# Treatment of HOsPitalised Inpatients for Hepatitis C (TOPIC): Strategic therapeutic intervention to enhance linkage to care in people who inject drugs

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**Date:** **7 February 2022**

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# 1 Protocol Synopsis

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| Title | **TOPIC**<br>**Treatment of HOsPitalised Inpatients for Hepatitis C:**<br>Strategic intervention to enhance uptake of treatment and linkage to care in people who inject drugs |
| Protocol registration no. | **NCT03981211** |
| Background and rationale | The excellent efficacy and tolerability of DAA regimens are now widely accepted in diverse patient populations and settings and pave the way for national and global hepatitis C (HCV) elimination policies. Even in populations considered traditionally difficult to treat, such as people who inject drugs (PWID), treatment response rates have been shown to be high and adherence generally good, confirming the rationale behind universal access policies.<br><br>However, whilst studies examining treatment of PWID in settings such as opioid substitution clinics, primary care practices and drug and alcohol treatment services have shown encouraging results, these represent only a selected group already engaged with health care services. A significantly greater challenge is to engage PWID, who do not traditionally link to these services, in HCV treatment and care. This group is at high risk of morbidity and mortality from co-existing illness and often have competing priorities, as well as being at high risk of ongoing HCV transmission through risk behaviour. To fully address the HCV elimination question, novel ways of engaging these individuals must be sought.<br><br>Admission to hospital with an injecting related infectious disease (IRID) such as cellulitis, endocarditis, osteomyelitis, occurs far more frequently in people with current injecting drug use than the general population, and of people admitted with IRID up to 75% have a history of HCV infection. Many of these IRID require inpatient management with prolonged intravenous antibiotic or antifungal administration (2-6 weeks).<br><br>The period of hospitalisation for management of IRID, particularly when prolonged, may represent an ideal opportunity to engage HCV-infected PWID. The current model of care in which DAA therapy is delayed to be dealt with as an outpatient after discharge is inadequate if high levels of engagement and treatment uptake are to be reached in this population. Given that recent PWID are at high risk of transmission and risk behavior post-discharge, eradication of HCV viremia with successful DAA therapy commenced during hospitalisation may be an important strategy for broader HCV elimination.<br><br>One of the greatest challenges to inpatient initiation lies in the completion of the therapeutic course after discharge. During the period of hospitalisation treatment can be observed and support provided, including engagement with drug and alcohol services and the potential provision of peer support workers. However, following discharge competing priorities may limit treatment completion and loss to follow-up is a real concern, thus it is imperative that as much of the treatment course is completed as possible during admission. This can be facilitated by two strategies<br>• The provision of point-of-care RNA testing on site. This will reduce the anticipated wait time between venepuncture and RNA result by several days and allow for HCV treatment initiation within the first few days of admission.<br>• The use of short course DAA regimens to minimise the period of outpatient treatment. |

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| | **Ultra short treatment evaluation (STRIVE-4 strategy)**<br><br>Current DAA regimens including the pan-genotypic regimen of G/P are given for 8-12 weeks. For patients without cirrhosis 8 weeks of G/P results in an overall SVR of >95%. However, even this duration will mean that much of the therapy will need to be continued post discharge, and a significant proportion of patients may fail to complete treatment thus defaulting to a sub-optimal treatment course.<br><br>Evaluation of potent ultra-short treatment regimens is ongoing. In various phase II studies evaluating 6 weeks of a triple combination with sofosbuvir (SOF), velpatasvir (VEL) and voxilaprevir (VOX) in treatment naïve patients without cirrhosis, SVR was 88% (29/33) among patients with genotype 2, 3, 4, or 6, 93% (14/15) in patients with genotype 1 and 3, and 71% (24/34) in patients with genotype 1. Non-published data (provided by Gilead Sciences) from the GT 1 study demonstrated a higher SVR (88%, 14/16) in the sub-population of patients with F0-2. Thus, in patients with relatively early liver disease virological failure is uncommon with 6-week SOF/VEL/VOX.<br><br>A number of small studies in select populations have pushed the barrier even further evaluating a 4-week duration of DAA therapy. In a study among young PWID with early liver disease (<50 years, F0-2) in Denmark (n=16), a 4-week regimen of SOF/ledipasvir plus ribavirin provided a per protocol (PP)(n=13) SVR of 92% (one relapse) with intention to treat (ITT) SVR of 75%. In the same study 16 PWID were treated with the same regimen plus pegylated interferon with PP and ITT SVR of 100% and 94%, respectively. Further evidence for the potential of ultra-short duration DAA therapy comes from a response-guided study in Hong Kong. Patients with HCV genotype 1b were treated with three different triple class DAA regimens, including SOF/ledipasvir + asunaprevir, SOF+ daclatasvir + simeprevir, or SOF + daclatasvir + asunaprevir, and those with an ultra-rapid virological response (HCV RNA <500 IU/mL at day 2; 18/26) had treatment duration shortened to three weeks. The SVR rate was 100% (18/18) in the three-week treated population.<br><br>A 4 week strategy of SOF/G/P is currently under evaluation amongst PWID with early liver disease in the community setting (STRIVE 4). However, given the significant potential for early treatment discontinuation and discontinuation with outpatient services amongst high risk PWID admitted to hospital with IRID, it is in this group that the benefit for ultra short 4 week regimens may outweigh any risk of relapse in a small number of patients.<br><br>In this proposal we will evaluate rapid point-of-care (POC) confirmation of viraemia in PWID hospitalized for IRID followed by enrollment into two sequential cohorts:<br>A) Dual regimen: G/P for 8 weeks (standard therapy), n=30<br>B) Triple regimen: SOF/G/P for 4 weeks (short therapy), n=30<br><br>Enrolment into cohort B will commence after cohort A completed and dependent on the results of the STRIVE-4 community cohort. |
| Study objectives | **Primary objective**<br><br>To evaluate the proportion of patients achieving confirmed SVR12 (undetectable HCV RNA at time point 12 weeks plus post treatment commencement) in patients hospitalized for IRID and commencing inpatient DAA treatment within public hospital services |

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| | **Secondary Objectives:**<br>• To evaluate and compare the proportion of patients with undetectable HCV RNA at 12 weeks post-treatment (SVR12) within each cohort<br>• To evaluate proportion of patients with HCV below LLOQ at week 4 of therapy and ETR<br>• To evaluate rates of discharge against medical advice (DAMA)<br>• To evaluate DAA treatment completion rates<br>• To evaluate adverse events secondary to drug:drug interactions<br>• To evaluate adherence during treatment via in hospital medication charts and outpatient weekly self-report<br>• To evaluate acceptability and feasibility of DAA commencement whilst an inpatient<br>• To evaluate performance of finger prick POC testing compared to plasma HCV RNA at screening<br>• To evaluate completion of duration of recommended inpatient stay and therapy for co-morbidities<br>• To determine effect of HCV treatment on quality of life<br>• To evaluate rate of re-call and re-infection at 6, 9- and 12-months post study enrolment<br>In those who inject drugs:<br>• To evaluate engagement with D&A services and rates of OST initiation<br>• To determine rates and patterns of injecting behaviour following therapy for HCV |
| Participant population | 60 participants will be enrolled from participating hospital inpatient services – 30 participants will be enrolled in Cohort A and 30 participants in Cohort B.<br><br>**Inclusion criteria**<br>Participants must meet all of the following inclusion criteria to be eligible to participate in this study.<br><br>1) Have voluntarily signed the informed consent form.<br>2) 18 years of age or older.<br>3) Injected drugs within the last 6 months OR be known to be HCV Ab positive<br>4) Hospitalized with an IRI with an anticipated inpatient stay of > 1 weeks [1]<br>5) HCV RNA positive<br>6) Compensated liver disease<br>7) Documented non-cirrhotic at enrolment with a qualifying liver FibroScan ≤ 9.5 kpA or an APRI < 2.0<br>8) If co-infection with HIV is documented, the subject must meet the following criteria:<br>a) ART naïve with CD4 T cell count >500 cells/mm3; OR<br>b) On a stable ART regimen (containing only permissible ART) for >4 weeks prior to screening visit, with CD4 T cell count ≥200 cells/mm3 and a plasma HIV RNA level below the limit of detection.<br><br>**Exclusion criteria**<br>Participants who meet any of the exclusion criteria are not to be enrolled in this study. |

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| | 1) Inability or unwillingness to provide informed consent or abide by the requirements of the study<br>2) Actively intoxicated.<br><br>Participants who meet any of the additional exclusion criteria are not to be treated in this study.<br><br>3) History of any of the following:<br>b. Clinical hepatic decompensation (i.e., ascites, encephalopathy or variceal haemorrhage)<br>c. Solid organ transplant<br>d. History of severe, life-threatening or other significant sensitivity to study drugs (glecaprevir/pibrentasvir/sofosbuvir) or any excipients of the study drugs<br>4) Creatinine clearance (CLcr) < 30 mL/min at screening (Cohort B only)<br>5) Pregnant or nursing female<br>6) Decompensated liver disease<br>7) Use of prohibited concomitant medications<br>8) Chronic use of systemically administered immunosuppressive agents (e.g., prednisone equivalent > 10 mg/day for >2 weeks)<br>9) Prior treatment failure with an NS5A based DAA regimen<br><br>[1] Although people who inject drugs are the focus of this study, patients without a recent history of IDU or IRID who are admitted with an expected duration of stay > 1 week may also be included at discretion of study team. In this case the questions on injecting behaviour will be omitted and additional data collected on nature of co-morbidities present. |
| Study design | This study will be conducted as a Phase IV, multicentre, sequential cohort trial.<br><br>Eligible patients will be enrolled into one of two treatment cohorts.<br>A) Immediate commencement whilst inpatient of 8 weeks of G/P with continuation of therapy and follow-up in viral hepatitis services post discharge (standard duration therapy)<br><br>Following successful completion of Cohort A, eligible patients will be enrolled into Cohort B:<br><br>B) Immediate commencement whilst inpatient of 4 weeks of SOF/G/P with continuation of therapy and follow-up in viral hepatitis services post discharge (short duration therapy)<br><br>Any patient with recurrent viraemia during follow-up will be genotyped +/- sequenced to exclude re-infection. If relapse is confirmed patient will be offered retreatment with SOC salvage therapy based on results of resistance testing. |
| Treatment of participants | Cohort A: Eligible participants will receive 8 weeks of glecaprevir G/P (300mg/120mg) as three tablets daily.<br>Cohort B: Participants will receive 4 weeks of SOF/G/P as four tablets daily.<br>Dose modifications are prohibited. |

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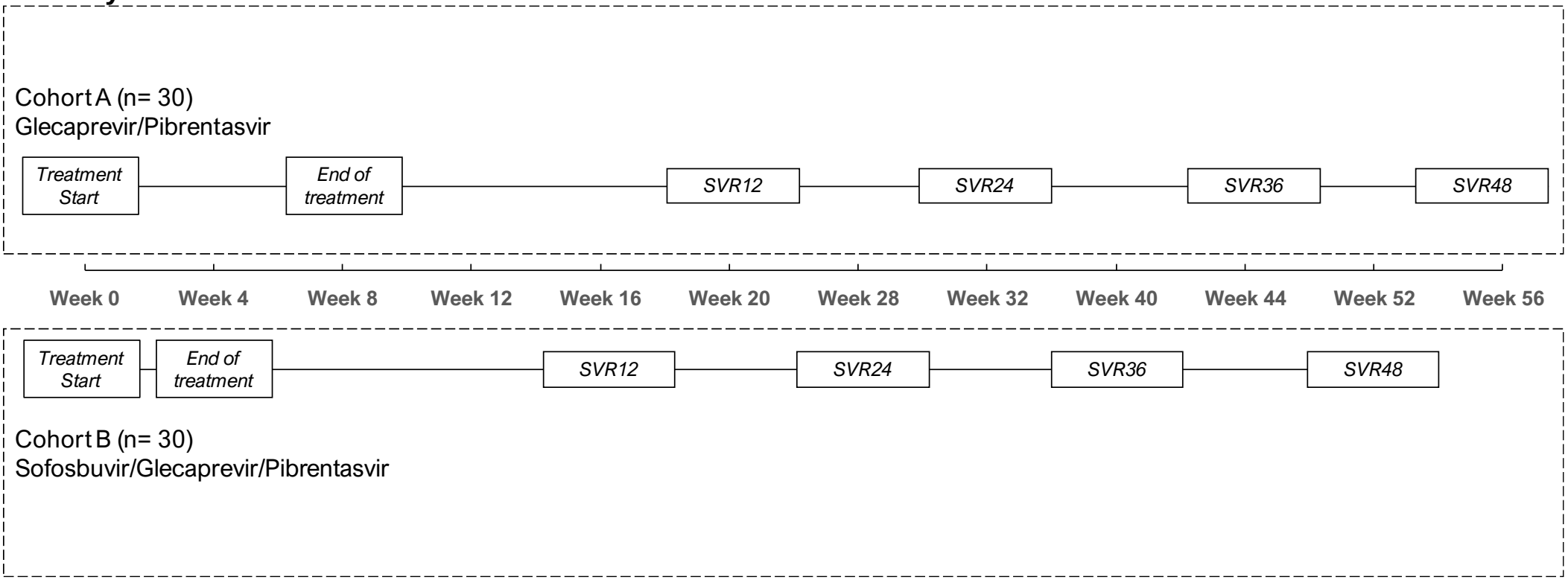
| Study procedures | Refer to the Schedule of Assessments |
| Statistics | **Sample Size**<br>This is a Phase IV study and with no formal sample size. A cohort of 30 patients for each regimen will provide sufficient preliminary data to inform a subsequent larger study size and design<br>**Endpoints**<br>**Primary Endpoint:**<br>• Proportion of patients achieving confirmed SVR12 (defined as HCV RNA below the lower limit of quantitation at 12 weeks post treatment) in the intention-to-treat population (defined as all enrolled participants who received at least one dose of study drug) commencing inpatient DAA treatment within public hospital services.<br>**Secondary Endpoints:**<br>• Proportion of patients achieving confirmed SVR12 (defined as HCV RNA below the lower limit of quantitation at 12 weeks post treatment) in the intention-to-treat population (defined as all enrolled participants who received at least one dose of study drug) consisting of patients hospitalised for IRID and commencing inpatient DAA treatment within public hospital services.<br>• Proportion of patients with HCV RNA below the level of detection at 12 weeks post-treatment (SVR12) within each cohort by both ITT and PP analyses<br>• Proportion of patients with HCV below LLOQ at week 4 of therapy and ETR<br>• Proportion of patients completing DAA treatment course<br>• Proportion of patients with full (100%) and partial adherence (<50%, 50-80%, 81-99%) during treatment as assessed by in hospital medication charts and outpatient weekly self-report.<br>• Uptake of DAA therapy during admission in patients suitable for study<br>• Safety: Rates and predictors of adverse events secondary to drug:drug interactions<br>• Sensitivity and specificity of finger prick POC testing compared to plasma HCV RNA at screening<br>• Proportion of patients completing recommended inpatient stay<br>• Changes in HRQOL<br>• Rates of re-attendance at subsequent planned study visits<br>• Rates and predictors of reinfection during follow-up<br>In those with a history of injecting drug use:<br>• Proportion of patients undergoing D&A evaluation during admission<br>• Proportion of patients initiating OST during admission<br>• Frequency and patterns of injecting behaviour following therapy for HCV |

## 2 Study Flow Chart



# 3 Schedule of Assessments – Cohort A

| Procedure | Screening | Baseline | On-treatment phase | | | SVR12 | Follow-up 1 (SVR24) | Follow-up 2 (SVR36) | Follow-up 3 (SVR48) |
|---|---|---|---|---|---|---|---|---|---|
| | | | Hospital discharge[1] | Week 4 | End of Treatment | | | | |
| **Study Week** | -6 to 0 | 0 | Variable | 4 | 8 | 20 | 32 | 44 | 56 |
| **Visit Window (Days)** | | | | | | | | | |
| Informed consent | X | | | | | | | | |
| Medical history | X | | X | | | | | | |
| Physical measurements (height and weight) | X | | | | | | | | |
| Liver function tests | X | X | | | X | X | X | X | X |
| Full blood count and biochemistry | X | | | | | | | | |
| HCV RNA testing (local laboratory) | X | | | X | X | X | X[8] | X[8] | X[8] |
| HCV RNA testing (finger-stick capillary whole-blood)[2] | X | | | | | X | X | X | X |
| HCV genotyping (local laboratory)[3] | X | | | | | X[8] | X[8] | X[8] | X[8] |
| HIV serology | X | | | | | | | | |
| HBsAg | X | | | | | | | | |
| Clinical assessment (including hepatic decompensation assessment) | X | | | | | | | | |
| Fibrosis assessment (FibroScan or APRI)[4] | X | | | | | | | | |
| Pregnancy test (females - serum or urine)[5] | X | X | | X | X | | | | |
| Treatment initiation | | X | | | | | | | |
| Behavioural survey | X | | | | | X | | | X |
| EQ-5D-5L | X | | | | | X | | | X |
| Concomitant medication assessment[6] | X | X | X | X | X | X | | | |
| Study drug adherence[7] | | | X | | | | | | |
| D&A evaluation | | X | X | | | | | | |
| **Research Specimen Collection** | | | | | | | | | |
| DBS Sample for Sequencing | X | | | | | X[8] | X[8] | X[8] | X[8] |
| EDTA Plasma for resistance testing (10mL) | | | | | | X[8] | X[8] | X[8] | X[8] |

**1** Week 4 and End of Treatment visits will be conducted during hospitalisation where possible. If the participant is discharged, whilst on-treatment, Week 4 and End of Treatment will occur at outpatient viral hepatitis services.
**2** HCV RNA finger-stick capillary whole-blood will be tested using the Xpert® HCV Viral Load assay on the Gene Xpert® II machine. During follow-up visits (SVR12, SVR24, SVR36 and SVR48), finger-stick capillary whole-blood will be used for HCV RNA and local laboratory HCV RNA may be performed if a positive HCV RNA is detected through the Xpert® HCV Viral Load assay.
**3** HCV genotyping will only be performed during follow-up for participants identified with recurrent viraemia
**4** Liver fibrosis will be assessed with a FibroScan if possible. Otherwise, an APRI score will be used for fibrosis assessment.
**5** Pregnancy testing is not required for females of non-childbearing potential.
**6** Concomitant medications will be assessed at Screening and updated at visits as appropriate. During follow-up concomitant medications will only be collected for those related to interactions with treatment of HCV.
**7** Study drug adherence will be collected via telephone on a weekly basis for participants who are discharged prior to treatment completion.
**8** Only performed if a detectable HCV RNA viral load on the Xpert® HCV Viral Load assay is found at a follow-up visit.

# 4 Schedule of Assessments – Cohort B

| Procedure | Screening | Baseline | On-treatment phase | | SVR12 | Follow-up 1 (SVR24) | Follow-up 2 (SVR36) | Follow-up 3 (SVR48) |
|---|---|---|---|---|---|---|---|---|
| | | | Hospital discharge[1] | End of Treatment | | | | |
| **Study Week** | X to 0 | 0 | Variable | 4 | 16 | 28 | 40 | 52 |
| **Visit Window (Days)** | | | | | | | | |
| Informed consent | X | | | | | | | |
| Medical history | X | | X | | | | | |
| Physical measurements (height and weight) | X | | | | | | | |
| Liver function tests | X | x | | X | X | X | X | X |
| Full blood count and Biochemistry | X | | | | | | | |
| HCV RNA testing (local laboratory) | X | | | X | X | X[8] | X[8] | X[8] |
| HCV RNA testing (finger-stick capillary whole-blood)[2] | X | | | | X | X | X | X |
| HCV genotyping (local laboratory)[3] | X | | | | X[8] | X[8] | X[8] | X[8] |
| HIV serology | X | | | | | | | |
| HBsAg | X | | | | | | | |
| Clinical assessment (including hepatic decompensation assessment) | X | | | | | | | |
| Fibrosis assessment (FibroScan or APRI)[4] | X | | | | | | | |
| Pregnancy test (females - serum or urine)[5] | X | X | | X | | | | |
| Treatment initiation | | X | | | | | | |
| Behavioural survey | X | | | | X | | | X |
| EQ-5D-5L | X | | | | X | | | X |
| Concomitant medication assessment[6] | X | X | X | X | X | | | |
| Study drug adherence[7] | | | X | | | | | |
| D&A evaluation | | X | X | | | | | |
| **Research Specimen Collection** | | | | | | | | |
| DBS Sample for sequencing | X | | | | X[8] | X[8] | X[8] | X[8] |
| EDTA Plasma for resistance testing (10mL) | | | | | X[8] | X[8] | X[8] | X[8] |

**1** End of Treatment visit will be conducted during hospitalisation where possible. If the participant is discharged, whilst on-treatment, End of Treatment will occur at outpatient viral hepatitis services.
**2** HCV RNA finger-stick capillary whole-blood will be tested using the Xpert® HCV Viral Load assay on the Gene Xpert® II machine. During follow-up visits (SVR12, SVR24, SVR36 and SVR48), finger-stick capillary whole-blood will be used for HCV RNA and local laboratory HCV RNA may be performed if a positive HCV RNA is detected through the Xpert® HCV Viral Load assay.
**3** HCV genotyping will only be performed during follow-up for participants identified with recurrent viraemia
**4** Liver fibrosis will be assessed with a FibroScan if possible. Otherwise, an APRI score will be used for fibrosis assessment.
**5** Pregnancy testing is not required for females of non-childbearing potential.
**6** Concomitant medications will be assessed at Screening and updated at visits as appropriate. During follow-up concomitant medications will only be collected for those related to interactions with treatment of HCV.
**7** Study drug adherence will be collected via telephone on a weekly basis for participants who are discharged prior to treatment completion.
**8** Only performed if a detectable HCV RNA viral load on the Xpert® HCV Viral Load assay is found at a follow-up visit.

# 5 Background and rationale

The excellent efficacy and tolerability of DAA regimens are now widely accepted in diverse patient populations and settings and pave the way for national and global hepatitis C (HCV) elimination policies. Even in populations considered traditionally difficult to treat, such as people who inject drugs (PWID), treatment response rates have been shown to be high and adherence generally good, confirming the rationale behind universal access policies [1,2].

However, whilst studies examining treatment of PWID in settings such as opioid substitution clinics, primary care practices and drug and alcohol treatment services have shown encouraging results, these represent only a selected group already engaged with health care services. A significantly greater challenge is to engage PWID who do not traditionally link to these services in HCV treatment and care. This group is at high risk of morbidity and mortality from co-existing illness and often have competing priorities, as well as being at high risk of ongoing HCV transmission through risk behaviour. To fully address the HCV elimination question, novel ways of engaging these individuals must be sought [3].

Admission to hospital with an injecting related infectious disease (IRID) such as cellulitis, endocarditis, osteomyelitis, occurs far more frequently in people with current injecting drug use than the general population, and of people admitted with IRID up to 75% have a history of HCV infection. Many of these IRID require inpatient management with prolonged intravenous antibiotic or antifungal administration (2-6 weeks).

The period of hospitalisation for management of IRID, particularly when prolonged, may represent an ideal opportunity to engage HCV-infected PWID. The current model of care in which DAA therapy is delayed to be dealt with as an outpatient after discharge is inadequate if high levels of engagement and treatment uptake are to be reached in this population. Given that recent PWID are at high risk of transmission and risk behavior post-discharge, eradication of HCV viremia with successful DAA therapy commenced during hospitalisation may be an important strategy for broader HCV elimination.

Data on the feasibility and success of HCV treatment commenced whilst patients are in hospital are limited. In a recent paper by Post and colleagues from the Prince of Wales Hospital, Sydney, Australia, 100 inpatients underwent opportunistic HCV assessment with the offer of HCV treatment initiated on or just after discharge [4]. Of 70 viraemic patients, 46 completed the assessment and commenced treatment (21 with DAA on discharge and 20 treated post discharge) and 80% of these went on to achieve SVR12, suggesting that engagement with HCV services during admission could facilitate subsequent treatment. However, a number of patients either did not complete the assessment or did not start treatment, with factors such as access to FibroScan and waiting time for HCV RNA and genotyping results identified as major barriers. Reducing these through the use of non-invasive fibrosis tests, removal of genotyping requirements and the use of POC RNA tests should facilitate rapid assessment and treatment commencement. In the Post study although the majority were admitted with infectious complications, only 26% were current PWID.

Data on testing and engagement in this group is particularly limited. In a recent retrospective clinical audit of HCV testing patterns in PWID admitted with IRID to a single centre Sydney tertiary hospital (Tan et al, AVHEC), only 30% of this group were appropriately tested for HCV during their period of admission, despite the average length of stay being 12 days. Clearly there is missed opportunity for testing, engaging and treating this high risk group during hospital admissions.

One of the greatest challenges to inpatient initiation lies in the completion of the therapeutic course after discharge. During the period of hospitalisation treatment can be observed and support provided, including engagement with drug and alcohol services and the potential provision of peer support workers. However, following discharge competing priorities may limit treatment completion and loss to follow-up is a real concern, thus it is imperative that as much of the treatment course is completed as possible during admission. This can be facilitated by two strategies

- The provision of point-of-care RNA testing on site. This will reduce the anticipated wait time between venepuncture and RNA result by several days and allow for HCV treatment initiation within the first few days of admission.
- The use of short course DAA regimens to minimise the period of outpatient treatment.

**Ultra short treatment evaluation (STRIVE-4 strategy)**

Current DAA regimens including the pan-genotypic regimen of G/P are given for 8-12 weeks. For patients without cirrhosis 8 weeks of G/P results in an overall SVR of >95% [6]. However, even this duration will mean that much of the therapy will need to be continued post discharge, and a significant proportion of patients may fail to complete treatment thus defaulting to a sub-optimal treatment course.

Evaluation of potent ultra-short treatment regimens is ongoing. In various phase II studies evaluating 6 weeks of a triple combination with sofosbuvir (SOF), velpatasvir (VEL) and voxilaprevir (VOX) in treatment naïve patients without cirrhosis, SVR was 88% (29/33) [7] among patients with genotype 2, 3, 4, or 6, 93% (14/15) in patients with genotype 1 and 3 [8], and 71% (24/34) in patients with genotype 1 [9]. Non-published data (provided by Gilead Sciences) from the GT 1 study demonstrated a higher SVR (88%, 14/16) in the sub-population of patients with F0-2. Thus, in patients with relatively early liver disease virological failure is uncommon with 6-week SOF/VEL/VOX.

A number of small studies in select populations have pushed the barrier even further evaluating a 4-week duration of DAA therapy. In a study among young PWID with early liver disease (<50 years, F0-2) in Denmark (n=16), a 4-week regimen of SOF/ledipasvir plus ribavirin provided a per protocol (PP)(n=13) SVR of 92% (one relapse) with intention to treat (ITT) SVR of 75% [10]. In the same study 16 PWID were treated with the same regimen plus pegylated interferon with PP and ITT SVR of 100% and 94%, respectively. Further evidence for the potential of ultra-short duration DAA therapy comes from a response-guided study in Hong Kong. Patients with HCV genotype 1b were treated with three different triple class DAA regimens, including SOF/ledipasvir + asunaprevir, SOF+ daclatasvir + simeprevir, or SOF + daclatasvir + asunaprevir, and those with an ultra-rapid virological response (HCV RNA <500 IU/mL at day 2; 18/26) had treatment duration shortened to three weeks [11]. The SVR rate was 100% (18/18) in the three-week treated population.

A 4 week strategy of SOF/G/P is currently under evaluation amongst PWID with early liver disease in the community setting (STRIVE 4). However, given the significant potential for early treatment discontinuation and discontinuation with outpatient services amongst high risk PWID admitted to hospital with IRID, it is in this group that the benefit for ultra short 4 week regimens may outweigh any risk of relapse in a small number of patients.

In this proposal we will evaluate rapid point-of-care (POC) confirmation of viraemia in PWID hospitalized for IRID followed by enrollment into two sequential cohorts:

C) Dual regimen: G/P for 8 weeks (standard therapy), n=30
D) Triple regimen: SOF/G/P for 4 weeks (short therapy), n=30

# 6 Hypotheses

1. Commencement of DAA therapy during in-patient hospitalization will be acceptable to the majority of patients, improve treatment follow-up and outcomes (SVR12) compared to standard of care referral and follow-up in outpatient HCV services (based on historical data)
2. Four weeks of therapy with SOF/G/P (Cohort B) will result in higher rates of treatment completion than 8 weeks of G/P with resultant higher SVR12 outcome.
3. Point of care testing performed immediately after hospital admission will shorten time to treatment initiation and enhance further linkage to care
4. Commencement of HCV treatment during in-patient hospitalization will improve engagement with health services including drug and alcohol, as compared to standard referral and follow-up in outpatient HCV services.

# 7 Study objectives

## 7.1 Primary objective

- To evaluate the proportion of patients achieving confirmed SVR12 (undetectable HCV RNA at time point 12 weeks plus post treatment commencement) in hospitalized patients commencing inpatient DAA treatment within public hospital services

### 7.2 Secondary Objectives

- To evaluate the proportion of patients achieving confirmed SVR12 (undetectable HCV RNA at time point 12 weeks plus post treatment commencement) in patients hospitalised for IRID and commencing inpatient DAA treatment within public hospital services
- To evaluate and compare the proportion of patients with undetectable HCV RNA at 12 weeks post-treatment (SVR12) within each cohort
- To evaluate proportion of patients with HCV below LLOQ at week 4 of therapy and ETR
- To evaluate DAA treatment completion rates
- To evaluate adherence during treatment via in hospital medication charts and outpatient weekly self-report
- To evaluate acceptability and feasibility of DAA commencement whilst an inpatient
- To evaluate adverse events secondary to drug:drug interactions
- To evaluate performance of finger prick POC testing compared to plasma HCV RNA at screening
- To evaluate completion of duration of recommended inpatient stay and therapy for co-morbidities
- To determine effect of HCV treatment on quality of life
- To evaluate rate of re-call and re-infection at 6, 9- and 12-months post study enrolment

In those who inject drugs:

- To evaluate engagement with D&A services and rates of OST initiation
- To determine rates and patterns of injecting behaviour following therapy for HCV

## 8 Participant population

### 8.1 Number of Participant and Participant Selection

Adults aged 18 years or older, who are admitted for in-patient care related to IRID (or other co-morbidities) with detectable HCV will be enrolled from Australian hospitals for TOPIC. 60 participants will be enrolled in total: 30 participants in Cohort A and 30 participants in Cohort B.

### 8.2 Inclusion criteria

Participants must meet all of the following inclusion criteria to be eligible to participate in this study.

1) Have voluntarily signed the informed consent form.
2) 18 years of age or older.
3) Injected drugs within the last 6 months OR be known to be HCV Ab positive
4) Hospitalized with an IRI with an anticipated inpatient stay of > 1 weeks[1]
5) HCV RNA positive
6) Compensated liver disease
7) Documented non-cirrhotic at enrolment with a qualifying liver FibroScan ≤ 9.5 kpA or an APRI < 2.0
8) If co-infection with HIV is documented, the subject must meet the following criteria:
   a. ART naïve with CD4 T cell count >500 cells/mm3;
      OR
   b. On a stable ART regimen (containing only permissible ART) for >4 weeks prior to screening visit, with CD4 T cell count ≥200 cells/mm3 and a plasma HIV RNA level below the limit of detection. Permissible ARTs include:
      - Raltegravir
      - Dolutegravir
      - Rilprivirine
      - Elvitegravir/cobicistat
      - Tenofovir disproxil fumerate
      - Tenofovir alafenamide

- Emtricitabine
- Lamivudine
- Abacavir

[1] Although people who inject drugs are the focus of this study, patients without a recent history of IDU or IRID who are admitted with an expected duration of stay > 1 week may also be included at discretion of study team. In this case the questions on injecting behaviour will be omitted and additional data collected on nature of co-morbidities present.

### 8.3 Exclusion criteria

Participants who meet any of the following exclusion criteria are not to be enrolled in this study.

1) Inability or unwillingness to provide informed consent or abide by the requirements of the study
2) Actively intoxicated.

Participants who meet any of the additional exclusion criteria are not to be treated in this study.

3) History of any of the following:
   a) Clinical hepatic decompensation (i.e. ascites, encephalopathy or variceal haemorrhage)
   b) Solid organ transplant
   c) History of severe, life-threatening or other significant sensitivity to study drugs (glecaprevir/pibrentasvir/sofosbuvir) or any excipients of the study drugs
4) Creatinine clearance (CLcr) < 30 mL/min at screening (Cohort B only)
5) Pregnant or nursing female
6) Decompensated liver disease
7) Use of prohibited concomitant medications
8) Chronic use of systemically administered immunosuppressive agents (e.g. prednisone equivalent > 10 mg/day for >2 weeks)
9) Prior treatment failure with an NS5A based DAA regimen

## 9 Study design

### 9.1 Summary of study design

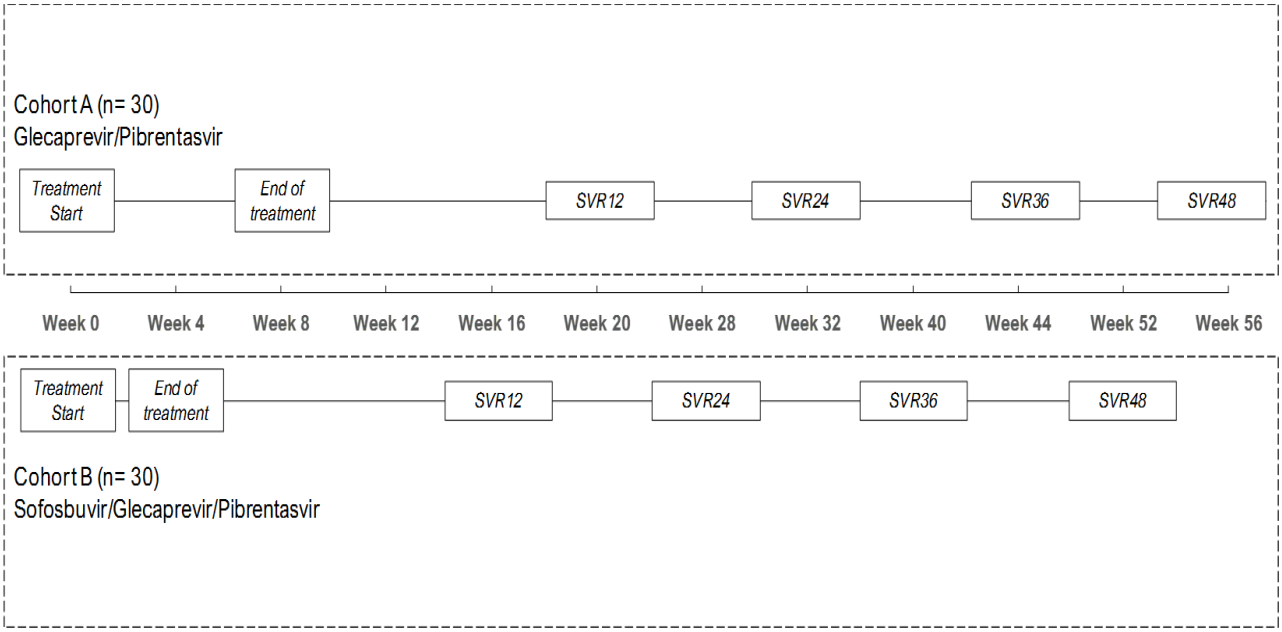
The study will be conducted as a Phase IV open-label single-arm multicenter study consisting of two sequential cohorts: Cohort A (8 weeks of glecaprevir/pibrentasvir) and Cohort B (4 weeks of sofosbuvir/glecaprevir/pibrentasvir).

### 9.2 Visit Schedule

Participants will be invited for Screening whilst they are inpatients of the hospital. Participants will be screened for a detectable HCV RNA using standard HCV RNA assays per their local laboratory and the Xpert® HCV Viral Load assay.

Eligible participants will be treated through standard of care with the applicable treatment regimen as per their enrolled cohort. All participants will commence treatment whilst they are inpatients and subsequent visits whilst on-treatment will be completed during their hospital stay where possible. For participants who are discharged before treatment completion, a hospital discharge visit will be conducted. These participants will continue their on-treatment visits through outpatient viral hepatitis services and receive weekly contact to measure treatment adherence.

Following the end of treatment, participants will be reviewed at 12, 24, 36 and 48-weeks post-treatment (SVR12, SVR24, SVR36 and SVR48). At follow-up visits, HCV RNA will be measured using the Xpert® HCV Viral Load assay. If HCV RNA is detected at a follow-up visit, local laboratory HCV RNA and genotype will be measured to determine re-infection.




### 9.3 Treatment discontinuation

Participants who cease study medication will, wherever possible, continue to be followed up according to the protocol study plan by completing the End of Treatment visit at the time of treatment termination and follow-up visits as per protocol. Participants may revoke consent for follow-up without jeopardizing their relationship with either their doctor or the UNSW/Sponsor. If a participant revokes consent then, if possible, all assessments scheduled for the final visit should be completed.

### 9.4 Unplanned discharge from hospital

In the event a participant is discharged unexpectedly from hospital prior to treatment completion (either self discharge against medical advice (DAMA) or discharge by medical staff e.g. over a weekend), then the study nurse should attempt to make contact with the patient as soon as is possible. Patient should be encouraged to remain on study drug and access to supply facilitated. Study nurse should complete an Early Discharge CRF and the participant should remain in the study as per study assessment schedule.

## 10 Treatment of participants

### 10.1 Treatment

Details of the study drugs are presented in Table 1.

*Table 1 Summary of study drugs*

| | **Cohort A** | **Cohort B** |
|---|---|---|
| **Study Drug** | Glecaprevir/Pibrentasvir (Mavyret) | Sofosbuvir/Glecaprevir/Pibrentasvir |
| **Dosage Form** | 3 x co-formulated tablets of glecaprevir (100mg) and pibrentasvir (40mg) | 1 x sofosbuvir (400mg) and 3 x co-formulated tablets of glecaprevir (100mg) and pibrentasvir (40mg) |
| **Mode of Administration** | Oral | Oral |
| **Dose Strength** | Glecaprevir 300mg<br>Pibrentasvir 120mg | Sofosbuvir 400 mg<br>Glecaprevir 300mg<br>Pibrentasvir 120mg |
| **Duration of Treatment** | 8 weeks | 4 weeks |

### 10.2 Dosing and Administration

Participants should be instructed to take study medication with food at approximately the same time each day. Dose modifications are prohibited. The first study drug dosing will commence in hospital at Baseline (day 0). The start date and the last dose of the regimen should be documented in the subject's source documents and appropriate eCRF.

Participants should be instructed to swallow the study drug tablets whole. Participants should be instructed to only remove the tablets from the packaging immediately prior to dosing.

For a missed dose of study drug, participants should be instructed to take the missed dose of study drug as soon as possible during the same day. However, no more than the daily dose of sofosbuvir and glecaprevir/pibrentasvir should be taken on any calendar day. Participants should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

**Dispensing**

Participants will be dispensed with their study medication daily prior to hospital discharge. At the hospital discharge visit, participants will be dispensed with the remaining study medication for the treatment regimen. Participants should receive counseling on the importance of adherence in regard to virologic response and potential development of resistance.

**Adherence**

Adherence monitoring will be daily observed, and the date and time will be recorded in the medical records prior to hospital discharge. Following hospital discharge, participants will be contacted weekly for self-reported treatment adherence.

## 10.3 Prior and concomitant medications

The prescribing information for all concomitant drugs should be consulted and reviewed carefully. The determinations listed in the respective contraindicated, warning, and precaution sections must be respected in order to prevent any potentially serious and/or life-threatening drug interactions.

Drug-drug interactions for each participant should be assessed on http://www.hep-druginteractions.org/. In case of any questions on potential interactions with a drug, please contact the study principal investigator.

Use of medications listed below within 2 weeks or 10 half-lives, whichever is longer, prior to study drug administration is contra-indicated (see Tables 1 and 2):

*Table 2 Contraindicated concomitant medications with glecaprevir/pibrentasvir*

| **Drug Class** | **Drug(s) within Class that are Contraindicated** | **Clinical Comments** |
|---|---|---|
| Anticoagulants | Dabigatran | May increase dabigatran concentration potentially increasing risk of bleeding |
| Anticonvulsants | Carbamazepine | May decrease DAA exposure leading to a potential loss of therapeutic activity. |
| Antimycobacterial | Rifampin | May decrease DAA exposure leading to a potential loss of therapeutic activity. |
| Ethinyl estradiol-containing products | Ethinyl estradiol-containing medications (such as combined oral contraceptives and hormone replacement therapy) | Potential for ALT elevation |
| Gastrointestinal pro-kinetic agent | Cisapride | |
| Herbal Product | St. John's Wort *(Hypericum perforatum)* | May decrease DAA exposure leading to a potential loss of therapeutic activity. |
| HIV non-nucleoside reverse transcriptase inhibitor | Efavirenz<br>Etravirine<br>Nevirapine | May decrease DAA exposure leading to a potential loss of therapeutic activity. |
| HIV protease inhibitor | Atazanavir<br>Darunavir | Potential for ALT elevation |
| HMG-CoA Reductase Inhibitors * | Atorvastatin<br>Lovastatin<br>Simvastatin | Potential for myopathy including rhabdomyolysis. |

| | | |
|---|---|---|
| Immunosuppressant | Cyclosporin | Co-administration not recommended with cyclosporin dose >100mg per day |

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with glecaprevir/pibrentasvir. Participants receiving these statins should either switch to pravastatin or rosuvastatin prior to the first dose of study drug or interrupt statin therapy throughout the treatment period and until 30 days after the last dose. If switching to or continuing pravastatin or rosuvastatin, it is recommended to reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg daily while on treatment.

*Table 3 Contraindicated concomitant medications with sofosbuvir*

| Drug Class | Drug(s) within Class that are contraindicated | Clinical Comments |
|---|---|---|
| Analeptics | Modafinil | Coadministration of sofosbuvir with modafinil is expected to decrease the concentration of sofosbuvir, leading to reduced therapeutic effect of sofosbuvir. Such coadministration is not recommended. |
| Antiarrhythmics | Amiodarone | Coadministration of amiodarone with another direct acting antiviral may result in symptomatic bradycardia. If coadministration is required, cardiac monitoring is recommended. |
| Anticoagulants | Vitamin K agonists | Close monitoring of the INR is recommended, as liver function may change with sofosbuvir treatment. |
| Anticonvulsants | Carbamazepine<br>Phenytoin<br>Phenobarbital<br>Oxcarbazepine | May decrease DAA exposure leading to a potential loss of therapeutic activity, therefore not recommended. |
| Antimycobacterials | Rifabutin<br>Rifampin<br>Rifapetine | May decrease DAA exposure leading to a potential loss of therapeutic activity, therefore not recommended. |
| Herbal Supplements | St John's wort | May decrease DAA exposure leading to a potential loss of therapeutic activity, therefore not recommended. |
| HIV Protease Inhibitors | Tipranavir<br>Ritonavir | May decrease DAA exposure leading to a potential loss of therapeutic activity, therefore not recommended. |

# 11 Study procedures

## Screening Visit (Week -6 to Week 0) – All participants

- Informed consent: At the screening visit, participants will provide written and informed consent prior to any study-specific procedures.
- Medical history: A medical history will be taken
- Physical measurements: Height and body weight.
- Clinical laboratory tests: At a minimum, liver function tests, biochemistry and full blood count tests will be collected at Screening (or used from admission bloods).
- HCV RNA (local laboratory): Quantitative HCV RNA
- HCV Genotype (local laboratory): HCV genotype should be collected at screening. Historical participant genotype results are acceptable if these were conducted within 5 years from Screening.
- HCV RNA (point-of-care): A finger-stick capillary whole-blood sample will be collected for the GeneXpert. This may be repeated if an invalid result is obtained in the absence of a local laboratory HCV RNA.

- HIV and HBV serology: Anti-HIV Ab and HBsAg results within 5 years prior to Screening are also acceptable.
- Fibrosis Assessment: Liver fibrosis will be measured using a FibroScan where possible. An AST to Platelet Ratio Index (APRI) will be considered as an acceptable alternative if a FibroScan is not possible.
- Pregnancy test: All females of child-bearing potential will have a serum or urine pregnancy test. This will not be required for females of non-childbearing potential. Determination of postmenopausal status will be recorded during the Screening period based on participant history.
- Behavioural survey and EQ-5D-5L.
- Clinical assessment and concomitant medication assessment / DDI assessment.
- Dried Blood Spot sample.

**<u>The following study visits are for participants who commence treatment only.</u>**

### Baseline visit (Week 0)

Eligible participants who meet the treatment inclusion criteria and meet none of the exclusion criteria will proceed to the baseline visit. This visit must be completed prior to hospital discharge. The following procedures will be conducted:

- Concomitant medications / DDI assessment: These will be updated from the Screening visit as necessary.
- Pregnancy test: Urine or serum pregnancy tests.
- Full blood count and biochemistry
- Treatment initiation: Participants will be administered the study drug at the site with dosing instructions at the baseline visit.

### Week 4 (Cohort A only)

Participants in Cohort A will have an on-treatment visit at Week 4. The following procedures will be conducted:

- HCV RNA testing (local laboratory)
- Pregnancy test (women of child-bearing potential; serum or urine)
- Concomitant medication assessment / DDI assessment
- Adherence

### End of Treatment – (Week 8 – Cohort A, Week 4 – Cohort B)

The date of the last dose of study medication will be collected. The end of treatment visit will be either Week 8 or Week 4, depending on the cohort. The following procedures will be conducted:

- HCV RNA testing (local laboratory)
- Liver function tests
- Pregnancy test (women of child-bearing potential; serum or urine)
- Concomitant medication assessment / DDI assessment
- Adherence

### Follow-up Visits (SVR12, SVR24, SVR36 and SVR48)

Participants will return for follow-up visits every 12 weeks after the last dose of study medication. All participants will have the following procedures conducted:

- HCV RNA testing (local laboratory or point of care)
- Behavioural survey and EQ-5D-5L: Participants will complete this questionnaire at SVR12 and SVR48.
- Liver function tests
- Concomitant medication assessment / DDI assessment (SVR12 only)

If a participant is found to be HCV RNA positive at SVR12, additional procedures will be conducted to determine re-infection/relapse. These procedures are:

- HCV Genotype
- Dried Blood Spot Sample for sequencing
- EDTA Plasma for resistance testing (10mL)

*All on-treatment visits will be conducted whilst the participant is still an in-patient. If the participant is discharged prior to treatment completion, visits will be conducted through outpatient viral hepatitis services.*

### Questionnaires

Health Outcomes Survey (EQ-5D-5L)

The EQ-5D-5L provides a simple descriptive profile and a single index value for health status. This information can then be translated into a health utility, which can be used for cost-effectiveness analyses.

Behavioural Questionnaire

Participants will complete a behavioural questionnaire at Screening, SVR12 and SVR48. The behavioural questionnaire will collect information on demographics, drug and alcohol usage, injecting risk behaviours.

# 12 Recording and reporting Adverse Events (AEs)

## 12.1 Adverse Event (AE) (including Adverse Drug Reactions)

The medications for this study are government approved DAA regimens. Adverse Events and adverse drug reactions will be reported to the Therapeutic Goods Administration as per standard practice for PBS prescribed medications.

## 12.2 Serious Adverse Event (SAE) (including Serious Adverse Drug Reaction)

The medications for this study are government approved DAA regimens. Serious Adverse Events and serious adverse drug reactions will be reported to the Therapeutic Goods Administration as per standard practice for PBS prescribed medications.

# 13 Packaging, labeling, storage and accountability of clinical trial supplies

The medications for this study are government approved DAA regimens. The packaging, labelling and accountability of prescribed treatment will be as per the approved product information. Study medication will be supplied by the Pharmaceutical Benefits Scheme (PBS).

# 14 Biological samples

Dried Blood Spot samples (DBS) will be collected at Screening for all participants. These will be dried and stored and later tested for hepatitis C. The samples will also be used to look at potential transmission patterns (known as phylogenetics). Leftover samples from consenting participants will be stored and may be used for future unspecified hepatitis C related research until all of the samples have been used up or are no longer viable. Any future research using these samples will be approved by a Human research Ethics Committee prior to starting.

For participants on treatment which are re-viraemic at SVR12 or subsequent follow-up visits, a DBS sample and 10 mL of EDTA plasma will be collected for viral sequencing and resistance testing respectively. They will be used to compare with the Screening samples to determine if the virus is homogenous or heterogenous.

# 15 Statistics

A total of 60 Participants are planned for enrolment and evaluation as the overall ITT population. Cohorts A and B (30 patients each) will be evaluated sequentially and subsequently together using both ITT and per protocol based analyses.

### 15.1 Primary endpoint

Proportion of patients achieving confirmed SVR12 (defined as HCV RNA below the lower limit of quantitation at 12 weeks post treatment) in the intention-to-treat population (defined as all enrolled participants who received at least one dose of study drug). The ITT population consisting of patients commencing inpatient DAA treatment within public hospital services

### 15.2 Secondary Endpoints

- Proportion of patients with HCV RNA below the level of detection at 12 weeks post-treatment (SVR12) within each cohort by both ITT and PP analyses
- Proportion of patients with HCV below LLOQ at week 4 of therapy and ETR
- Proportion of patients completing DAA treatment course
- Proportion of patients with full (100%) and partial adherence (<50%, 50-80%, 81-99%) during treatment as assessed by in hospital medication charts and outpatient weekly self-report
- Uptake of DAA therapy during admission in patients suitable for study
- Safety: Rates and predictors of adverse events secondary to drug:drug interactions
- Sensitivity and specificity of finger prick POC testing compared to plasma HCV RNA at screening
- Proportion of patients completing recommended inpatient stay
- Changes in HRQOL
- Rates of re-attendance at subsequent planned study visits
- Rates and predictors of reinfection during follow-up

In those with a history of injecting drug use:

- Proportion of patients undergoing D&A evaluation during admission
- Proportion of patients initiating OST during admission
- Frequency and patterns of injecting behaviour following therapy for HCV

### 15.3 Analyses

Proportions and 95% confidence intervals will be reported for both the primary and secondary virological endpoints. These will be assessed for both the PP and the ITT populations. Results will be stratified by HCV genotype/subtype.

Sub-group analysis of treatment efficacy (SVR12) in the ITT population will be evaluated for the following variables: demographic factors (age, gender); virological factors (pre-treatment HCV RNA, genotype); HIV co-infection. Additional treatment efficacy evaluations will be conducted among the per protocol study population, defined as Participants who receive >80% of planned treatment.

The impact of adherence (<50%, 50-80%, 81-99%), 100/100 adherence, on-treatment adherence and early discontinuation on SVR will also be evaluated.

A final full statistical analysis plan will be written and signed off by the Protocol Steering Committee prior to final study data lock.

## 16 Data Safety and Monitoring Board (DSMB)

This project is conducted as a Phase IV trial using PBS approved medication and as such, a DSMB will not be used. The medical monitor, Dr Marianne Martinello will oversee all serious adverse events for TOPIC. As Dr Martinello is also Co-Investigator and clinician at Prince of Wales Hospital, which is one of the recruiting sites, should an SAE occur in a patient under Dr Martinello's care, the

project team will seek an independent review of the SAE from a suitably qualified independent Infectious Diseases Specialist or Hepatologist.

# 17 Data collection, source documents and record retention

## 17.1 Submission of data

Following each participant visit the designated site staff will complete the visit specific eCRF. Once all required information is received the eCRF shall be considered complete. Project Team staff will then monitor the data for completeness and accuracy. Any eCRF discrepancies, either manual or automatic, will be addressed with the site staff for clarification.

The site Principal Investigator is responsible for ensuring the completion of accurate source documentation to support data collected on case report forms. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the trial. Source documents include, but are not limited to; participant medical records, laboratory reports, ECG tracings, X-rays, radiologist reports, participant diaries, biopsy reports, ultrasound images, participant progress notes, pharmacy records and any other reports or records of procedures performed in accordance with the protocol.

It is not acceptable for the CRF to be the only record of study participation and progress must also be recorded in the each person's medical record. This is to ensure that anyone accessing the medical record has adequate knowledge that the person is a clinical trial participant.

Any document that acts as a source document (the point of the initial recording of a piece of data) should be signed and dated by the person recording or reviewing the data for issues of medical significance (for example the review of laboratory reports). Persons signing the source documents must be listed as a site staff member.

The sponsor's monitor may visit sites to conduct source document verification. The number of visits will depend upon the recruitment rate.

The site Principal Investigator is responsible for retaining all the essential documents listed in ICH Good Clinical Practice guidelines. These must be organised in a comprehensive filing system that is accessible to study monitors and other relevant personnel.

# 18 Archiving

The site Principal Investigator is responsible for ensuring all study documents are retained for a minimum of 15 years following completion and publication of the study.

# 19 Ethics committee/regulatory approval and informed consent

The sponsor is responsible for ensuring regulatory approval for the study is obtained.

The site Principal Investigator is responsible for obtaining IRB/EC approval for the protocol and participant information and informed consent form in compliance with local regulatory requirements prior to entering any participant into the study. The approval letter/document must clearly identify the protocol and all documents approved by the IRB/EC including version number & date of the protocol and participant information and consent form. A copy of the approval document must be sent to the study sponsor.

The site Principal Investigator must also obtain approval for any amendments to the protocol or participant information and informed consent form. The Principal Investigator must comply with all IRB/EC reporting requirements for all adverse events, annual updates and end of study reports and must agree to abide by any IRB/EC conditions of approval.

The site Principal Investigator (or designee) is responsible for ensuring freely-given consent is obtained from each potential participant prior to the conduct of any protocol-specific procedures. The Principal Investigator may delegate the task of obtaining consent to appropriately qualified Sub-investigator(s). Consent must be documented by the participant's dated signature on the

participant information and consent form together with the dated signature of the person conducting the consent discussion.

If the participant is illiterate, an impartial witness should be present during the entire consent discussion. Once the discussion is complete, the participant must sign and date the informed consent form, if capable. The impartial witness must also sign and date the consent form along with the person who conducted the consent discussion.

If the participant is legally incompetent (i.e. under 18 years of age or mentally incapacitated) the written consent of a parent, guardian or legally authorised representative must be obtained.

A copy of the signed and dated participant information and consent form must be given to the person prior to study participation. The participant or their legally authorised representative must be informed in a timely manner of any new information that becomes available during the course of the study that may affect his/her willingness to continue study participation.

This study shall be conducted in accordance with the ethical principles laid out in the Declaration of Helsinki (most current issued version) and the National Statement on Ethical Conduct in Research Involving Humans (most current issued version).

# 20 Confidentiality of data

### Confidentiality of participant records

Participant confidentiality will be maintained at all times and no documents containing the participant's name or other identifying information will be collected by the sponsor. It may be necessary for the sponsor's representatives, the IRB/EC and regulatory authority representatives to have direct access to the participant's medical records. If study documents need to be photocopied during the process of verifying case report form data, the participant will be identified by a unique code only; full names and other identifying information will be masked.

### Confidentiality of study data

By signing the Clinical Trial Agreement, the site Principal Investigator affirms to the sponsor that information provided to them by the sponsor will be maintained in confidence and divulged only as necessary to the ethics committee and institution employees directly involved in the study. Both ethics committee members and employees must also understand the confidentiality requirements for any information divulged to them. The data generated by this study will be considered confidential, except where it is included in a publication as agreed in the publication policy of this protocol.

At sites where regulations restrict the collection of full date of birth and/or participant initials, the following conventions will be used:

- Date of birth will be entered as 01/01/YYYY
- Initials will be entered as AA-AA, BB-BB, CC-CC etc.

# 21 Governance

This national research protocol is funded by Kirby Institute UNSW Sydney. The study drugs will be accessed via the PBS. The study is sponsored by the University of New South Wales (UNSW) and coordinated through the Kirby Institute for infection and immunity in society. The Kirby Institute has established governance and implementation structures which use resources efficiently to deliver program objectives on schedule.

# 22 Quality Control (QC) and Quality Assurance (QA)

The sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice standards and all applicable local laws and regulations relating to the conduct of a clinical trial.

# 23 Publication Policy

The results of this study may be published and presented at scientific meetings. Publication of data derived from this protocol will be governed by the Protocol Steering Committee. All published data will be non-identifiable grouped data and will follow the guidelines set forth by the International Committee of Medical Journal Editors (ICMJE).

# 24 Abbreviations List

| Abbreviation/Acronym | Description |
|---|---|
| AE | Adverse Event |
| ART | Antiretroviral Therapy |
| D&A | Drug & Alcohol |
| DAA | Direct Acting Antiviral |
| DBS | Dried Blood Spot |
| DDI | Drug-Drug Interaction |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Form |
| ETR | End of Treatment |
| G | Glecaprevir |
| GT | Genotype |
| HCV | Hepatitis C Virus |
| IRB | Institutional Review Board |
| IRID | Injecting Related Infectious Disease |
| ITT | Intent-to-treat |
| LLOQ | Lower Limit of Quantification |
| OST | Opioid Substitution Therapy |
| P | Pibrentasvir |
| POC | Point-of-care |
| PP | Per protocol |
| PWID | People Who Inject Drugs |
| RNA | Ribonucleic Acid |
| SOF | Sofosbuvir |
| SVR | Sustained Virological Response |
| VEL | Velpatasvir |
| VOX | Voxilaprevir |

# 25 References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