**Study Protocol**

**P**oint **O**f **C**are Hepatitis C testing and subsequent treatment uptake in **A**ddiction **M**edicine residential withdrawal unit (POCAM): a pilot study

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# Protocol synopsis

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| Study Title | **P**oint **O**f **C**are Hepatitis C testing and subsequent treatment uptake in **A**ddiction **M**edicine residential withdrawal unit (POCAM): a pilot study. |
| Protocol number |  |
| Study site | Depaul House, 9 Brunswick St Fitzroy 3065 VIC |
| Background and rationale | Chronic infection with hepatitis C virus (HCV) is a major public health burden with an estimated 71 million individuals infected worldwide. Over 180,000 people in Australia were estimated to be living with chronic hepatitis C (CHC) in 2018. If left untreated, individuals with CHC can develop complications including cirrhosis, end-stage liver failure and hepatocellular carcinoma.  The introduction of direct-acting antiviral (DAA) therapy offered patients an alternative to interferon-based therapies and has revolutionised the treatment of patients with CHC with cure rates in excess of 95%. Along with high cure rates and being well tolerated, cure of HCV with DAA therapy is associated with significant reduction in liver related morbidity as well as all-cause mortality.  In medium-to-high income countries like Australia the predominant mode of transmission of HCV is through injecting drug use with an estimated 80% of new cases of HCV infection occurring among people who inject drugs (PWID) and 50% of existing infections being among former and current PWID.  In context of public health burden, the WHO has drafted HCV elimination targets with proposed reduction of 80% in incidence along with a 65% reduction in HCV-related deaths by 2030. Australian modelling data has shown that in order to achieve the WHO targets, approximately 4,700 treatment courses per year are required among PWID infected with HCV with the priority being to engage individuals who are actively injecting to address the incidence of new HCV infection.  Engagement of this population with traditional healthcare has historically proven challenging due to difficulties relating to socioeconomic circumstances and conflicting priorities such as substance dependence. Particularly conventional HCV testing offers numerous obstacles to HCV diagnosis and treatment due to the complexity of the care cascade. Patients undergo multiple diagnostic steps; first to obtain a HCV antibody test, receive these results and then to obtain a HCV RNA test to determine if current infection, and later to receive test results and finally be linked into treatment. The attrition to healthcare engagement is reflected by only 19% of individuals diagnosed with CHC having received DAA therapy in 2017.  Substance withdrawal in the dependent individual often precipitates physical and psychological symptoms that require medical assistance. Admission to a withdrawal unit offers individuals the first step to longer term abstinence by providing access to medical and nursing staff. Depaul House (DPH) is a 12-bed community withdrawal unit attached to St Vincent’s Hospital Melbourne. Preliminary retrospective data of prior DPH admissions reveals that approximately 70% of clients underwent initial HCV screening with serology but only 4% had HCV PCR sent and available by time of discharge with no clients being commenced on DAA therapy.  The period of hospitalisation for inpatient withdrawal may represent an ideal opportunity to engage individuals at increased risk for blood-borne virus (BBV) with screening and HCV care. Given that recent PWID are at high risk of transmission and risk behaviour post-discharge, eradication of HCV viremia with successful DAA therapy commenced during admission for inpatient substance withdrawal may be an important strategy for broader HCV elimination.  This pilot study will extend HCV screening by targeting a high-risk population engaged with inpatient services through a novel model of care using rapid HCV point-of-care (POC) testing, liver assessment and treatment initiation at the residential withdrawal unit attached to St Vincent’s Hospital Melbourne in Fitzroy. It will investigate whether providing rapid POC HCV diagnostic testing using the rapid Cepheid Xpert HCV Viral Load (VL) Fingerstick test with notification of results within 60 minutes combined with same-day assessment of severity of liver disease, overcomes a major barrier to HCV treatment uptake among people who inject drugs (PWID) or with active substance misuse. |
| Objectives | To evaluate the uptake and acceptability of POC testing using the Xpert HCV VL Fingerstick test in individuals with substance dependence presenting to a residential withdrawal unit.  Further, we seek to evaluate the initiation (prescription and/or dispensing) of DAA therapy in participants offered POC testing, compared to initiation among participants who have undergone standard-of-care (SOC) HCV testing at the residential withdrawal over a similar time period. |
| Study design | This prospective cohort study will recruit consecutive clients attending the withdrawal unit over a 12 month period and offer them rapid POC testing for HCV PCR. This will be compared to current SOC HCV testing through a retrospective analysis of testing and treatment over the preceding 12 month period. The primary study location will be Depaul House, which is a residential withdrawal unit attached to St Vincent’s Hospital Melbourne and located at 9 Brunswick St Fitzroy 3065 VIC. |
| Target population | Individuals over the age of 18 electively admitted to the residential withdrawal unit will be recruited and consented to the study. Participants unable to provide informed consent will be excluded.  Inclusion criteria are:   * Aged ≥18 years; * Admitted to the St Vincent’s Hospital residential withdrawal unit, Depaul House, during the recruitment phase of the study; * Willing and able to provide written informed consent; * Consent to completion of questionnaires; * Consent to a venous blood sample for routine blood tests; * Not currently engaged in care for treatment of hepatitis C infection; * Fulfils study criteria for HCV diagnosis to initiate treatment.   Participants who meet any of the following criteria will not be included in the study:   * Inability or unwillingness to provide informed consent * Pregnant or breastfeeding at time of commencement of HCV antiviral treatment; * Decompensated liver disease * Creatinine clearance <30 mL/min * History of solid organ transplant * Diagnosed and/or undergoing treatment for hepatocellular carcinoma; * Awaiting liver transplantation; * Currently engaged in care for treatment of hepatitis C infection or HIV * Use of prohibited concomitant medications |
| Study timeline | The pilot study will run for 12 months, which will comprise 6-9 months for recruitment and treatment initiation, up to 3-6 months for treatment completion, follow-up and data analysis. |
| Study endpoints | Primary outcome measures:   * Uptake and acceptance of POC testing with the Xpert HCV VL Fingerstick test; * DAA treatment prescription and/or dispensing following Xpert HCV VL Fingerstick testing compared to SOC HCV testing;   Secondary outcome measures:   * Prevalence of HCV Ab and HCV RNA positivity amongst the study population; * The number of participants who receive a POC Xpert HCV VL Fingerstick result on the same day as testing; * The average time to treatment initiation of DAAs following a positive Xpert HCV VL Fingerstick result, compared to SOC HCV testing; * Among participants who are HCV RNA positive, the number that are prescribed and/or dispensed DAA treatment during their residential withdrawal stay * Uptake of DAA therapy during admission in patients suitable for study * The number of participants who commence DAA therapy who return at week 4 and/or week 8 (if applicable) for ongoing treatment; * The number of participants who complete DAA therapy; * Rates of negativity of end of treatment HCV PCR; * The number of participants followed up at >4 weeks post treatment for HCV RNA testing and among these, the number of participants who are HCV RNA negative at >4 weeks post treatment completion (sustained virological response, SVR4+); * Relapse or re-infection rates; * Client perceptions of screening and treatment process. |
| Governance | A protocol steering committee comprising the project’s principal and associate investigators will oversee the operational aspects of the study. |
| Data management and analysis | Data storage will be on a secure, password protected database using REDCap electronic data capture tools hosted at The University of Melbourne.  Data management and analysis will be centralised through the gastroenterology department at St Vincent’s Hospital, Melbourne. |
| Blood and tissue storage | Any pathology outside the POC testing will be performed using local pathology providers (St Vincent’s Pathology) as per current standard of care practice at Depaul House.  As per routine care for patients being treated for HCV, blood samples taken at enrolment, end of treatment and >4 weeks post-treatment will be kept for storage for future testing (genotyping, resistance-associated substitution testing) in the event of HCV recurrence post treatment completion. |

# Glossary

Ab Antibody

AE Adverse event

ALA Australian Liver Associated

APRI Score that can be a predictor of hepatic fibrosis in chronic hepatitis C

CRF Clinical report form

DAA Direct-acting antiviral agent/s

DPH Depaul House

EIA Enzyme immunoassay

FBE Full blood examination

GESA Gastroenterological Society of Australia

GHB Gamma-hydroxybutyrate

GP General practitioner

HCV Hepatitis C virus

HREC Human Research Ethics Committee

LFT Liver function test

PCR Polymerase chain reaction

POC Point of care

PWID People/person who inject/s drugs

RNA Ribonucleic acid

SOC Standard of care

SVR4+ Sustained virological response, defined as undetectable circulating HCV RNA 4+ weeks post-treatment completion

# Background and rationale

Chronic infection with hepatitis C virus (HCV) is a major public health burden with an estimated 71 million individuals infected worldwide. Over 180,000 people in Australia were estimated to be living with chronic hepatitis C (CHC) in 2018.1 If left untreated, individuals with CHC can develop complications including cirrhosis, end-stage liver failure and hepatocellular carcinoma.2

The introduction of direct-acting antiviral (DAA) therapy offered patients an alternative to interferon-based therapies and has revolutionised the treatment of patients with CHC with cure rates in excess of 95%.3 Along with high cure rates and being well tolerated, cure of HCV with DAA therapy is associated with significant reduction in liver related morbidity as well as all-cause mortality.4

In medium-to-high income countries like Australia the predominant mode of transmission of HCV is through injecting drug use with an estimated 80% of new cases of HCV infection occurring among people who inject drugs (PWID) and 50% of existing infections being among former and current PWID.5

In context of public health burden, the WHO has drafted HCV elimination targets with proposed reduction of 80% in incidence along with a 65% reduction in HCV-related deaths by 2030. Australian modelling data has shown that in order to achieve the WHO targets, approximately 4,700 treatment courses per year are required among PWID infected with HCV with the priority being to engage individuals who are actively injecting to address the incidence of new HCV infection.6

Engagement of this population with traditional healthcare has historically proven challenging due to difficulties relating to socioeconomic circumstances and conflicting priorities such as substance dependence. Particularly conventional HCV testing offers numerous obstacles to HCV diagnosis and treatment due to the complexity of the care cascade. Patients undergo multiple diagnostic steps; first to obtain a HCV antibody test, receive these results and then to obtain a HCV RNA test to determine if current infection, and later to receive test results and finally be linked into treatment. The attrition to healthcare engagement is reflected by only 19% of individuals diagnosed with CHC having received DAA therapy in 2017.7

Substance withdrawal in the dependent individual often precipitates physical and psychological symptoms that require medical assistance. Admission to a withdrawal unit offers individuals the first step to longer term abstinence by providing access to medical and nursing staff. Depaul House (DPH) is a 12-bed community withdrawal unit attached to St Vincent’s Hospital Melbourne. Preliminary retrospective data of prior DPH admissions reveals that approximately 70% of clients underwent initial HCV screening with serology but only 4% had HCV PCR sent and available by time of discharge with no clients being commenced on DAA therapy.

The period of hospitalisation for inpatient withdrawal may represent an ideal opportunity to engage individuals at increased risk for blood-borne virus (BBV) with screening and HCV care. Current model of care for HCV screening during withdrawal admission possesses limitations with HCV PCR rarely being performed and available for individuals shown to have positive HCV serology by the end of their admission; as a result access to DAA therapy is potentially delayed to outpatient follow-up, presenting additional barriers to a population already struggling with treatment uptake. Given that recent PWID are at high risk of transmission and risk behaviour post-discharge, eradication of HCV viremia with successful DAA therapy commenced during admission for inpatient substance withdrawal may be an important strategy for broader HCV elimination.

This pilot study will extend HCV screening by targeting a high-risk population engaged with inpatient services through a novel model of care using rapid HCV point-of-care (POC) testing, liver assessment and treatment initiation at the residential withdrawal unit attached to St Vincent’s Hospital Melbourne in Fitzroy. It will investigate whether providing rapid POC HCV diagnostic testing using the rapid Cepheid Xpert HCV Viral Load (VL) Fingerstick test with notification of results within 60 minutes combined with same-day assessment of severity of liver disease, overcomes a major barrier to HCV treatment uptake among people who inject drugs (PWID) or with active substance misuse.

*Point-of-care HCV RNA test*

Establishing the presence of HCV RNA (in order to make a diagnosis of hepatitis C) has traditionally been done via qualitative PCR testing in laboratory facilities. However, recently progress has been made in development of rapid POC tests that can detect HCV RNA without the need for samples to be sent to laboratories for complex nucleic acid testing. The Cepheid Xpert HCV VL test is run on the Cepheid GeneXpert platform, which is a benchtop machine that performs real-time PCR in a self-contained cartridge. The Xpert HCV VL test has been validated for use with whole blood collected via fingerstick sample and has been approved by the TGA in May 2020.8 The time from obtaining a fingerstick sample to result is 60 to 90 minutes and in a real-world study sensitivity was 100% (95% CI 93.9-100%) and specificity 100% (95% CI 96.6-100%).9

It is hypothesised that offering POC RNA testing may reduce attrition between confirmation of HCV exposure (HCV antibody positive), confirmation of active HCV infection (HCV PCR positive) and commencing DAA treatment by allowing a person to determine their hepatitis C infective status without the requirement for repeated venepuncture. It is hypothesised that PWID who are reluctant to complete venepuncture may be more willing to do so once a diagnosis is confirmed, with venepuncture undertaken only to enable treatment (i.e. fibrosis assessment), rather than ascertaining hepatitis C status. In turn it is hypothesised that rapid confirmation of active HCV through POC testing will positively impact on an individual’s willingness to engage in treatment which can be quickly initiated during their inpatient stay at a residential withdrawal unit.

# Study objectives

The aim is to determine the most effective strategy to increase diagnosis of hepatitis C and uptake of DAA treatment amongst a high-risk population with substance dependence during a period of engagement with healthcare.

## Hypothesis

We hypothesise that:

* POC testing with the Xpert HCV VL Fingerstick will be acceptable to a majority of clients at residential withdrawal unit;
* POC testing will lead to higher screening rates and more timely receipt of HCV results than previous standard of care practice at the residential withdrawal unit;
* More participants will be prescribed and initiate DAA therapy during inpatient stay following POC Xpert HCV VL Fingerstick testing than standard of care;
* Participants who undergo POC testing and are provided directly with DAA therapy during the same admission as testing will be more likely to complete the prescribed course of HCV treatment;
* Participants who undergo POC testing and are provided directly with DAA therapy will be more likely to achieve a sustained virological response at 4+ weeks post treatment completion (SVR4+) due to increased engagement with HCV care.

## Objective

* To evaluate the uptake and acceptability of POC testing using the Xpert HCV VL Fingerstick test in individuals with substance dependence presenting to a residential withdrawal unit.
* To evaluate if the use of POC testing shortens time to result and improves rates of initiation of DAA therapy during admission to residential withdrawal unit.
* To evaluate if the initiation (prescription and/or dispensing) of DAA therapy in participants offered POC testing at the residential withdrawal unit improves outcomes (treatment adherence, treatment completion and SVR4+)

# Study design

This prospective pilot study will recruit consecutive clients attending the withdrawal unit over a 12 month period. All participants will be offered POC Xpert HCV VL Fingerstick testing. This will allow for rapid HCV diagnosis and same day treatment initiation. All participants who return a positive HCV RNA result will be offered treatment with DAA therapy as per Australian Liver Association (ALA)/Gastroenterological Society of Australia (GESA) guidelines.10

Following completion of DAA therapy, all participants will be followed up for a minimum period of a further 4 weeks to obtain SVR4+; utilisation of SVR4+ as a surrogate for successful eradication of HCV is based on recently presented international data reflecting high concordance with SVR12 and deemed most appropriate to mitigate the risk of the study population being lost to follow-up.11 This will result in a minimum follow up period of 12-16 weeks following a positive HCV RNA result and initiation of treatment with DAA therapy.

The primary outcomes will be compared to the results obtained from a retrospective analysis of HCV testing and treatment at the withdrawal unit over the preceding 12 month period which represents the current model of care at the withdrawal unit.

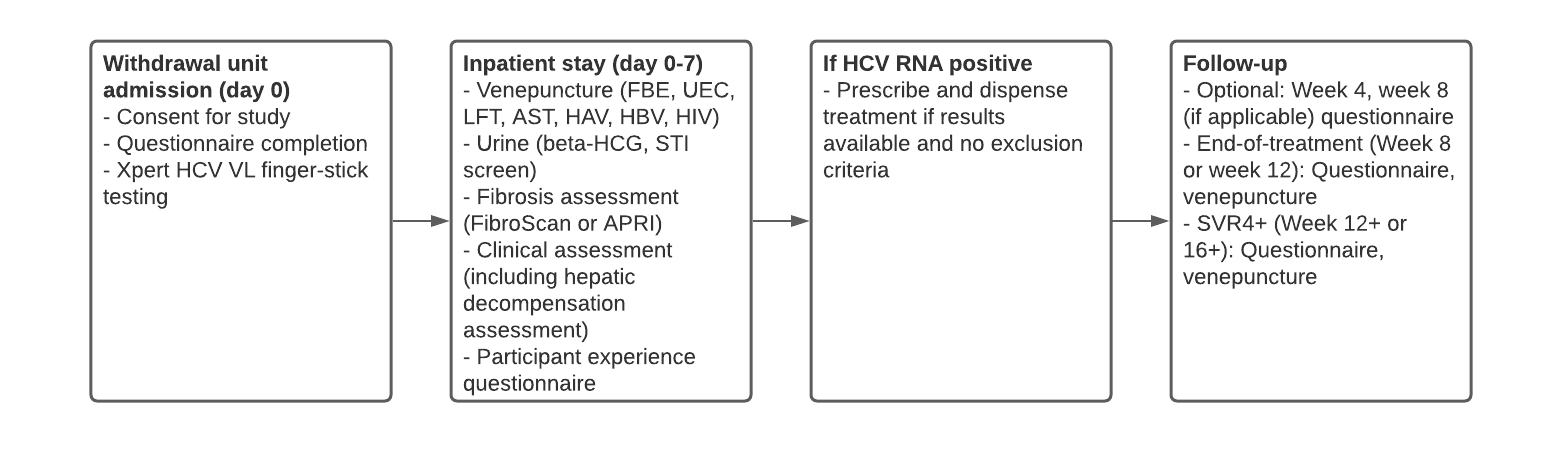
The trial design is shown in Figure 1. 

Figure 1. Study design flow diagram.

# Study setting

This study will be conducted at Depaul House (DPH), which is a residential withdrawal unit attached to St Vincent’s Hospital Melbourne and located at 9 Brunswick St Fitzroy 3065 VIC. The clients attending DPH have substance dependence and are admitted for inpatient withdrawal.

# Participant population

Enrolment of clients over the age of 18 years who present to DPH for inpatient management of substance dependence will occur over a total time period of 12 months. Consecutive clients attending DPH during the study period will be offered POC Xpert HCV VL finger-stick testing. All participants who return a positive HCV RNA result will be offered treatment with DAA therapy as Australian Liver Association (ALA)/Gastroenterological Society of Australia (GESA) guidelines.10

We aim to recruit at least 100 participants, with an estimated 10% of participants expected to return a positive HCV RNA result and be offered treatment initiation.

## Study inclusion criteria

* Aged ≥18 years;
* Admitted to the residential withdrawal unit of St Vincent’s Hospital Melbourne, Depaul House, during the recruitment phase of the study;
* Willing and able to provide written informed consent;
* Consent to completion of questionnaires;
* Consent to a venous blood sample for storage at pre-specified time points during the study for HCV sequencing if required, as it current SOC;
* Not currently engaged in care for treatment of hepatitis C infection;
* Fulfils study criteria for HCV diagnosis to initiate treatment.

Potential participants must meet routine clinical care criteria for commencing HCV treatment, in accordance with Australian licensing, prescribing restrictions, manufacturers’ recommendations and best-practice clinical care.

## Study exclusion criteria

* Inability or unwillingness to provide informed consent
* Pregnant or breastfeeding at time of commencement of HCV antiviral treatment;
* Decompensated liver disease
* Creatinine clearance <30 mL/min
* History of solid organ transplant
* Diagnosed and/or undergoing treatment for hepatocellular carcinoma;
* Awaiting liver transplantation;
* Currently engaged in care for treatment of hepatitis C infection or HIV
* Use of prohibited concomitant medications

## Participant withdrawal

All participants have the right to withdraw from the study at any stage and for any reason without prejudice or penalty. Further, the study nurses, doctors and other investigators have the right to withdraw a participant from the study if it is in the best interest of the participant. Any participant who expresses a desire to withdraw from the project will be encouraged to attend a non-compulsory follow-up visit prior to withdrawal to discuss the reasons for their withdrawal and use of their study data collected to date, in addition to safety issues for those participants who cease anti-HCV treatment, which would occur in routine clinical practice regardless of study participation status.

The process for withdrawal is outlined in the participant information and consent form (PICF).

# Study procedures

## Standard of care testing comparison group

The control arm will consist of a retrospective analysis of the standard of care model of hepatitis C screening and treatment at Depaul House over the preceding 12 month period. A separate low risk ethics including waiver of consent for this retrospective analysis will be submitted.

For this, admissions to Depaul House for elective substance withdrawal over a 12 month period from 1st August 2020 to 31st July 2021 were compiled from the intake database. Data was then extracted from St Vincent’s Hospital medical records along with a search of pathology results ordered by St Vincent’s Hospital. Data collected included patient demographics, markers of patient vulnerability, substance use history, hepatitis C testing results (including date of testing and date of result availability), other pathology results as well as details of hepatitis C treatment including outcomes, rates of relapse and re-infection.

This retrospective analysis revealed that of 130 clients attending DPH for substance withdrawal over the three month period,

* 89 (68.5%) consented to hepatitis C testing during DPH admission
* Of 56 clients who reported history of injecting drugs, 17 (30.4%) did not undergo bloodborne virus screening during DPH admission
* Of 17 HCV Ab +ve, four (23.5%) received a HCV PCR result during DPH admission
* Of four HCV PCR +ve, zero (0%) commenced DAA therapy during DPH admission

## Point of care testing

The Cepheid Xpert HCV VL Fingerstick test is a quantitative RNA assay that will provide a result from a fingerstick collection of capillary blood (sample size 100µl) into a collection device (minivette) within 60 minutes. The reverse transcriptase polymerase-based chain reaction amplification technology (RT-PCR) is performed using the GeneXpert platform. It can detect RNA levels of >35 IU/mL, with a limit of quantification of >100 IU/mL for the 100µl sample volume.

## Screening for other bloodborne viruses

As is standard of care practice for HCV pre-treatment evaluation, all participants will undergo screening for other blood borne viruses, including hepatitis B and HIV. Participants will receive appropriate pre- and post-test counselling. Participants found to have chronic hepatitis B will be referred to a specialist-led clinic gastroenterology clinic at St Vincent’s Hospital Melbourne for assessment and follow up. Participants found to have HIV will be referred to the appropriate infectious diseases unit for work up and treatment.

## Fibrosis assessment

Participants will undergo liver fibrosis assessment as part of routine clinical care using the aspartate to platelet ratio (APRI) score and FibroScan. All participants will be included in the current study regardless of fibrosis stage.

### APRI score

The APRI score is a blood-based non-invasive marker for predicting hepatic fibrosis and cirrhosis. The APRI score will be calculated from the blood tests ordered at the first visit. Those participants with an APRI score >1.0 (indicative of advanced fibrosis) and advanced fibrosis or cirrhosis confirmed on FibroScan (see below) will be referred to a specialist-led clinic at St Vincent’s Hospital Melbourne for liver assessment and follow up as per the ALA/GESA Australian HCV National Consensus Statement.10 These participants will still be eligible for participation and treatment through this study.

### FibroScanTM

FibroScanTM (transient elastography) allows a rapid, non-invasive evaluation of liver fibrosis via the measurement of liver stiffness.12 Appropriate members of the study team (integrated hepatitis nurse, doctors) will have pre-existing appropriate expertise to perform FibroScan. A FibroScan will be performed in participants deemed as high risk for hepatic fibrosis with APRI score > 1.0 following recruitment on their first study visit, as outlined in the study schedule. Attempts will be made to ensure participants are fasted for at least 2 hours prior to FibroScan being performed, however this may not always be possible.

If a successful FibroScan cannot be performed, the results of a previous FibroScan performed by trained personnel within the previous 12 months or liver biopsy within the previous 24 months can be used for the assessment of fibrosis if available.

Participants will be assessed as potentially having cirrhosis if their FibroScan score is

≥12.5 kPa, provide a clinical history of previous diagnosis of advanced fibrosis, have an APRI score >1.0 or have a platelet count <150 cells/109 without a previously identified cause. Participants with cirrhosis will be referred to a specialist-led clinic at St Vincent’s Hospital Melbourne for liver assessment and follow up as per the ALA/GESA Australian HCV National Consensus Statement.10

## Data collection and management

Clinical data will be recorded on paper or electronic data collection tools at each visit, and entered into a secure, password-protected database using REDCap electronic data capture tools hosted at The University of Melbourne.

### Participant tracking log

A log of participants who have been consented for this study will be maintained at the DPH. This will contain the participants unique study ID and contact details, and track completion of study activities including follow-up and return of results to the participant. No readily identifiable data will be stored in this log. The participants study ID will be used to track participants’ data throughout the study and allow re-identification if required. This log will be stored electronically, in a password-protected server and only accessible to authorised members of the study team, and as such, re-identification of other study materials would only be possible to these pre-approved personnel. It will be managed separately to participant data used for analysis.

### Test results and clinical data

A member of the study team will use the participants study ID to enter clinical data into a secure, password-protected database using REDCap electronic data capture tools hosted at The University of Melbourne. This will be only accessible to approved members of the research team.

The capture tool will be used to collect data on hepatitis C testing and results, patient-provider contact, questionnaire results, pathology and FibroScan results, if DAA treatment was started during admission as well as treatment details and outcomes. Background clinical information and relevant prior pathology or other investigation results will be obtained from St Vincent’s Hospital electronic medical records. Participant consent will include access to previous medical records and relevant investigations.

Clinical data collected through the study will also be entered into the St Vincent’s Hospital electronic medical records in a standardised format along with a printed version kept in the DPH admission file. This will be done to ensure DPH staff are aware of participant involvement in the study and that relevant clinical information is available to clinicians providing non-HCV related care for participants both during the study period and following study conclusion. This clinical information will include (but is not limited to) results of HCV testing, treatment details including medication regimen, duration, adherence, response, all pathology results (including HIV and Hepatitis B results) and FibroScan results.

# Study Schedule

All enrolled participants will complete the following visits and procedures:

## Attendance 1A – Recruitment, assessment, screening

Attendance 1A refers to the initial point of contact on elective admission to DPH. Participants will be assessed for eligibility, recruited and undergo HCV screening. After clients have been registered with SVHM unit record number they will be informed of the study either by DPH staff member or a member of the study team. Recruitment may take place in the entry zone of DPH prior to transfer to residential quarters or from any other area of DPH within 48 hours of admission if the client is deemed competent and has capacity to consent for study participation.

All clients will be approached by a member of the study team to outline details of the study and if interested will be discussed further in a private consultation room in the entry zone of DPH. A member of the study team will provide detailed information (verbal and written) for informed consent, carry out an assessment of eligibility for the study, perform HCV screening via Fingerstick testing and ask patients to complete a brief questionnaire.

### Screening process

On admission, clients with risk factors for HCV will be identified and informed of the study. Those interested will be referred to a member of the study team for consent and testing. When clients attend the entry zone of DPH for admission and registration, they will be informed of the study.

Potential participants will then be given a detailed explanation of the study by a member of the study team and provided with the PICF to read in a space that maintains confidentiality. The project will be explained to participants verbally and they will be given the opportunity to ask questions. Potential participants will be given as much time as required to read, comprehend and ask questions about the PICF. Potential participants will be advised that they may withdraw from the project at any stage and for any reason without prejudice or penalty, and routine testing and care for HCV will still be available. It will be clearly communicated that non-participation in the project will not in any way affect any of the services offered during DPH admission or the ability to request screening for and treatment of HCV (and other blood borne viruses) through the standard of care process that currently exists at the DPH. All potential participants will be offered a leaflet on HCV infection, emphasising that highly effective treatments are now available for HCV infection that they can access through their primary care physician or clinic nurse outside of this study (see Attachment E).12 Potential participants will be asked to provide written consent if they choose to participate, via a PICF.

After consent has been provided, a member of the study team will verify the eligibility criteria with each participant. If participants have previously received treatment, they will still be offered testing due to the potential for re-infection. However, a note will be made that the participant has previously received treatment for HCV. If participants have previously been diagnosed with HCV, they will be eligible to participate in the study if they are not currently engaged in care for hepatitis C. Engagement in care includes: awaiting a planned visit with a doctor or nurse to discuss treatment, awaiting work-up for treatment (including FibroScan or blood tests), currently receiving treatment and/or awaiting follow up to confirm treatment outcomes.

All participants deemed eligible for study inclusion that have given consent will be assigned a unique study ID number.

### Questionnaire

All participants will be asked to complete a short questionnaire which asks about key demographic information, risk factors for HCV, current perspectives on HCV testing and treatment, and relevant HCV related and non-HCV related health information including substance use history. The questionnaire (see Attachment A) will seek information on:

* Prior HCV testing and treatment
  + Previous testing for HCV by venepuncture
  + Previous POC testing for HCV Ab or PCR by either oral swab, fingerstick or venepuncture
  + Previous treatment for HCV
  + Current treatment for HCV
* Key HCV risk factors
  + History of incarceration
  + HIV infection
  + Hepatitis B infection
  + Known history of chronic liver disease or significant liver dysfunction
* Other health information:
  + Current medications
  + Drug allergies
* Demographic information:
  + Gender
  + Country of birth
  + Aboriginal and Torres Strait Islander status
  + Housing status
  + Employment status
* Injecting drug behaviour
  + Frequency of injecting drug use
  + Preferred or most commonly used substance for injecting drug use
  + Previously shared needles for injecting drug use
  + History of chronic liver disease
* Opioid substitution treatment
* Other substance use history
  + Alcohol
  + Tobacco
  + Cannabis
  + Benzodiazepine
  + Methamphetamine
  + Opioids
  + Gamma-hydroxybutyrate (GHB)

### Treatment with DAA therapy in participants who are HCV RNA positive

Participants will be provided with information on DAA treatment for HCV whilst undergoing screening. This is to ensure that participants are competent to understand the treatment regimens offered, treatment schedules and administration, requirements to present for ongoing treatment and potential treatment adverse effects. This information will be provided both in verbal and written form (PICF).

Only those who subsequently return a positive HCV PCR result will be offered treatment.

### HCV POC testing procedure

All participants will be offered testing using POC Xpert HCV VL Fingerstick test, which takes approximately 60 minutes to return a result. Participants will be notified of result when available.

After recruitment, participants will have the POC Xpert HV VL Fingerstick testing explained to them. Participants will be informed that standard HCV and other blood tests still need to be performed via venepuncture to confirm the results, allow assessment of liver function, screen for associated conditions as per routine work up for HCV treatment, and allow storage of blood samples for future testing in the event of treatment failure.

Xpert HCV VL Fingerstick testing will be collected by a member of the study team. The fingerstick sample will then berun on a Cepheid GeneXpert® IV machine which will be present on site.

If insufficient blood can be collected for all pathology tests then confirmatory testing for HCV Ab and PCR should be prioritised. The next tests to be prioritised are those that allow for assessment of fibrosis stage – AST and FBE. In the event that not all pathology tests can be completed, this will be documented in the REDCap database.

Participants will not be excluded from the study if pathology (other than HCV RNA) cannot be obtained.

The blood tests will be performed by either DPH staff, visiting St Vincent’s Pathology phlebotomist or member of the study team, all of whom will be competent in phlebotomy. The Xpert HCV VL Fingerstick test will be performed by a member of the study team, all of whom will be competent in pre-and post-test discussion and utilisation of the Cepheid GeneXpert® IV test machine.

### Providing the HCV RNA test result

Participants will be notified of their Xpert HCV VL Fingerstick test result by a member of the study team on the same day of testing. In the cases of early discharge from DPH, attempts will be made to contact participants with positive HCV RNA PCR result to inform them of test result and initiate treatment discussion. Such participants will be contacted via telephone by a member of the study team to be advised of the positive result and arrange an agreed upon time for a future visit through addiction medicine outpatient clinic to discuss treatment initiation. A total of three attempts to contact participants via telephone will be made, after which if they cannot be contacted an electronic alert will be created on their St Vincent’s Hospital file so that staff can notify the participant of the result and either i) discuss with study team if still within study timeline, or ii) refer to St Vincent’s Hospital hepatitis clinic for HCV treatment as per current standard practice at DPH if it is beyond the study timeline.

All members of the research team will have undergone training in pre- and post-test discussion. The time from obtaining a positive HCV RNA result to receiving a prescription of DAA therapy will be recorded by a member of the research team.

## Attendance 1B – Fibrosis assessment, HCV test experience and treatment discussion

Attendance 1B refers to subsequent points of contact during withdrawal admission for an anticipated duration of seven days. During this time, participants will undergo an assessment of liver disease and associated conditions (via pathology and FibroScan), along with completion of a participant questionnaire to determine acceptability and perspectives of HCV testing and prescribing of treatment in appropriate cases. These will occur in the consulting area of DPH after HCV Fingerstick testing and results counselling has occurred.

Members of the study team will be responsible for performing an assessment of liver disease and questionnaire administration. Only medical practitioners will prescribe DAA medications to those participants in whom treatment is to be initiated.

Participants will complete the following:

1. A brief survey of participant experience to determine acceptability and perspectives of POC HCV testing (See Attachment B)
2. FibroScan for assessment of liver fibrosis (see section 8.4.2 FibroScanTM)
3. Standard HCV clinical care blood tests, including HCV antibody, HCV RNA and viral load, HCV genotype, HIV serology (with counselling), hepatitis A serology, hepatitis B serology, liver function test panel including ALT, AST, albumin and bilirubin, FBE and INR. A β-HCG will also be done if the participant is a female of reproductive age as per standard of care. The platelet count (FBE) and AST will be used to calculate the APRI score as per standard of care.

Participants with an available HCV RNA test result will receive this result during DPH inpatient admission. If the result is positive, participants will receive counselling about the result and potential implications from a member of the study team. Participants with a positive result will be offered treatment with DAA therapy, with the option to start treatment that day. If participants agree to commence treatment, they will be prescribed and dispensed DAA therapy during inpatient stay at DPH through St Vincent’s Hospital outpatient pharmacy.

If a HCV RNA positive participant does not wish to start treatment on the same day as screening, either by choice or they do not wish to wait for results, but elect to start treatment at a future date within the study window, these individuals will still be eligible for participation.

Participants assessed as potentially having cirrhosis, defined as an APRI >1.0 and/or FibroScan ≥12.5 kPa, provide a clinical history of previous diagnosis of advanced fibrosis or have a platelet count <150 cells/109 without a previously identified cause will be referred to a specialist-led clinic at St Vincent’s Hospital Melbourne for liver assessment and follow up as per the ALA/ GESA Australian HCV National Consensus Statement.10

### Questionnaire on participant experience of rapid HCV POC testing

A questionnaire (see Attachment B) about experience of HCV testing and preferences for HCV testing will be administered when the participant completes all required testing. This will be performed in a private and confidential setting by a member of the study team in the consulting area of DPH. If participants do not wish to complete the questionnaire at the first visit, they will be offered the opportunity to do so on a subsequent visit to the MSIR.

## DAA treatment offered to participants who are HCV RNA positive

Participants who are eligible and return a positive HCV RNA result will be offered treatment with a DAA regimen in accordance GESA/ALA guidelines.10

Participants will be prescribed treatment during DPH admission. Participants who are started on treatment may receive up to twelve weeks of DAA treatment at a time. This decision will be at the discretion of the prescribing physician and/or study team member.

DAA therapy primarily offered will include the following two regimens:

1. Glecaprevir (100mg) plus pibrentasvir (40mg) three tablets daily for 8 weeks (non-cirrhotic) or 12 weeks (cirrhotic), or
2. Sofosbuvir (400mg) plus velpatasvir (100mg) one tablet once daily for 12 weeks (non-cirrhotic and cirrhotic).

Both regimens have equal efficacy and are pan-genotypic. Treatment choice will be at the treating doctor’s discretion based on co-morbidities, drug-drug interactions and participant preference with regards to pill burden and treatment duration.

Treatment choice and duration for patients with HCV is influenced by participants prior HCV treatment experiences. In participants who have previously been treated for HCV with either DAA therapy or interferon therapy, treatment choice and duration may differ from the above two described regimens. In these cases, alternative regimens and durations may be prescribed and this will be left to the discretion and clinical judgement of the prescribing physician. All treatment regimens and durations will be in keeping with GESA/ALA guidelines.10

All participants commenced on treatment will be contacted (either in person on visitation to St Vincent’s Hospital Addiction Medicine outpatient clinic or via telephone) at weeks four and eight (where applicable) to provide a prescription for ongoing supply of DAA therapy.

### Safety considerations

The HCV treatment regimens have been proven to be very safe and well tolerated in real world data. A detailed medication history will be taken from each participant prior to commencement of therapy to ensure there are no drug-drug interactions that would preclude the use of either DAA regimen being offered. If drug-drug interactions are present, these will be assessed by the prescribing clinician if safe and appropriate alterations can be made to pre-existing medications to allow treatment or alternative DAA regimens may be more appropriate. If significant drug-drug interactions are present that preclude participants from participation, these cases will be referred for HCV treatment at a tertiary hospital (St Vincent’s Hospital, Melbourne) viral hepatitis service.

Whilst adverse effects (AE) are rare with DAA therapy, the most commonly reported AE’s are:

1. Glecaprevir plus pibrentasvir (Maviret): Headache, fatigue, lethargy, nausea, diarrhoea and unconjugated hyperbilirubinaemia.
2. Sofosbuvir plus velpatasvir (Epclusa): Headache, fatigue, nausea.

If participants who are prescribed HCV medication experience adverse or serious adverse events, they will be advised to notify DPH staff if an inpatient who can relay concerns to the integrated hepatitis nurse or study team member; otherwise they will be advised to contact the integrated hepatitis nurse directly if in the community. The adverse event will be triaged by the integrated hepatitis nurse, with input from medical practitioners who are part of the research team if required, to determine if the symptoms require routine or urgent medical follow up. If discharged from DPH and non-urgent review is required, this will be conducted at a mutually convenient time in the outpatient clinic. If urgent review is required, participants will be advised to present to the nearest hospital emergency department.

Any serious adverse events reported by a study participation that is related to the study will be appropriately recorded and reviewed by the study steering committee, with appropriate management and reporting to the ethics committee if required.

## Follow-up of clinical outcomes

Follow up will occur at:

* Week 4 (optional): An optional follow up visit at week 4 (either via telephone or in person) will be available to assess treatment compliance, ensure ongoing medication supply is available, and evaluate for adverse effects. Participants will also be offered an optional Xpert HCV VL Fingerstick test, which will act as a surrogate marker for treatment adherence (adherence indicated through a reduction in HCV viral load or a negative HCV PCR result). Participants will also be asked to complete a brief optional questionnaire (Attachment C) about treatment compliance, adverse effects and HCV testing and treatment preferences.
* Week 8:
  + Those participants commenced on a 12-week treatment course will have an optional follow up visit at week 8 (either via telephone or in person) to assess treatment compliance, ensure ongoing medication supply is available, and evaluate for adverse effects. Participants will also be offered an optional Xpert HCV VL Fingerstick test, which will act as a surrogate marker for treatment adherence (adherence indicated through a reduction in HCV viral load or a negative HCV PCR result). Participants will also be asked to complete a brief optional questionnaire (Attachment C) about treatment compliance, adverse effects and HCV testing and treatment preferences.
  + Those participants commenced on an eight-week treatment course will perform an end-of-treatment questionnaire (Attachment D) about treatment compliance, adverse effects, HCV testing preferences and treatment satisfaction. End of treatment response will be assessed through HCV PCR testing via either a Xpert HCV VL Fingerstick test or venepuncture (guided by client preference).
* Week 12: Those participants commenced on a 12-week treatment course will perform an end-of-treatment questionnaire (Attachment D) about treatment compliance, adverse effects, HCV testing preferences and treatment satisfaction. End of treatment response will be assessed through HCV PCR testing via either a Xpert HCV VL Fingerstick test or venepuncture (guided by client preference).
* >4 weeks post treatment completion: Participants will have venepuncture or Xpert HCV VL Fingerstick testing performed for HCV PCR to assess for SVR4+ (guided by client preference).

The follow up time points are outlined in figure 2.

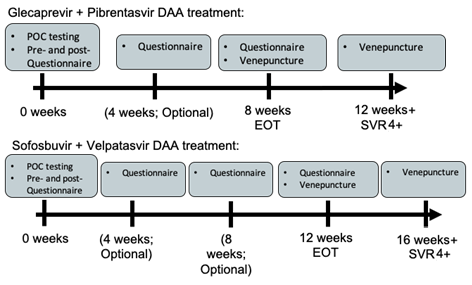


Figure 2. Study time points and follow-up

## Attendances 2 and 3 – Optional

All participants commenced on treatment will be contacted (either in person or by telephone) at weeks four and eight (where applicable) to provide a prescription for ongoing supply of treatment medication.

In addition, there will be optional additional visits at regular intervals during the treatment course at week four (visit 2) and week eight (visit 3), where applicable (i.e. those undergoing a 12 week treatment course). At these visits a questionnaire will be administered by a member of the study team (see Attachment C). The questionnaire will assess treatment adherence, potential medication adverse effects and perspectives on HCV screening and treatment.

## Attendance 4 – End-of-treatment data collection

The duration of DAA treatment varies for 8 to 12 weeks. At the end-of-treatment attendance (attendance 4), either a Xpert HCV VL Fingerstick test or venepuncture will be performed for HCV PCR testing. End-of-treatment HCV PCR results will also be used as a surrogate marker of treatment adherence, as given the extremely high cure rates with DAA therapy, it can be assumed that those who are subsequently HCV PCR negative completed a substantial portion of the prescribed treatment regimen. Participants will also complete a questionnaire about their experiences with and perspectives on HCV testing and treatment (see Attachment D).

## Attendance 5 – SVR4+ data collection

Achievement of SVR4+ in participants who obtain treatment will be determined via either Xpert HCV VL Fingerstick or venepuncture testing performed as part of standard of care by a member of the study team >4 weeks after completion of HCV treatment as per guidelines.

## Follow up at alternative locations

Participants who are commenced on DAA therapy and choose to continue their HCV care in an alternative location will still be included in the study and final analysis. Alternative locations may include, but are not limited to, general practice clinics and other community health services. These participants will be contacted at the relevant study time points and be either:

1. Provided directly with prescription(s) to complete DAA treatment course and pathology requests for appropriate blood testing at end of treatment and SVR4+ time points by members of the study team.
2. Encouraged to have ongoing prescription of DAA treatment course and pathology for appropriate blood testing at end-of-treatment and SVR4+ time points by a health practitioner at the alternative location. With patient consent, the nominated health practitioner at an alternative location will be contacted by a member of the study team if required to provide guidance on treatment, study timeline and follow-up pathology required (end-of-treatment and SVR4+).

Participants will be also be contact to complete questionnaires over the phone at the relevant time points.

All participants will be included in the current study regardless of whether they elect to continue HCV care through St Vincent’s Hospital or alternative location.

## Management of failure to attend

Participants who fail to attend for receipt of HCV PCR results, prescription of ongoing DAA treatment once initiated or a mandatory study visit will be contacted via telephone by a member of the study team to be a arrange an agreed upon time for a future visit to outpatient clinic.

A total of three attempts to contact participants via telephone will be made, after which if they cannot be contacted an electronic alert will be created on their St Vincent’s Hospital file so that staff can notify the participant of the result and either i) discuss with study team if still within study timeline, or ii) refer to St Vincent’s Hospital hepatitis clinic for appropriate follow-up action if it is beyond the study timeline.

# Adverse event recording and reporting

Any serious adverse events reported by a study participant that is related to the study will be appropriately recorded and reviewed by the study steering committee, with appropriate management and reporting to the Ethics committee if required.

# Blood collection, labelling and transport

Standard of care venepuncture will be performed at attendance 1, as well as offered as an alternative to POC Xpert HCV VL Fingerstick testing at attendances 4 and 5 (as specified in the study plan above). These samples will be processed by the usual pathology service used (St Vincent’s Pathology).

## Delivery of blood test results

The results of blood tests will be relayed to participants in complete confidence and with full discussion by a member of the study team. Full pre-test discussion will be performed prior to blood collection.

# Statistical analysis

## Study outcomes

The primary outcome measures are:

* Uptake and acceptance of POC testing with the Xpert HCV VL Fingerstick test;
* DAA treatment prescription and/or dispensing following Xpert HCV VL Fingerstick testing compared to SOC HCV testing;

The secondary outcome measures will be to assess:

* Prevalence of HCV Ab and HCV RNA positivity amongst the study population;
* The number of participants who receive a POC Xpert HCV VL Fingerstick result on the same day as testing;
* The average time to treatment initiation of DAAs following a positive Xpert HCV VL Fingerstick result, compared to SOC HCV testing;
* Among participants who are HCV RNA positive, the number that are prescribed and/or dispensed DAA treatment during their residential withdrawal stay
* Uptake of DAA therapy during admission in patients suitable for study
* The number of participants who commence DAA therapy who return at week 4 and/or week 8 (if applicable) for ongoing treatment;
* The number of participants who complete DAA therapy;
* Rates of negativity of end of treatment HCV PCR;
* The number of participants followed up at >4 weeks post treatment for HCV RNA testing and among these, the number of participants who are HCV RNA negative at >4 weeks post treatment completion (sustained virological response, SVR4+);
* Relapse or re-infection rates;
* Client perceptions of screening and treatment process

## Assessment of study endpoints

HCV prevalence will be determined by proportion of study participants with a positive HCV RNA test. The proportion of individuals commencing HCV treatment will be defined as the number of participants who received at least one dose of HCV treatment amongst all study participants who returned a positive HCV RNA result during the study. SVR4+ will be determined either using the Xpert HCV VL Fingerstick test or SOC qualitative HCV RNA by venepuncture in those that have undergone HCV treatment.

Given this is a pilot study for the implementation of POC testing, interpretation of findings will be primarily descriptive. Categorical data will be presented as frequencies and continuous data will be presented as medians with interquartile range. Logistic regression will be used to identify clinical, sociodemographic and behavioural predictors (age, gender, fixed abode, fibrosis stage, injecting behaviours, treatment regimen and drug and alcohol use) of a positive diagnosis and predictors of linkage to treatment. Comparisons will be made using

Pearson’s chi2/fisher exact for categorical data and Mann-Whitney U test for continuous variables. Two tailed tests of significance at p<0.05 will be used in all inferential tests.

# Ethical issues

## Ethics Review

Ethics approval will be sought from the St Vincent’s Hospital Human Research Ethics Committee (HREC).

## Recruitment

All clients attending DPH will be provided the opportunity to participate in the study within 48 hours of admission.

## Consent procedures

Informed consent will be obtained for research related to HCV infection and treatment. Potential participants will then be given a detailed explanation of the study and provided with the PICF to read in a space that maintains confidentiality by a member of the study team. The project will be explained to participants verbally and they will be given the opportunity to ask questions. Potential participants will be given as much time as required to read, comprehend and ask questions about the PICF. Participants will be reassured that their answers will be confidential and that they will not influence or affect their medical care, especially their ability to be treated for HCV infection and treatment not related to HCV.

Participants will be made aware that participation is entirely voluntary and it will be clearly communicated that non-participation in the project will not in any way affect any of the services offered through DPH. Potential participants will be asked to provide written consent if they choose to participate, via a PICF.

## Confidentiality

All participants will be assigned a unique study identification number when enrolled to the study. All data will be stored in a secure, password-protected database using REDCap electronic data capture tools hosted at The University of Melbourne. No identifying information will be included in any report, presentation or publication relating to the findings of the study.

## Electronic data storage

Electronic quantitative survey data, results of HCV testing, fibrosis assessment and other study results will be stored on a secure, password-protected database using REDCap electronic data capture tools hosted at The University of Melbourne.

All staff involved in data collection for the study will be familiarised with electronic data collection and storage (including issues associated with participant privacy, confidentiality and anonymity).

Clinical data collected through the study will also be entered into the St Vincent’s Hospital electronic medical records in a standardised format along with a printed version kept in the DPH admission file. This will be done to ensure that staff working at DPH are aware of client involvement in the study and that relevant clinical information is available for clinicians providing non-HCV related care for clients. This clinical information will include (but is not limited to) results of HCV testing, treatment details including medication regimen, duration, compliance, and response, all pathology results and FibroScan results.

## Other ethical considerations

Specific ethical considerations have been considered given the environment within which this research project will be conducted and the targeted participant population.

* Stigma may exist among the targeted population around injecting drug use and HCV diagnosis and treatment, and they may have experienced prior discrimination in other HCV diagnosis and treatment settings.
* Lower treatment adherence and follow up rates (influenced by the above). In addition to injecting drug use, there are also high rates of homelessness and incarceration amongst the participant cohort. Given this, we anticipate high participant attrition, especially when it comes to collecting SVR4+ data.
* Recruitment of participants potentially involved in illegal activities. Whilst the study involves a population of PWID and will collect information on substance use, we will not be directly collecting any information relating to non-drug related activities. It is possible that clients of DPH will disclose details of potential drug-related (or other) illegal activities occurring outside of DPH during the course of the study. As is current practice, there will be no obligation to disclose details to law enforcement agencies by members of the study team unless it is deemed that such activities may be at risk of causing serious harm to self or others, or if we have been required to disclose information by police or a court of law. Every effort will be made to discuss these cases with the participant directly prior to any action being taken. Participants will be informed of this via the participant information and consent form (PICF).
* Recruitment of clients who are substance affected. A majority of clients that attend DPH for assistance with withdrawal from substance use present intoxicated or in acute withdrawal which can impede clients’ capacity to provide informed consent. Members of the study team will need to be adequately satisfied that participants have understood and comprehended the nature of the study prior to obtaining informed consent. This will be left to the discretion of the member of the study team at the time of consent. If the member of the study team deems the client to be unable to provide informed consent, it can be re-explored with the client within the first 48 hours of the admission. Potential participants who are not deemed to be able to provide informed consent will be excluded.
* Recruitment of culturally diverse participants, in particular the potentially high representation of Aboriginal and Torres Straight Islanders. It is documented that Aboriginal and Torres Strait Islanders have higher rates of illicit substance use, with previous reports suggesting up to a quarter of Indigenous peoples have used illicit substances in the last 12 months (comparable figure for non-indigenous Australians is 15%). It is therefore not unexpected that a significant number of clients attending DPH, and as such potential participants in the current study, will be Aboriginal or Torres Strait Islanders. All members of the research team have appropriate experience and expertise in cultural competency, through prior training at the primary site of employment (St Vincent’s Hospital Melbourne). Appropriate respect of cultural differences will be displayed in all encounters. Traditional knowledge and traditional cultural expressions of Indigenous participants will be respected, protected and maintained throughout the duration of the study period. No participants will be excluded on the basis of cultural background or ethnicity and all participants will be treated equally, fairly and with respect.

# Governance

## Data Safety and Monitoring Board (DSMB)

The study will use the Xpert HCV VL Fingerstick test which is run on the GeneXpert platform.

This device received TGA approval in May 2020.8 This device has no significant adverse effects. This study does not involve any unapproved drug therapies and all treatment proposed is in accordance with standard of care practice.

# Competing interests

Some of the study investigators have received funding for other investigator initiated research or speaking duties from pharmaceutical companies that manufacture medications for the treatment for hepatitis C. However, the investigators will follow a pre-defined treatment algorithm.

Participants will be treated with primarily one of two DAA regimens (glecaprevir (100mg) plus pibrentasvir (40mg) or sofobuvir (400mg) plus velpatasvir (100mg)). The choice of regimen will be made based on co-morbidities, drug-drug interactions and participant preference with regards to pill burden and treatment duration. This is current standard of practice in everyday care of patients with HCV.

In participants who have previously been treated for HCV with either DAA therapy or interferon therapy, treatment choice and duration may differ from the above two described regimens. This will be left to the discretion and clinical judgement of the prescribing physician.

All treatment regimens and durations will be in keeping with GESA/ALA guidelines20 and as such, this will not represent a competing interest.

# Publication policy

The results of the project may be published or presented at scientific meetings. All published quantitative data will be non-identifiable grouped data, none of which will be specific to a participant. Authorship for publications arising from this study will adhere to the International Committee of Medical Journal Editors guidelines.

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