in the linkage study, for example). Page 11, Line 38. Why is universal healthcare coverage predicted to increase inpatient antimicrobial treatment completion? Most PDDs are driven not by insurance or payment issues but by issues related to housing, social/family obligations, addiction, violation of hospital-based rules prohibiting drug use or smoking, etc. Page 11, Line 42. What are the considerations in Australian hospitals regarding enrolment in OPAT? This might be included an in earlier section as well as a clarification of the definition of OPAT (by location). Page 11, line 47 If more than 4 patients get oral antimicrobials or long-acting infusions, the study will be underpowered for the primary analysis. How confident can you be that 146/150 participants will get IV therapy (inpatient or outpatient)? Page 11, Line 57 If the primary analysis is inpatient IV v OPAT, you need to both clarify that patients in home OPAT and facility-based OPAT will be lumped into the OPAT group. Is this justified? D'Couto et al (OFID 2018) found higher OPAT completion at home (81%) than in a facility (64%) for people with substance use disorder. Page 12, line 15 The preferred terminology for methadone and buprenorphine is "Medication for Opioid Use Disorder" or "MOUD," rather than opioid replacement therapy. Note Suboxone is a brand name and better avoided. Are you including oral or injectable naltrexone?

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1
Many thanks for sharing this study protocol with me. I think this study addresses an important research question.
Generally, I would have liked a greater focus on the descriptive elements of the analysis, eg. what are the characteristics of patients and infections, what is the ratio of different treatment modalities, what is

the rate of treatment completion, etc.

RESPONSE: The EMU study is predominantly a descriptive study, with 'Aim 1' of the study being descriptive. The manuscript has now been updated to clarify this with increased information provided in the 'outcome measures' and 'sample size' sections. The wording of 'Aim 1' has also been changed from 'define' to 'describe' for clarity. See updated text in revised manuscript below:

Pp10-11: 'The EMU study will also provide significant descriptive analysis to inform objective one of the study. This will include baseline characteristics of patients including age, sex, housing status, psychiatric history and smoking and injecting drug history. A description of clinical presentations, infective diagnosis and microbiology will be provided. The treatment modalities received will also be described including rates of completion.'

Pp11: 'The primary objective of this study is descriptive.'

Pp14: 'Furthermore, the primary aim of the EMU study is descriptive and thus we hope EMU will provide significant data regarding this under studied research area.'

The primary analysis will compare completion of antibiotic treatment between an inpatient and outpatient group.
The key problem likely to be confounding by indication. The allocation between treatment groups will be based on the type of infection, the clinical severity, and the likelihood that the patient will complete treatment in that setting.
The analysis will adjust for "active injecting drug use (within the last three months), current homelessness, predominant injecting substance (opioid versus amphetamine), and opioid agonist therapy (methadone/ buprenorphine with naloxone (suboxone)/ buprenorphine.)" I am not sure these variables will control much of the confounding. Why are you not controlling for the type and severity of infection and comorbidities, for example? (Apologies if the analysis does control for these factors and I misunderstood.) It may be worth developing a causal model / DAG to guide your selection of confounders and help readers understand why you chose these variables.

RESPONSE: We agree that confounding by indication is a key issue related to Aim 2. The confounders selected (active injecting drug use, homelessness, predominant injecting substance and opioid agonist therapy) were chosen as they have traditionally influenced whether patients are eligible for discharge with OPAT in Australian hospitals. Whilst discharge planning should occur once patients are stable, we have included intensive care unit admission into our confounding analysis, as a marker of illness severity. Currently however, hospital policy for acceptance onto an OPAT program varies substantially. Thus, describing the currently utilised modalities will also be a key feature of the EMU study. See updated text in revised manuscript below:

Pp4: 'Management at Australian hospitals is significantly influenced by policy at an institution level rather than individual patient characteristics, and can vary from refusing anyone with a history of injecting drug use onto outpatient parenteral antimicrobial therapy (OPAT) programs to supporting their transition to community-based care.'

Pp12: 'Confounders will include active injecting drug use (within the last three months), current homelessness, predominant injecting substance (opioid versus amphetamine), and opioid agonist therapy (methadone/ buprenorphine with naloxone (suboxone)/ buprenorphine) as these have traditionally influenced whether patients are considered appropriate for discharge with an OPAT system in Australian hospitals. We will also adjust for intensive care unit admission as a marker of illness severity.'

Pp14: 'The EMU study design does incur the risk of confounding by indication. Once clinically stable, acceptance of people who inject drugs into OPAT services for completion of intravenous antimicrobial therapy is substantially influenced by hospital policy rather than patient-level characteristics. This variation between rather than within institution effectively represents a natural experiment. However, we will account for potential patient-level confounders by including these as covariates in multivariable regression, and include hospitals as a random effect to account for clustering at organisation level. Furthermore, the primary aim of the EMU study is descriptive and will provide valuable data to inform future interventional research.'

Are there any "natural experiments" that might provide more robust causal inference? For example are there any hospitals that prefer one treatment modality over another, or any areas where one treatment modality is simply not available?

RESPONSE: Thanks for this question, which provides the opportunity to clarify this component of our study. The EMU study has been designed as a multi-site cohort study, as currently in Australia, hospital policy varies widely regarding acceptance of people who inject drugs onto OPAT programs. As such, the description of management strategies utilised will be informed by individual hospital policies. In this way, the EMU study is indeed a natural experiment. The manuscript has been updated to clarify these points. See updated text in revised manuscript below:

Pp4: 'Management at Australian hospitals is significantly influenced by policy at an institution level rather than individual patient characteristics, and can vary from refusing anyone with a history of injecting drug use onto outpatient parenteral antimicrobial therapy (OPAT) programs to supporting their transition to community-based care.'

Pp14: 'The EMU study design does incur the risk of confounding by indication. Once clinically stable, acceptance of people who inject drugs into OPAT services for completion of intravenous antimicrobial therapy is substantially influenced by hospital policy rather than patient-level characteristics. This variation between rather than within institution effectively represents a natural experiment. However, we will account for potential patient-level confounders by including these as covariates in multivariable regression, and include hospitals as a random effect to account for clustering at organisation level. Furthermore, the primary aim of the EMU study is descriptive and will provide valuable data to inform future interventional research.'

Finally, in terms of power, it sounds like the power calculation assumes equal numbers in two groups. However, the study has 4 groups and it sounds like the group sizes may not be equal. My "gut feeling" is that 73 patients per group is likely to have quite low power. The anticipated difference is large (65% vs. 85% complete) and even if this is the "true" difference you may get quite imprecise results.

RESPONSE: We anticipate the number of participants recruited into the 'long-acting lipoglycopeptide' and 'early oral antimicrobial' groups to be small, and analysis in these groups will be descriptive only (Aim 1). The sample size calculation has been determined for comparison between the 'inpatient intravenous antimicrobial' and 'outpatient parenteral antimicrobial therapy' groups only. This is explained more clearly in the first paragraph of the statistical analysis section and we have also added more detail in the sample size section. We agree that the sizes between these two groups may not be equal, so we have calculated the sample size required for varying scenarios (i.e., 1:1, 2:1 and 3:1 ratios) and now report this in the text:

Pp11: 'Assuming 80% power and an alpha of 0.05, 73 participants per treatment group will allow the detection of a difference between a confirmed completion rate of 65% in the inpatient treatment group and 85% in the OPAT treatment group. We aim to recruit 146 participants in groups 1 and 2 of the exposure of interest groups (inpatient intravenous antimicrobials and outpatient parenteral antimicrobial therapy) combined. However, as rate of recruitment is dependent in part on hospital policies regarding discharging people who inject drugs onto OPAT, we have calculated different sample size scenarios that will still allow us to detect this difference depending on recruitment (Table 2). The ratio of recruitment will be assessed six months after commencing multi-site enrolment and the sample adapted, if needed.'

Table 2. Sample size for EMU depending on recruitment

Recruitment ratio	Group 1: Inpatient intravenous antimicrobials	Group 2: Outpatient parenteral antimicrobial therapy	Total
1:1	73	73	146
2:1	112	56	168
3:1	153	51	204

REVIEWER 2
Page 6, line 40:

Provide a reference to the SPIROS statement. I found papers about the process of creating the SPIROS criteria but not a clear reference document. Is a partial list of the STROBE criteria not sufficient?

RESPONSE: We have updated the manuscript to reflect that we used the STROBE criteria. See inclusion in revised manuscript below:

Pp5: 'The EMU protocol was drafted adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[25]'

Page 6, Line 57:
Inclusion criteria
- Self report of IDU: how is that recorded? This is addressed briefly in the Study Summary, but should be expanded here.

RESPONSE: The inclusion criteria has been expanded briefly to provide further clarity regarding the identification of these patients. However, we note that there are inherent limitations with this recruitment strategy, as are discussed in the discussion section (previously study summary section.) See inclusion in revised manuscript below:

Pp6: 'Asking about a history of injecting drug use is standard of care when investigating invasive infections. Thus, documentation of this history is expected to be recorded within the medical history of patients with invasive infections.'

Page 7 line 35
Clarify "Victorian participants"– presumably one of the study sites?

RESPONSE: Victoria is a state of Australia and data linkage will only occur for participants recruited from this state. The manuscript has been updated to provide more clarity regarding study sites, see inclusion in revised manuscript below:

Pp5: 'Study sites are Australian public hospitals who provide care to PWID with invasive infections. These sites can include hospitals from all states and territories in Australia, though it is expected that most sites will be in the state of Victoria due to the location of the study authors.'

Pp6: 'Individuals with no method of contact for follow up questionnaires will be excluded from EMU-Cohort, but participants from hospitals within the state of Victoria may consent to data linkage component only. Data linkage will not be available for participants from hospitals outside of Victoria, please see further information about data-linkage in the 'Data collection' section below.'

Page 7, line 41
"Participants will be identified by reviewing ID inpatients and consults"… but some sites don't have ID service? How does that work?

RESPONSE: Sites do not need to have an infectious diseases inpatient service, but will need to have a consult service to identify patients. The manuscript has been updated to clarify this distinction.

See pp5: 'Participating sites do not need to have a dedicated infectious diseases inpatient team, though will have an infectious diseases consult service as a minimum. Patients can be admitted to other medical or surgical units.'

Page 8 Line 37
It is not clear to me that EMU-Audit will collect discharge data to assess the primary outcome. If I correctly understand the later outcome/analysis discussion, the primary outcome will be based on Audit alone. It is not clear that the data included here (EMU-Audit: Discharge Data) includes the data or the time points that will allow for categorization in the primary outcomes.

RESPONSE: EMU-Audit will collect antimicrobials received and the primary outcome is confirmed completion of planned antimicrobial therapy 'as recorded in medical records.' It is expected that the majority of participants will be managed in the inpatient intravenous antimicrobial group or in the

OPAT group (see 'Sample Size' section for further discussion.) Patients remain 'admitted' under a hospital service whilst receiving care in an OPAT program in Australian hospitals. As such, the EMU-Audit discharge data will be able to collect information regarding the primary outcome. The manuscript has been updated to clarify these points, please see inclusion in revised manuscript below:

See Pp8: 'Information about antimicrobials received will also include the planned duration of antimicrobials, whether the participant received that duration and if not, how long a participant did receive antimicrobials for. For participants discharged with an OPAT service, this information will be collected at the end of their OPAT admission. This is because in Australian hospitals, participants remain 'admitted' under a hospital service whilst with an OPAT service.'

Page 8 line 41
explain/define Code Greys

RESPONSE: Thank you for highlighting this site-specific detail. We have changed 'Code Greys' in the text to the more specific 'personal threat code.'

Page 8 line 58
"Follow up via a private social media messaging". What kind of service is that? Is it secure?

RESPONSE: Consenting participants will be asked to give the name they use on Facebook messenger. A message would be sent via this platform to follow up about the 30-day and 90-day post discharge interviews if we are unable to contact them via phone. We would not include any confidential material in this platform, rather it would help facilitate ongoing follow up. This technique has been utilised successfully in other studies that work with people who inject drugs, including the Melbourne SuperMIX study.
(https://www.burnet.edu.au/news/1571_the_supermix_team_connecting_in_covid_times_with_people_who_inject_drugs)

Page 9, Line 18
Data linkage – will all participants in EMU-Cohort be linked to their EMU-Audit records? Or only at Victorian sites? How many sites are Victorian?
Need some description of the number and nature of the sites.

RESPONSE: All participants in EMU-Cohort will be linked to their EMU-Audit records. However, only Victorian participants will be eligible to participate in data-linkage as we will use the Victorian data available for linkage. Recruitment of sites is ongoing at present, and a full description of the number and nature of sites will be provided in the final publication of the EMU study results.

Page 9, line 55
Please define OPAT more clearly. Sometimes it is used to describe IV antibiotics through a long-term IV access device at home, at a daily outpatient infusion center, in a skilled nursing facility, and/or in residential drug-treatment facility.

RESPONSE: Thank you for highlighting this difference. In Australia, OPAT services predominantly describe a 'Hospital In The Home' model with daily visits from skilled nursing staff. Unlike North America, we do not have OPAT daily infusion centres or discharge to nursing facilities. This has been clarified in the manuscript:

Pp9: 'Note: In Australia, OPAT services are based around a 'Hospital In The Home' model where patients are discharged home (their own home or a family/friends home) with long-term intravenous access via a peripherally inserted central catheter (PICC). Skilled nursing staff visit patients daily to administer antimicrobials or change infusion pumps as required. OPAT via a skilled nursing facility or with patients administering medications themselves, as is frequently utilised in North America, is not routine in Australia.'

Page 10, line 7
How will you categorize a patient who receives 10 days of inpatient IV and 7 days of outpatient PO? Admittedly this would be an unusual regimen, but it would meet both the inpatient IV criteria (for

>50%) and the early oral therapy (for <2 weeks of IV).

RESPONSE: In cases where a participant satisfies criteria for both inpatient intravenous therapy and early oral switch, the participant will be allocated to inpatient intravenous antimicrobial group as the majority of their treatment is based around the inpatient management. We appreciate that the current definitions of groups may not be applicable to all patients. However, hopefully the EMU study will provide a description of what management strategies are currently utilised in Australian hospitals, which is not currently available.

Page 10, line 26
Primary outcome assessment
- Are you accessing medical records for EMU-Cohort? Is this only for the Victorian participants? If not, I don't know where you describe medical record review for EMU-Cohort.
- How will you assess loss to follow up?
o This is answered in table 1, but could be clarified at Page 10, line 34.
- How do you account for long-term suppression with oral antimicrobials? Some physicians prescribe months or years of oral antibiotics after completing a primary course (IV or po) if infected hardware is retained. You note that deaths during oral antimicrobials will be counted as mortality and failure to complete planned therapy, but this might be misapplied for someone taking oral suppressive therapy for 2 years (in the linkage study, for example).

RESPONSE: All participants in EMU-Cohort are part of EMU-Audit. As such, medical records will be accessed for all participants involved in EMU-Cohort. If participants are unable to be contacted at 30- or 90-day follow up, they will be classified as lost to follow up. This has been clarified in the 'EMU-Cohort discharge data' section.

Pp8: 'Participants who are unable to be contacted at 30- or 90-day follow up will be classified lost to follow up.'

Thank you for highlighting the situation where participants may be discharged on prolonged oral antimicrobials. The initial failure to complete therapy will be determined prior to linkage (given the delays in obtaining linkage data.) As such, mortality two years later would not be misapplied in this fashion. We also anticipate that it will be difficult to determine whether oral antimicrobials have been completed and as such, groups 3 and 4 of the exposure of interest (long-acting lipoglycopeptides and early oral antimicrobials) will be purely descriptive.

Page 11, Line 38.
Why is universal healthcare coverage predicted to increase inpatient antimicrobial treatment completion? Most PDDs are driven not by insurance or payment issues but by issues related to housing, social/family obligations, addiction, violation of hospital-based rules prohibiting drug use or smoking, etc.

RESPONSE: Whilst we agree that the majority of PDDs are driven by other social stressors, financial stress and employment concerns do contribute to a patients wish to leave a hospital admission early. In Australia, social security services can be provided to patients who are unable to work due to a medical reason, which may decrease one stressor limiting a patient's ability to engage in medical care.

Page 11, Line 42.
What are the considerations in Australian hospitals regarding enrolment in OPAT? This might be included an in earlier section as well as a clarification of the definition of OPAT (by location).

RESPONSE: The considerations in Australian hospitals regarding enrolment in OPAT vary by individual hospital policy. As such, this is very institution dependent. We have clarified this throughout the manuscript. Please see updated text below:

Pp4: 'Management at Australian hospitals is significantly influenced by policy at an institution level rather than individual patient characteristics, and can vary from refusing anyone with a history of injecting drug use onto outpatient parenteral antimicrobial therapy (OPAT) programs to supporting their transition to community-based care.'

Pp12: ‘Confounders will include active injecting drug use (within the last three months), current homelessness, predominant injecting substance (opioid versus amphetamine), and opioid agonist therapy (methadone/ buprenorphine with naloxone (suboxone)/ buprenorphine) as these have traditionally influenced whether patients are considered appropriate for discharge with an OPAT system in Australian hospitals. We will also adjust for intensive care unit admission as a marker of illness severity.’

Pp14: ‘The EMU study design does incur the risk of confounding by indication. Once clinically stable, acceptance of people who inject drugs into OPAT services for completion of intravenous antimicrobial therapy is substantially influenced by hospital policy rather than patient-level characteristics. This variation between rather than within institution effectively represents a natural experiment. However, we will account for potential patient-level confounders by including these as covariates in multivariable regression, and include hospitals as a random effect to account for clustering at organisation level. Furthermore, the primary aim of the EMU study is descriptive and will provide valuable data to inform future interventional research.’

Page 11, line 47
If more than 4 patients get oral antimicrobials or long-acting infusions, the study will be underpowered for the primary analysis. How confident can you be that 146/150 participants will get IV therapy (inpatient or outpatient)?

RESPONSE: Results from the ‘early oral antimicrobial’ and ‘long-acting lipoglycopeptide’ groups will be descriptive only. The sample size calculation has been determined for the comparison between the ‘inpatient intravenous antimicrobial’ and ‘outpatient parenteral antimicrobial therapy’ groups only. This is explained in more detail in the first paragraph of the statistical analysis section, and we have also clarified this in the text:

Pp11: Assuming 80% power and an alpha of 0.05, 73 participants per treatment group will allow the detection of a difference between a confirmed completion rate of 65% in the inpatient treatment group and 85% in the OPAT treatment group. We aim to recruit 146 participants in groups 1 and 2 of the exposure of interest groups (inpatient intravenous antimicrobials and outpatient parenteral antimicrobial therapy) combined.’

Page 11, Line 57
If the primary analysis is inpatient IV v OPAT, you need to both clarify that patients in home OPAT and facility-based OPAT will be lumped into the OPAT group. Is this justified? D’Couto et al (OFID 2018) found higher OPAT completion at home (81%) than in a facility (64%) for people with substance use disorder.

RESPONSE: Facility-based OPAT is not utilised in Australia, with OPAT referring to a ‘Hospital In The Home’ model. The manuscript has been updated to clarify this service difference. See updated text in revised manuscript below:

Pp9: ‘In Australia, OPAT services are based around a ‘Hospital In The Home’ model where patients are discharged home (their own home or a family/friends home) with long-term intravenous access via a peripherally inserted central catheter (PICC). Skilled nursing staff visit patients daily to administer antimicrobials or change infusion pumps as required. OPAT via a skilled nursing facility or with patients administering medications themselves, as is frequently utilised in North America, is not routine in Australia.’

Page 12, line 15
The preferred terminology for methadone and buprenorphine is “Medication for Opioid Use Disorder” or “MOUD,” rather than opioid replacement therapy. Note Suboxone is a brand name and better avoided. Are you including oral or injectable naltrexone?

RESPONSE: We prefer to use the terms that label the therapy (such as ‘opioid agonist therapy’ (OAT) or ‘opioid substitution therapy’ (OST)) rather than terms that label the patient/behaviour such as ‘medication for opioid use dependence’ (MOUD.) We have changed ‘opioid replacement therapy’ in the manuscript to ‘opioid agonist therapy’ to mirror the terminology utilised recently by Santo Jr and

colleagues in their systematic review and meta analysis. (Santo T, Clark B, Hickman M, et al. Association of Opioid Agonist Treatment With All-Cause Mortality and Specific Causes of Death Among People With Opioid Dependence: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2021;78(9):979–993. doi:10.1001/jamapsychiatry.2021.0976)
Thank you for highlighting our oversite with the use of the brand name for suboxone – the manuscript has been updated.
Naltrexone is not commonly used in Australia as treatment for opioid dependence. Instead, it is available for free for anyone who may experience, or witness, an opioid overdose or adverse reaction. (https://www.health.gov.au/our-work/take-home-naloxone-program/about-the-take-home-naloxone-program#:~:text=The%20Australian%20Government%20is%20investing,opioid%20overdose%20or%20adverse%20reaction.) As such, we will describe whether participants in EMU are discharged from hospital with naloxone.
See updated text in revised manuscript below:

Pp12: 'Confounders will include active injecting drug use (within the last three months), current homelessness, predominant injecting substance (opioid versus amphetamine), and opioid agonist therapy (methadone/ buprenorphine with naloxone (suboxone)/ buprenorphine) as these have traditionally influenced whether patients are considered appropriate for discharge with an OPAT system in Australian hospitals.'

Pp11: 'Injecting drug history will also describe whether opioid agonist therapy was provided and whether patients received naloxone on discharge.'

VERSION 2 – REVIEW

REVIEWER	Lewer, Dan University College London, Institute of Epidemiology and Healthcare
REVIEW RETURNED	01-Feb-2023

GENERAL COMMENTS	Many thanks for sending me this manuscript. The authors have read my feedback and made some adjustments to the manuscript, and I believe this study will produce useful results. Many observational studies still do not publish protocols and it is excellent to see this group publishing a protocol before collecting data. I feel the study stills have the major limitations of low power and confounding by indication, and would ideally like to see these limitations (and their impact on the interpretation of the results) more prominently highlighted and discussed.

REVIEWER	Traver, Edward University of Maryland School of Medicine I am involved in similar research regarding infections related to substance use.
REVIEW RETURNED	14-Feb-2023

GENERAL COMMENTS	The authors describe a 2-part investigation into epidemiology and treatment outcomes of infections related to injection drug use. The revision included here has addressed concerns related to inclusion protocol, data collection, intervention design, and the number of participants.

VERSION 2 – AUTHOR RESPONSE

The authors describe a 2-part investigation into epidemiology and treatment outcomes of infections related to injection drug use. The revision included here has addressed concerns related to inclusion protocol, data collection, intervention design, and the number of participants.