


BMJ Open Epidemiology and Management of invasive infections among people who Use drugs (EMU): protocol for a prospective, multicentre cohort study

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ABSTRACT

Introduction People who inject drugs (PWID) are at risk of invasive infections such as bloodstream infections, endocarditis, osteomyelitis and septic arthritis. Such infections require prolonged antibiotic therapy, but there is limited evidence about the optimal care model to deliver to this population. The Epidemiology and Management of invasive infections among people who Use drugs (EMU) study aims to (1) describe the current burden, clinical spectrum, management and outcomes of invasive infections in PWID; (2) determine the impact of currently available models of care on completion of planned antimicrobials for PWID admitted to hospital with invasive infections and (3) determine postdischarge outcomes of PWID admitted with invasive infections at 30 and 90 days.

Methods and analysis EMU is a prospective multicentre cohort study of Australian public hospitals who provide care to PWIDs with invasive infections. All patients who have injected drugs in the previous six months and are admitted to a participating site for management of an invasive infection are eligible. EMU has two components: (1) EMU-Audit will collect information from medical records, including demographics, clinical presentation, management and outcomes; (2) EMU-Cohort will augment this with interviews at baseline, 30 and 90 days post-discharge, and data linkage examining readmission rates and mortality. The primary exposure is antimicrobial treatment modality, categorised as inpatient intravenous antimicrobials, outpatient antimicrobial therapy, early oral antibiotics or lipoglycopeptide. The primary outcome is confirmed completion of planned antimicrobials. We aim to recruit 146 participants over a 2-year period.

Ethics and dissemination EMU has been approved by the Alfred Hospital Human Research Ethics Committee (Project number 78815.) EMU-Audit will collect non-identifiable data with a waiver of consent. EMU-Cohort will collect identifiable data with informed consent. Findings will be presented at scientific conferences and disseminated by peer-review publications.

Trial registration number ACTRN12622001173785; Pre-results.

INTRODUCTION

Background and rationale

Bacterial and fungal infections are a preventable cause of morbidity and mortality in

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This multicentre study will be the largest prospective description of people who inject drugs (PWID) hospitalised for invasive infection in Australia, and heterogeneity of treatment modalities between sites will facilitate comparison of antimicrobial treatment plans.
- ⇒ The two components of the Epidemiology and Management of invasive infections among people who Use drugs (EMU) study will optimise recruitment for this population who have been traditionally under-represented in research: waiver of consent to collect non-identifiable epidemiological and clinical data from all participants (EMU-Audit), with more detailed patient experience measures during hospitalisation, post-discharge follow-up and data-linkage of the subset of consenting participants (EMU-Cohort).
- ⇒ Results of this study have the potential to inform a patient-centred multidisciplinary model of care for PWID admitted to hospital with invasive infections and will provide valuable descriptive data to inform future randomised trials.
- ⇒ Participants may be missed if accurate histories regarding drug use are not sought or documented in hospital records.
- ⇒ While we aim to measure and adjust for confounders, a risk of residual bias from unmeasured confounding remains and the direction of this bias is difficult to predict.

people who inject drugs (PWID). Infections can range from localised skin and soft-tissue infections such as cellulitis, to systemic invasive infections such as bloodstream infections, infective endocarditis (IE), bone and joint infections and epidural abscesses.^{1–4}

Worldwide, hospitalisations for infections related to injecting drug use are increasing.^{1 2 5–11} In the USA, there was an 18-fold increase in hospitalisations for ‘bacteraemia/sepsis’ among PWIDs in Oregon between 2008 and 2018¹² while the

proportion of candidaemia cases with a documented history of injecting drug use in the past 12 months more than doubled across four US sites between 2014 and 2017.¹³ In England, there has been an annual increase in hospital admission linked to opioid-use related bacterial infections in all age groups since 2012.¹ This increase has also been seen in Australia, with the rate of IE related to injecting drug use rising from 0.9 to 1.8 per 100 000 people per year between 2009 and 2014.¹¹

Management of these invasive infections is complex and often requires prolonged antimicrobial courses and/or surgery as well as the assessment of substance dependence, mental health and social issues.^{14–16} Furthermore, PWID hospitalised with infectious complications often incur longer hospital admissions and are readmitted more frequently than non-injecting drug use related hospitalisations for the same infections.^{1 7 17 18} However, the burden, clinical-spectrum, management and outcomes of invasive infections among PWIDs in Australia are poorly described. Current prevalence data are predominantly driven by self-reporting, with significant gaps in objective data describing the burden of invasive infections.³ These gaps are reflected in the substantial variation in care delivery between hospitals and clinicians. 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) programmes to supporting their transition to community-based care.

Understanding the epidemiology and outcomes of invasive infections in PWID is essential to inform an evidence-based model of care for this population. Among PWIDs with invasive infections, completion of planned antimicrobial therapy is likely to be an important predictor of patient outcomes including treatment success and engagement with care. Current antimicrobial management strategies for invasive infections in PWID can be broadly divided into receipt of mainly inpatient intravenous antimicrobials, predominantly outpatient intravenous antimicrobials or prolonged oral antimicrobials. There is also emerging use of long-acting antimicrobials such as lipoglycopeptides (eg, dalbavancin).^{19–23} While there has traditionally been a resistance to enrolling PWID in OPAT programmes,⁴ there is an increasing evidence base indicating that OPAT is likely safe and effective in PWID, with comparable rates of therapy completion to people without a history of injecting drug use.²⁴ However, there is a paucity of evidence to quantify the effect different models of care may have on the probability of completion of planned antimicrobial therapy.

Objectives

We will perform a prospective multicentre cohort study of PWID admitted to public hospitals for the treatment of invasive infections to address these knowledge gaps. Our study aims are as follows:

1. Describe the current burden, clinical spectrum, management and outcomes of invasive infections in PWID.
2. Determine the impact of currently available models of care on completion of planned antimicrobials for PWID admitted to hospital with invasive infections.
3. Determine postdischarge outcomes of PWID admitted with invasive infections at 30 and 90 days.

Hypothesis

Objective 1 is descriptive. The main hypothesis related to objective 2 is that PWIDs with invasive infections are more likely to complete antimicrobial therapy delivered through OPAT services compared with remaining an inpatient for the duration of antimicrobials.

METHODS AND ANALYSIS

Study design

The Epidemiology and Management of invasive infections among people who Use drugs (EMU) study is a prospective multicentre cohort study with two separate components: EMU-Audit and EMU-Cohort. With a waiver of consent, EMU-Audit will collect non-identifiable standard of care information regarding patient admission, demographics, management and outcomes. EMU-Cohort is a subset of EMU-Audit participants who consent to baseline, 30-day and 90-day post-discharge interviews and/or data linkage for eligible Victorian participants.

PWID are frequently excluded or under-represented in clinical trials, which has limited the evidence base available to make treatment recommendations in this population. The waiver of consent will allow standard of care data to be collected for all eligible participants in EMU-Audit. EMU-Cohort will allow the collection of more detailed demographic, epidemiological and outcome data as well as follow-up of consenting participants.

The EMU protocol was drafted adhering to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.²⁵

Study setting

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. 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. All sites will participate in EMU-Audit but may elect not to participate in EMU-Cohort. Study recruitment period will be November 2021–November 2023.

Participants

Inclusion criteria

Participants are eligible if they are aged ≥ 18 years, self-report injecting drug use within the previous 6 months

and are admitted to hospital for management of a proven or presumed invasive infection. 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.

We define invasive infections as treating physician diagnosis (proven or presumed) of the following infections: IE, epidural abscess, bone and joint infections (including acute osteomyelitis, septic arthritis or acute prosthetic joint infections), deep abscess (such as muscle/lung/liver/spleen/cerebral) and bloodstream infections.

Participants can be enrolled in EMU-Audit multiple times if they have multiple eligible admissions during the study period. If participants represent to a study site with an eligible infection after a planned discharge, or 48 hours or more after patient directed discharge (PDD), we will include them as a new record in EMU-Audit and note the study ID of their previous record. A PDD is a discharge led by the patient, which has previously been referred to as ‘discharge against medical advice.’

Exclusion criteria

Participants admitted for management of infections other than invasive bacterial or fungal infections are not eligible. This includes those admitted for the management of acute bacterial skin and skin structure infections²⁶ only, viral infection only (including hepatitis A virus, hepatitis B virus, hepatitis C virus and HIV), or viral or bacterial meningitis only with no evidence of invasive infection as defined above. Individuals who are admitted for a reason unrelated to an acute infection (such as trauma), who subsequently develop an invasive infection are not eligible.

Exclusion criteria for EMU-Cohort are as above but also include the refusal or inability to provide informed consent. The study team may miss the opportunity of discussing the project with potential participants during their admission if they are not medically stable or there are behavioural concerns impacting clinical care and deemed not suitable to approach for research. 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. A participant can only be enrolled in EMU-Cohort once.

Participant recruitment and sampling strategy

Eligible participants will be identified by site investigators by reviewing infectious diseases inpatients and consults for individuals who meet the above eligibility criteria. Site investigators may be notified of eligible individuals by treating teams. Participants will receive their planned care as per their treating physician, with no input by

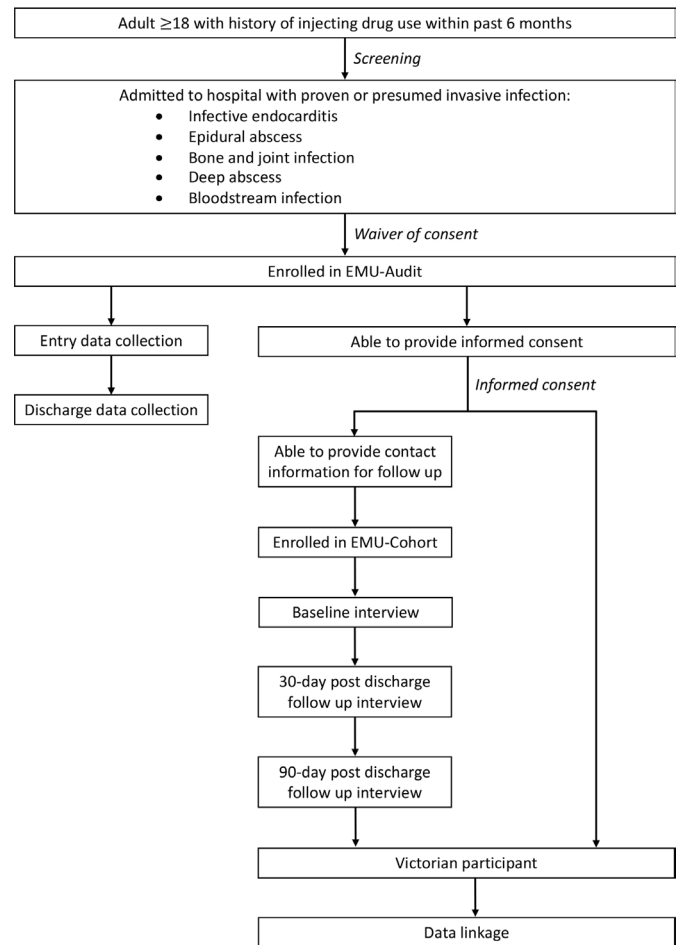


Figure 1 The EMU study recruitment and follow-up process. EMU, Epidemiology and Management of invasive infections among people who Use drugs.

researchers. **Figure 1** demonstrates the overall study recruitment and data recording process.

EMU-Audit

As EMU-Audit will only collect standard of care information from medical records, this arm of the study will be performed with a waiver of participant consent. All consecutive eligible patients will be enrolled.

EMU-Cohort

At sites participating in EMU-Cohort, EMU-Audit participants will be provided with a patient information sheet/consent form (PICF) and verbal information about the study by investigators not involved in the participant’s clinical care. This will be done either in person or via telephone during their inpatient admission. Verbal consent may be requested if in person recruitment cannot take place.

Data collection

Data collection will occur for each participant on study entry and at the completion of EMU-Audit follow-up, which is defined by death, planned discharge or PDD if the participant does not return for ongoing inpatient care with 48 hours. Participant discharge is defined as

the end of a hospital episode, which includes inpatient admission and OPAT admission. Participants enrolled in EMU-Cohort will have additional data collected on enrolment during hospitalisation, and at 30 and 90 days post-discharge. Individual entries will be allocated a unique study ID. Short breaks in therapy during an admission period, including PDD, will be captured in one case file if a break in treatment is not greater than 48 hours and readmission permits the continued planned antimicrobial therapy without any new confirmed or presumed infection. A new REDCap²⁷ case entry will be required if there is a PDD >48 hours or there is a new infection. If a site indicates within REDCap that the participant has had a previous EMU-Audit admission documented, they will be asked to record the study ID of that previous record.

EMU-Audit: entry data

On entry into EMU-Audit, baseline information will be collected using REDCap data collection forms with site specific access allocated to study investigators at each site. Baseline information will include participant demographics, limited comorbidities, drug history and clinical presentation. This information will be non-identifiable with only standard of care information collected.

EMU-Audit: discharge data

Discharge data collected will include discharge diagnosis and microbiology, management including surgery, addiction medicine review and intensive care unit requirements, antimicrobials received and associated complications, personal threat codes for behaviours impacting care, mortality in hospital, length of stay and discharge disposition. 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 while with an OPAT service. At the Alfred Hospital site, bacterial isolates from standard of care clinical samples collected during participants' admission will be stored with a non-identifiable study code, for potential future analysis.

EMU-Cohort: entry data

On enrolment into EMU-Cohort, participants will undergo an interview with a study investigator by contact on a dedicated study mobile phone or in person. This interview will collect more detailed information relating to previous invasive infections and drug history. Participants will be asked to complete an abbreviated version of the Australian Hospital Patient Experience Question Set (AHPEQS), a patient-reported experience measure (PREM), prior to discharge from the service (inpatient or OPAT).²⁸ Consent will be obtained to contact the participant via a private social media messaging, their next of

kin, or their general practitioner, to facilitate follow-up at 30-day and 90-day postdischarge.

EMU-Cohort: 30-day and 90-day post-discharge data

Two calls will be made to participants recruited into EMU-Cohort by the investigators at 30-day and 90-day post-discharge to collect information regarding their post-discharge progress and repeat the collection of AHPEQS. If the participant is not able to be contacted, the next of kin or general practitioner may be contacted as discussed with the participant at the enrolment interview. Participants who are unable to be contacted at 30-day or 90-day follow-up will be classified lost to follow-up. The data collected at these 30 and 90 days will include readmission requirements, treatment failures, completion of planned oral antimicrobials and ongoing engagement in follow-up.

EMU-Cohort: data linkage

Victorian EMU-Cohort study participants will have the option to consent to participate in data linkage. The Centre for Victorian Data Linkage (CVDL) will link cohort data from participating Victorian sites to facilitate postdischarge follow-up for emergency department presentations (Victorian Emergency Minimum Dataset, VEMD), hospital admissions (Victorian Admitted Episodes Dataset) and mortality status (Victorian Death Index). This will be used to assess mortality and readmission rates at 30 days, 90 days and over subsequent years. Datasets will be linked by deterministic linkage, utilising Medicare number, first name, last name, hospital unique record number (URN), date of birth and sex. A separation principle will be applied to data flow to ensure participant confidentiality. It is anticipated that data linkage extractions will occur at the three time points, to provide crucial information about short-term, medium-term and long-term outcomes of this cohort. The time points are: 12 months following last participant recruited, to obtain 30-day and 90-day follow-up data; 3 years post last participant recruited, to obtain 2 year follow-up data; and 6 years post last participant recruited, to obtain 5 year follow-up data.

Exposure of interest

The primary exposure of interest is the treatment modality used to administer antimicrobial therapy for each individual participant. Participants will be allocated into one of four groups, according to the management strategy selected by their treating clinician.

1. Inpatient intravenous antimicrobials: Participants will be allocated into the inpatient intravenous antimicrobial group if they remain an inpatient for the duration of their intravenous antimicrobial therapy or if they remain an inpatient for intravenous antimicrobial therapy for >50% of their planned antimicrobial duration (allowing for an oral antimicrobial 'tail' following completion of intravenous antimicrobials). If the participant is transferred to a different facility to continue

- intravenous antimicrobials (such as a rehabilitation hospital), they will continue to be classified in the inpatient intravenous antimicrobial group.
2. OPAT: Participants discharged with an OPAT service to complete intravenous antimicrobial therapy will be allocated into the OPAT group. The participant may have received any duration of intravenous antimicrobials as an inpatient while being medically stabilised prior to discharge with OPAT. These antimicrobials will be recorded as part of the participant's management strategy.
 - a. 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. 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.
 3. Early oral antimicrobial therapy: Participants who are discharged on oral antimicrobials having received less than 2 weeks of intravenous antimicrobials, will be allocated into the early oral antimicrobial therapy group. This includes participants who are discharged on early oral antimicrobials as part of the primary treatment plan and those who are discharged on oral antimicrobials as part of a PDD.

4. Long-acting lipoglycopeptide: A participant will be included in this group if they receive dalbavancin or oritavancin at any point of their treatment, irrespective of the duration of previous intravenous antimicrobials. Participants who die or have PDD within the first 7 days will not be analysed as part of any of the above groups. They will still be eligible to have data included in EMU-Audit and interviewed as part of EMU-Cohort.

Outcome measures

The primary outcome is confirmed completion of planned antimicrobial therapy as recorded in medical records. Any cessation of antimicrobials prior to planned completion date will be determined as a failure of completion of planned antimicrobial therapy. The primary outcome will not be achieved if there is a PDD with duration greater than 48 hours from either inpatient or ambulatory services providing intravenous antimicrobials, eviction from inpatient or OPAT care, self-reported discontinuation of oral antimicrobial therapy, lost to follow-up or mortality during antimicrobial therapy (including OPAT or oral antimicrobials if discharged on continuing therapy.) Missed doses of antimicrobials but continued treatment until planned completion date will be considered treatment success if the primary physician is satisfied planned completion date is achieved.

The secondary outcomes assessed are listed in [table 1](#). Secondary outcomes include length of hospital stay, analysis of clinical outcomes, frequency of readmission for both treatment and infection-related complications, numbers of lost to follow-up (defined as participant

Table 1 Secondary outcomes measured and inclusion in EMU-Audit and/or EMU-Cohort

Outcome	Outcome measures	EMU-Audit	EMU-Cohort
Clinical outcomes	<ul style="list-style-type: none"> ▶ Length of hospital±OPAT admission (days) ▶ Mortality during admission for invasive infection ▶ ICU admission requirement, length of stay (days), intubation requirement ▶ Surgery requirement ▶ Unplanned discharge from either inpatient or OPAT admission ▶ Patient directed discharge ▶ Personal threat codes for behaviours impacting care and/or formation of behavioural contract ▶ Healthcare associated bloodstream infection ▶ Treatment failure—worsening or ongoing infection resulting in prolonged therapy 	✓	✓
Patient-reported experience	▶ Australian Hospital Patient Experience Question Set	✗	✓
Readmission	<ul style="list-style-type: none"> ▶ Readmission for infection or treatment-related complications during OPAT/oral antimicrobial discharge period ▶ Unplanned readmission for any reason in 30-day period following discharge for invasive infection ▶ Readmission free survival 30 days postdischarge ▶ Readmission free survival 90 days postdischarge 	✗	✓
Lost to follow-up	▶ Participant unable to be contacted at 30-day or 90-day follow-up	✗	✓

EMU, Epidemiology and Management of invasive infections among people who Use drugs; ICU, intensive care unit; OPAT, outpatient parenteral antimicrobial therapy.

unable to be contacted for 30-day and/or 90-day postdischarge follow-up interviews) and PREM.

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. Injecting drug history will also describe whether opioid agonist therapy was provided and whether patients received naloxone on discharge. A description of clinical presentations, infective diagnosis and microbiology will be provided. The treatment modalities received will also be described including rates of completion.

Sample size

The primary objective of this study is descriptive. Sample size calculations apply to objective two. Previous studies have demonstrated a 49% and 55% completion rate for PWID receiving inpatient antimicrobials respectively.^{29 30} We conservatively assumed a higher completion rate as the study by Marks *et al*²⁹ found that 28% of patients had 'negotiated discharges' (ie, received oral antimicrobials to complete their treatment) and their study was conducted in an American setting (compared with the Australian setting which has universal healthcare coverage). Therefore, a completion rate of 65% was assumed for the inpatient treatment group in this study.

Previous studies of OPAT completion in PWID have demonstrated completion rates ranging from 72% to 100%.²⁴ Many of these studies only enrolled PWID who met strict enrolment criteria. In this study, hospitals will not necessarily require such strict enrolment for participation in OPAT. We estimated a completion rate in the outpatient group of 85%.

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 OPAT) combined. However, as rate of recruitment is dependent in part on hospital policies regarding discharging PWIDs 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 6 months after commencing multisite enrolment and the sample adapted, if needed.

Statistical analysis

The primary outcome will be the comparison of confirmed completion of planned antimicrobials for those in the inpatient intravenous antimicrobial group compared with those in the OPAT group. The completion rates for participants in the early oral antimicrobial therapy group and the long acting lipoglycopeptide groups will be analysed as secondary outcomes. However, it is expected the number of participants in these groups will be small,

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

EMU, Epidemiology and Management of invasive infections among people who Use drugs.

hence the study has been powered to compare the two major treatment modalities currently used in clinical practice.

Treatment groups are defined by participation in existing treatment modalities for the treatment of infections in PWID. The impact of treatment modality on completion of planned antimicrobial will be determined using logistic regression with random effects for hospital (if needed) and adjusted for confounders. Confounders will include active injecting drug use (within the last 3 months), current homelessness, predominant injecting substance (opioid vs 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.

Secondary outcomes will be compared based on treatment modality received, if numbers permit. A χ^2 or Fisher's exact test will be used for dichotomous variables and continuous variables will be compared using a Student's t-test or Mann-Whitney U test, depending on distribution. Length of admission will be compared using Kaplan-Meier curves and the appropriate test to assess the equality of the survivor functions.

Data management

Identifiers will not be collected for EMU-Audit participants who have not consented to participate in EMU-Cohort. Each participant will be assigned a study ID. Study IDs will be generated sequentially by REDCap. The data collected during the study (eg, medical and demographic information) will be subjected to computerisation and statistical analysis. All data will be collected and stored on REDCap hosted on secure Monash University servers. Site investigators will only be able to access data on their site's participants. During analysis, electronic data will be kept on password-protected folders within the hospital/universities IT system. Only the coordinating primary investigator and principal investigators will be able to access data from all sites. Any site-level hard copy data, such as hard copy PICF forms, will be stored at study site

research offices, in a locked cabinet in a locked office of the site investigator.

Data will be destroyed 7 years after completion of research project in accordance to Alfred Health Guidelines on Archiving/Storage of Research Records. Participating sites will follow their own local governance requirements for site retained study documents.

Patient and public involvement

There was no patient or public involvement in the design and conduct of this study. However, study authors JSD and PH have extensive experience collaborating with people with lived experience of drug use and this informed EMU study design.

ETHICS AND DISSEMINATION

Ethics approval

The EMU Study has been approved by the Alfred Hospital Human Research Ethics Committee Project Number 78815 (Local Reference: Project 529/21).

Risks to participants

Patients will be fully informed regarding potential risks as part of the consent process. We may discuss issues that are difficult for participants to talk about, and which could cause distress. If this happens, investigators are trained to provide support and referral to support services if needed. Participants also have the right to decline answering any questions that make them feel uncomfortable.

We will also ask participants about potentially illegal behaviours such as their use of drugs. Participants will be informed that we cannot keep this information confidential if we:

- ▶ Think they are going to seriously harm themselves.
- ▶ Think they are going to seriously harm someone else.
- ▶ Have been asked to provide this information by a court of law.
- ▶ Learn information concerning the protective safety of children.

Over many years of research, we have never been required by law to provide our research information to anyone else. If we were, we would do our best to tell participants.

Withdrawal of consent

A participant has the right to withdraw from the study at any time and for any reason without affecting the receipt of care. Data collected on study subjects up to the time of withdrawal will remain in study database and utilised in analysis. Study participants withdrawing their consent will not be replaced.

Dissemination of results

The principal investigators will be jointly responsible for the dissemination of results arising from this project. Results will be disseminated in a variety of ways including abstracts, posters and presentations at scientific and public health conferences and published manuscripts

in peer-reviewed journals. Reports will also be made to hospitals that participated in and supported the study. Criteria for authorship will be in accordance with the International Committee of Medical Journal Editors and as described in research agreements.

DISCUSSION

To our knowledge, the EMU study is the first prospective multisite cohort study comparing currently used management strategies for invasive infections in PWID. Our study design has the distinct advantage of providing flexibility to recruiting sites through the two components of EMU-Audit and EMU-Cohort. This will allow for recruitment of participants with a waiver of consent, to ensure collection of crucial data in a patient population who are often excluded, under-represented or not able to engage in research. The novel data produced from the EMU study will help contribute to the design of a patient-informed evidence-based model of care for the management of invasive infections in PWID. Furthermore, the data from this study may help contribute to strategies to prevent invasive infections and hospitalisations in PWID. Preventing invasive infections and averting non-invasive infections from progressing to invasive infections would also not only decrease morbidity but also limit healthcare costs.

Despite the strengths of the study, the design presents some inherent limitations. First, EMU-Audit relies on information documented in the medical records. PWID frequently describe stigma, especially during healthcare encounters.^{31 32} Injecting drug use may not be disclosed by patients due to concern regarding stigma and altered management when seeking care. If a patient does not disclose their injecting history, they will not be recruited. However, asking about injecting habits is standard of care when investigating invasive infections and thus should be captured in the admission information. For EMU-Audit, collection of outcomes is limited to those that occurred within the healthcare system with care captured within the medical chart. Of note, we will be unable to collect the primary outcome for participants in EMU-Audit discharged on early oral antimicrobials. The subset of EMU-Cohort will provide further in-depth analysis for data missing in the EMU-Audit group. We acknowledge that the follow-up of EMU-Cohort participants at 30-day and 90-day may pose a challenge. To encourage participation and thank participants for their time, small monetary reimbursements are provided to participants after each EMU-cohort interview.

As an observational study comparing treatment options, EMU is at risk of confounding by indication. While we will measure and adjust for factors likely to confound the relationship between acceptance into OPAT and completion of planned antimicrobial therapy (such as drug use history, unstable housing, engagement in opioid agonist therapy and illness severity), we acknowledge the risk of residual bias. Once clinically stable, acceptance



of PWIDs 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. We also acknowledge that there is the risk of a lack of precision in results due to our chosen sample size. However, the chosen differences in completion rates (65% vs 85%) were based on recently published literature.^{24 29 30} Results will also be reported with CIs to convey uncertainty in our estimates. Furthermore, the primary aim of the EMU study is descriptive and will provide valuable data to inform further interventional research.

In conclusion, the EMU study represents an innovative project design to gain better insights into the current burden of invasive infections among PWID as well as the outcomes related to the management strategy received. The knowledge gained from this cohort study will be instrumental in developing an evidence-based patient-centred model of care for PWID with invasive infections. In the long run, we aim to improve the prevention and management of invasive infections in PWID leading to improved outcomes in this stigmatised population.

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Contributors LOA conceived the study design and protocol development. AJS assisted in the technical design of the study. SJL and AJS provided statistical support. MB, JSD, PH and OV provided expert input and guidance in the development of the final study protocol. LOA, MB, JSD and AJS helped in coordinating site investigators. All authors approved the final version of the paper manuscript.

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Competing interests PH has received investigator-driven research funding from Gilead Sciences and AbbVie for work on hepatitis C unrelated to this manuscript. JSD's institution has received investigator-initiated research funding from Gilead Sciences and AbbVie and honoraria from Gilead Sciences and AbbVie. AJS's institution has received investigator-initiated research funding from Merck, Sharp and Dohme.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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