Scale-up of treatment for hepatitis C infection among people who inject drugs:

A phase IV, open-label, single arm, multicentre trial of elbasvir/grazoprevir for genotype 1 or 4 in people with chronic hepatitis C virus infection and recent injecting drug use or receiving opioid substitution therapy

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Name of sponsor: UNSW Australia
The Kirby Institute
Wallace Wurth Building (C27)
Sydney, NSW 2052
Australia

Title and name of Co-Coordinating Principal Investigators (CPI):

Coordinating Co-Principal Investigators (CPI):

Professor Gregory Dore
The Kirby Institute
UNSW Australia
Wallace Wurth Building (C27)
Sydney NSW 2052
Australia
E: gdore@kirby.unsw.edu.au

P: +61 2 9385 0900
F: +61 2 9385 9214

Professor Jason Grebely
The Kirby Institute
UNSW Australia
Wallace Wurth Building (C27)
Sydney NSW 2052
Australia
E: jgrebely@kirby.unsw.edu.au

P: +61 2 9385 0957
F: +61 2 9385 9214

Medical Monitor:

A/Professor Gail Matthews
The Kirby Institute
UNSW Australia
Wallace Wurth Building (C27)
Sydney NSW 2052
Australia
E: gmatthews@kirby.unsw.edu.au

P: +61 2 9385 0877
F: +61 2 9385 9214

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Protocol Synopsis

Title	Scale-up of treatment for hepatitis C infection among people who inject drugs: A phase IV, open-label, single arm, multicentre trial of elbasvir/grazoprevir for genotype 1 or 4 in people with chronic hepatitis C virus infection and recent injecting drug use or receiving opioid substitution therapy (OST).
Protocol registration no.	NCT02940691
Background and rationale	People who inject drugs (PWID) account for the majority of new (80%) and existing (60%) cases of HCV in high-income countries[1,2]. Development of chronic HCV infection may lead to progressive hepatic fibrosis, cirrhosis, and complications of liver failure or hepatocellular carcinoma[3]. The ageing cohort of PWID populations means that liver disease-related mortality is increasing[4-7]. However, treatment can attenuate HCV-related disease consequences, including all-cause mortality[8]. HCV transmission also continues to occur among PWID[9]. Estimated HCV incidence among PWID ranges from 5-45% per annum[10]. The risk of HCV infection is highest among recent initiates into injecting drug use. Harm reduction strategies, such as needle syringe programs (NSP) and opioid substitution treatment (OST) have been successful for HIV prevention among PWID, but have been less effective for HCV prevention[11-15]. In many countries, low coverage of NSP and OST further hinders HCV prevention efforts[16]. Given that HCV transmission continues to occur among PWID and there is no HCV vaccine, strategies to achieve HCV elimination among PWID must be explored. Data from mathematical modelling suggests that substantial reductions in HCV prevalence and incidence could be achieved among PWID with modest increases in treatment uptake with interferon-free HCV regimens[17]. Given the potential prevention benefits, HCV treatment among PWID is also cost-effective[18, 19]. In fact, combining interferon-free HCV therapies with high coverage OST and NSP may lead to even greater reductions in HCV prevalence[20]. As such, combination prevention strategies including “HCV Treatment as Prevention”, OST and NSP are critical for achieving reductions in HCV prevalence/transmission to very

	low levels[18]. Targeted treatment to those at risk of transmission could be used as an HCV "Treatment as Prevention" strategy to reduce onward transmission. One of the most important breakthroughs in clinical medicine in recent decades is the advent of well-tolerated, simple, short-course interferon-free direct acting antiviral (DAA) HCV regimens with cure rates >95%[21]. The interferon-free dual DAA regimen of elbasvir 50 mg once-daily (NS5A inhibitor) and grazoprevir 100 mg once-daily (NS3/4A protease inhibitor) has demonstrated high efficacy (95% SVR12 overall, 97% SVR12 in those with cirrhosis) with a treatment duration of 12 weeks in treatment-naïve patients with HCV genotypes 1 or , 4 infection[22], including those with HIV co-infection (95% SVR12)[24]. Elbasvir/grazoprevir was also the first DAA regimen to be evaluated in a phase III program among a study population of people on opioid substitution (OST) treatment, including those with ongoing drug use. Results from the CO-STAR study demonstrated 99% of patients had >90% adherence to elbasvir/grazoprevir or placebo and the overall SVR12 in the full analysis set was 92%. These data suggest that interferon-free treatments, such as elbasvir/grazoprevir, will be feasible for the treatment of PWID with recent injecting drug use or receiving OST. One limitation of the CO-STAR study is that inclusion in this study required participants being on stable OST therapy prior to study entry. As such, only 59% of the total study population tested positive for illicit drugs at the time of treatment initiation. Among people enrolled in the 3YFU study, injecting drug use in the past 6 months was only reported by 25% of participants. Further, this study used an innovative adherence reminder device, which may have led to improved outcomes in this population. As such, further data is needed on responses to elbasvir/grazoprevir among recent PWID and people receiving OST in the "real-world". In addition, long-term follow-up to better characterize HCV reinfection in those with recent injecting drug use and successful therapy is essential. Australia is an ideal setting for a study to evaluate elbasvir/grazoprevir

	therapy among recent PWID and people receiving OST. First, Australia has a strong foundation of health services for HCV testing (>80% of PWID have been HCV tested and diagnosed) and care among PWID. Second, there is a well-established network of clinical sites experienced in clinical trial research. Third, Australia has a high coverage of NSP and OST services for PWID, which could act in combination with HCV treatment scale-up to achieve greater prevention benefits. Lastly, Australia is the first country in the world to have broad access to government-funded interferon-free DAA HCV therapies without disease-based and drug and alcohol use-based restrictions and including specialist and general practitioner prescribing. Within the context of an HCV treatment scale-up project, this would enable the evaluation of elbasvir/grazoprevir for people with HCV genotype 1 or 4 and recent injecting drug use or receiving OST. Drug and alcohol clinics and primary health care clinics are logical venues for expanding HCV care, given the large burden of HCV and an existing framework for the provision of care for PWID. These settings are ideal for a study to evaluate HCV treatment scale-up among PWID with recent injecting drug use or receiving OST in the tertiary, drug and alcohol and primary health care settings. This project will build on the existing clinical capacity at these clinics and utilize the internationally leading Kirby Institute Viral Hepatitis Clinical Research Program expertise and clinical research operational capacity.
Study objectives	**Hypothesis** Interferon-free and ribavirin-free DAA HCV therapy with elbasvir/grazoprevir will lead to SVR12 >90% among PWID with recent injecting drug use or receiving OST and chronic HCV genotype 1 or 4 infection. **Primary Objective** To evaluate the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment (SVR12) following interferon-free and ribavirin-free DAA therapy with elbasvir/grazoprevir among PWID with recent injecting drug use or receiving OST and chronic HCV genotype 1 or 4 infection and evaluate demographic and clinical predictors of non-response.

	Secondary Objective To evaluate the rate of HCV reinfection up to three years following interferon-free and ribavirin-free DAA therapy with elbasvir/grazoprevir. **Exploratory Objectives** 1) To evaluate factors associated with SVR12 (e.g. drug use at baseline and during therapy, adherence); 2) To evaluate the adherence to therapy and associated factors; 3) To evaluate safety and tolerability; 4) To evaluate injecting risk behaviours during and following HCV treatment; 5) To evaluate HCV phylogenetic clustering and molecular epidemiology; 6) To evaluate the prevalence of resistance associated substitutions; 7) To determine the sensitivity and specificity of the Xpert® HCV Viral Load assay for HCV RNA detection in samples collected by finger-stick capillary whole-blood.
Participant population	A total of 150 participants will be recruited from tertiary, drug and alcohol and primary health care services in Sydney, Australia. ***Inclusion criteria*** 1) Participants have voluntarily signed the informed consent form. 2) Be ≥18 years of age on day of signing informed consent form. 3) Have chronic HCV genotype 1 or 4 infection (defined as detectable HCV RNA). 4) Recent injecting drug use (previous 6 months) or receiving opioid substitution therapy (OST). 5) HIV-1 infected subjects enrolled in the study must meet the following criteria: a) Have HIV infection documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry (Baseline) and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, or plasma HIV-1 RNA viral load. b) Be on HIV Antiretroviral Therapy (ART) for at least 4 weeks

prior to study entry using an ART regimen that is allowable with the intended DAA regimen as determined by the current PI and the Liverpool drug interaction website (http://www.hiv-druginteractions.org/) or current prescribing guidelines for elbasvir/grazoprevir OR be naive to treatment with any antiretroviral therapy (ART) with a baseline CD4 count of >200 and have no plans to initiate ART treatment while participating in this study and through to at least Follow-up Week 4.

6) Negative pregnancy test at screening and baseline (females of childbearing potential only).
7) All fertile males and females must be using effective contraception during treatment and during 14 days after treatment end.

Exclusion criteria

The subject must be excluded from participating in the trial if the subject:

1) Is taking or plans to take any prohibited medications as per DAA Product Information or herbal supplements, including but not limited to St. John's Wort (*Hypericum perforatum*) within 2 weeks of Baseline.
2) Is currently using or intends to use barbiturates.
3) Is a female and is pregnant or breast-feeding, or expecting to conceive or donate eggs from Baseline and continue throughout treatment, and after the last dose of study medication (as per the regimen requirements), or longer if dictated by local regulations.
4) Has any condition or pre-study laboratory abnormality, ECG abnormality or history of any illness, which, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering the study drugs to the subject.
5) Had a life-threatening SAE during the screening period.
6) Has exclusionary laboratory values as listed below:

Laboratory Assessment	**Value**
Haemoglobin	< 9.5 g/dL for both males and females
Platelets	< 75 x 10^3 /µL
Serum albumin	< 3.0 g/dL

	9) Has Child Pugh-B or C decompensated cirrhosis. 10) Has previous HCV treatment-experience. 11) Has ongoing severe psychiatric disease as judged by the treating physician. 12) Has frequent injecting drug use that is judged by the treating physician to compromise treatment safety. 14) Is unable or unwilling to provide informed consent or abide by the requirements of the study. 15) Is Hepatitis B surface antigen (HBsAg) positive.
Study design	The study will be conducted as a phase IV, open-label single arm multicentre trial. A total of 150 participants with chronic hepatitis C virus infection genotype 1 or 4 with recent injecting drug use or receiving OST will be enrolled. The study consists of a treatment phase of 12 weeks and a follow up phase of up to 3 years. Participants will be followed up every 3 months for the first year and every 6 months in year's 2-3 to evaluate treatment response and reinfection.
Treatment of participants	Participants with chronic hepatitis C infection genotype 1 or 4 will receive 12 weeks of open-label elbasvir/grazoprevir (50mg/100mg) in a once daily fixed combination.
Study procedures	Refer to the Schedule of Assessments and Study Procedures (Section 6)
Statistics	**Primary Objective:** To evaluate the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment (SVR12) following elbasvir/grazoprevir therapy among PWID with recent injecting drug use or receiving OST and chronic HCV genotype 1 or 4 infection and evaluate demographic and clinical predictors of non-response. Assuming an overall SVR of 90% (135 of 150), the 95% confidence interval around this estimate will be 84.0% to 94.3%. This study will have robust power to examine the effect of treatment setting on SVR: e.g. 80% power to detect an odds ratio of 0.39 or 2.59 or more extreme (with alpha=0.05)

	for a variable that is 50% prevalent. **Secondary Objective**: Estimate incidence and predictors of HCV reinfection after successful elbasvir/grazoprevir.

Schedule of Assessments

Assessment / Procedure	Screen	Baseline	W4	Safety	Study Treatment (weeks)	Follow-up (weeks)							
Study weeks	**-6 to 0**	**0**	**4**	**8**	**12 (ETR)**	**24 (SVR12)**	**36 (FU1)**	**48 (FU2)**	**60 (FU3)**	**84 (FU4)**	**108 (FU5)**	**132 (FU6)**	**156 (FU7)**
Study Days	**-42 to 0**	**0**	**28**	**56**	**84**	**168**	**252**	**336**	**420**	**588**	**756**	**924**	**1092**
Visit Window (Days)			**+/- 7**	**+/- 7**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**	**+/- 14**
Informed consent, medical history	x												
Vital signs & physical measurements	x	x											
HCV-RNA testing (Local Laboratory)	x[a]		x[a]		x	x	x[d]						
HCV genotyping (Local Laboratory)	x												
Behavioural survey	x												
Abbreviated behavioural survey		x			x	x	x	x	x	x	x	x	x
Adherence survey and pill count			x	x	x								
Health outcomes survey (EQ-5D)	x				x	x							
Liver function tests/ Full blood count/ Biochemistry	x	x		x[c]	x	x							
HIV & HBV serology	x												
Fibroscan	x												
Pregnancy Test	x	x	x	x	x	x[f]							
Serious Adverse Events		x	x	x	x	x[e]							
Concomitant medication	x	x			x								
Research Sample (10 mL EDTA plasma and Whole Blood)	x[b]	x[b]	x	x	x	x	x	x	x	x	x	x	x
HCV sequencing/resistance testing (tested at Central lab using 10ml of research sample)	x[g]												
Finger-stick point-of-care HCV RNA testing (sub-study sites only)	x	x	x			x	x	x	x	x	x	x	x

[a] must be quantitative HCV RNA, [b] 4ml whole Blood and 20mL EDTA at Screening and Baseline only, [c] ALT only, [d] as per standard of care, [e] to week 16 only, [f] at 14 days post end of treatment (home test allowed) [g] To evaluate the prevalence of resistance associated substitutions and for relapse or reinfection as needed

1. Background and rationale

People who inject drugs (PWID) account for the majority of new (80%) and existing (60%) cases of HCV in high-income countries[1, 2]. Development of chronic HCV infection may lead to progressive hepatic fibrosis, cirrhosis, and complications of liver failure or hepatocellular carcinoma[3]. The ageing cohort of PWID populations means that liver disease-related mortality is increasing[4-7]. However, treatment can attenuate HCV-related disease consequences, including all-cause mortality[8]. HCV transmission also continues to occur among PWID[9]. Estimated HCV incidence among PWID ranges from 5-45% per annum[10]. The risk of HCV infection is highest among recent initiates into injecting drug use. Harm reduction strategies, such as needle syringe programs (NSP) and opioid substitution treatment (OST) have been successful for HIV prevention among PWID, but have been less effective for HCV prevention[11-15]. In many countries, low coverage of NSP and OST further hinders HCV prevention efforts[16]. Given that HCV transmission continues to occur among PWID and there is no HCV vaccine, strategies to achieve HCV elimination among PWID must be explored.

Data from mathematical modelling suggests that substantial reductions in HCV prevalence and incidence could be achieved among PWID with modest increases in treatment uptake with interferon-free HCV regimens[17]. Given the potential prevention benefits, HCV treatment among PWID is also cost-effective[18, 19]. In fact, combining interferon-free HCV therapies with high coverage OST and NSP may lead to even greater reductions in HCV prevalence[20]. As such, combination prevention strategies including "HCV Treatment as Prevention", OST and NSP are critical for achieving reductions in HCV prevalence/transmission to very low levels[18]. Targeted treatment to those at risk of transmission could be used as an HCV "Treatment as Prevention" strategy to reduce onward transmission.

One of the most important breakthroughs in clinical medicine in recent decades is the advent of well-tolerated, simple, short-course interferon-free direct acting antiviral (DAA) HCV regimens with cure rates >95%[21]. The interferon-free dual DAA regimen of elbasvir 50 mg once-daily (NS5A inhibitor) and grazoprevir 100 mg once-daily (NS3/4A protease inhibitor) has demonstrated high efficacy (95% SVR12 overall, 97% SVR12 in those with cirrhosis) with a treatment duration of 12 weeks in treatment-naïve patients with HCV genotypes 1 or , 4 infection[22], including those with HIV co-infection (95% SVR12)[24]. Elbasvir/grazoprevir was also the first DAA regimen to be evaluated in a phase III program among a study population of people on opioid substitution (OST) treatment, including those with ongoing drug use. Results from the CO-STAR study demonstrated 99% of patients had >90% adherence to elbasvir/grazoprevir or placebo and the overall SVR12 in the full analysis set was 92%. These data suggest that interferon-free treatments, such as elbasvir/grazoprevir, will be feasible for the treatment of PWID with recent injecting drug use and people receiving OST.

However, treatment failure due to resistance associated substitutions (RASs) has been described following therapy with elbasvir and grazoprevir [25]. In particular, reduced response to HCV therapy has been observed in certain sub-groups of patients, specifically HCV genotype 1a, with pre-existing RASs, such as M28L/T/V, Q30H/L/R, L31M, or Y93C/H/N/S[26-30] More recently, the Australian product information for elbasvir/grazoprevir and the Australian Recommendations for the Management of Hepatitis C Infection have no recommendation for resistance testing prior to initiation of elbasvir/grazoprevir given the low prevalence of resistance mutations in the Australian population.

One limitation of the CO-STAR study is that inclusion in this study required participants being on stable OST therapy prior to study entry. As such, only 59% of the total study population tested positive for illicit drugs at the time of treatment initiation. Among people enrolled in the 3YFU study, injecting drug use in the past 6 months was only reported by 25% of participants. Further, this study used an innovative adherence reminder device, which may have led to improved outcomes in this population. As such, further data is needed on responses to elbasvir/grazoprevir among recent PWID and people receiving OST in the "real-world". In addition, long-term follow-up to better characterize HCV reinfection in those with recent injecting drug use and successful therapy is essential.

Australia is an ideal setting for a study to evaluate elbasvir/grazoprevir therapy among recent PWID. First, Australia has a strong foundation of health services for HCV testing (>80% of PWID have been HCV tested and diagnosed) and care among PWID and people receiving OST. Second, there is a well-established network of clinical sites experienced in clinical trial research. Third, Australia has a high coverage of NSP and OST services for PWID, which could act in combination with HCV treatment scale-up to achieve greater prevention benefits. Lastly, Australia is the first country in the world to have broad access to government-funded interferon-free DAA HCV therapies without disease-based and drug and alcohol use-based restrictions and including specialist and general practitioner prescribing. Within the context of an HCV treatment scale-up project, this would enable the evaluation of elbasvir/grazoprevir for people with HCV genotype 1 or 4 and recent injecting drug use or receiving OST.

Drug and alcohol clinics and primary health care clinics are logical venues for expanding HCV care, given the large burden of HCV and an existing framework for the provision of care for PWID. These settings are ideal for a study to evaluate HCV treatment scale-up among PWID with recent injecting drug use or receiving OST in the tertiary, drug and alcohol and primary health care settings. This project will build on the existing clinical capacity at these clinics and utilize the internationally leading Kirby Institute Viral Hepatitis Clinical Research Program expertise and clinical research operational capacity.

2. Study objectives

Primary Hypothesis

Interferon-free and ribavirin-free DAA HCV therapy with elbasvir/grazoprevir will lead to SVR12 >90% among PWID with recent injecting drug use or receiving OST and chronic HCV genotype 1 or 4 infection.

Secondary Hypothesis

The incidence of HCV reinfection following successful interferon-free and ribavirin-free DAA therapy with elbasvir/grazoprevir will be <8 per 100 p-yrs among people with recent injecting drug use or receiving OST.

Primary Objective

To evaluate the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment (SVR12) following interferon-free and ribavirin-free DAA therapy with elbasvir/grazoprevir among PWID with recent injecting drug use or receiving OST and chronic HCV genotype 1 or 4 infection and evaluate demographic and clinical predictors of non-response.

Secondary Objective

To evaluate the rate of HCV reinfection up to three years following interferon-free and ribavirin-free DAA therapy with elbasvir/grazoprevir.

Exploratory Objectives

1) To evaluate factors associated with SVR12 (e.g. drug use at baseline and during therapy, adherence);
2) To evaluate the adherence to therapy and associated factors;
3) To evaluate safety and tolerability;
4) To evaluate injecting risk behaviours during and following HCV treatment;
5) To evaluate HCV phylogenetic clustering and molecular epidemiology;
6) To evaluate the prevalence of resistance associated substitutions;
7) To determine the sensitivity and specificity of the Xpert® HCV Viral Load assay for HCV RNA detection in samples collected by finger-stick capillary whole-blood.

3. Participant population

Participants will be recruited from tertiary, drug and alcohol and primary health care services in Sydney, Australia.

All patients must be eligible for PBS treatment with elbasvir/grazoprevir as per the prescribing guidelines. In addition the following inclusion and exclusion criteria apply.

Inclusion criteria

1) Participants have voluntarily signed the informed consent form.
2) Be ≥18 years of age on day of signing informed consent form.
3) Have chronic HCV genotype 1 or 4 infection (defined as detectable HCV RNA).
4) Recent injecting drug use (previous 6 months) or receiving opioid substitution therapy.
5) HIV-1 infected subjects enrolled in the study must meet the following criteria:
    a) Have HIV infection documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry (Baseline) and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 p24 antigen, or plasma HIV-1 RNA viral load.
    b) Be on HIV Antiretroviral Therapy (ART) for at least 4 weeks prior to study entry using an ART regimen that is allowable with the intended DAA regimen as determined by the current PI and the Liverpool drug interaction website (http://www.hiv-druginteractions.org/) or current prescribing guidelines for elbasvir/grazoprevir OR be naive to treatment with any antiretroviral therapy (ART) with a baseline CD4 count of >200 and have no plans to initiate ART treatment while participating in this study and through to at least Follow-up Week 4.
6) Negative pregnancy test at screening and baseline (females of childbearing potential only).
7) All fertile males and females must be using effective contraception during treatment and during 14 days after treatment end.

Exclusion criteria

The subject must be excluded from participating in the trial if the subject:

1) Is taking or plans to take any prohibited medications as per DAA Product Information or herbal supplements, including but not limited to St. John's Wort (*Hypericum perforatum*) within 2 weeks of Baseline.
2) Is currently using or intends to use barbiturates.
3) Is a female and is pregnant or breast-feeding, or expecting to conceive or donate eggs from Baseline and continue throughout treatment, and after the last dose of study medication (as per the regimen requirements), or longer if dictated by local regulations.
4) Has any condition or pre-study laboratory abnormality, ECG abnormality or history of any illness, which, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering the study drugs to the subject.
5) Had a life-threatening SAE during the screening period.

6) Has exclusionary laboratory values as listed below:

Laboratory Assessment	Value
Haemoglobin	< 9.5 g/dL for both males and females
Platelets	< 75 x 10^3 /µL
Serum albumin	< 3.0 g/dL

9) Has Child Pugh-B or C decompensated cirrhosis.

10) Has previous HCV treatment-experience.

11) Has ongoing severe psychiatric disease as judged by the treating physician.

12) Has frequent injecting drug use that is judged by the treating physician to compromise treatment safety.

13) Is unable or unwilling to provide informed consent or abide by the requirements of the study.

15) Is Hepatitis B surface antigen (HBsAg) positive.

4. Study design

The primary objective of this project is to evaluate the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment (SVR12) following therapy with elbasvir/grazoprevir among PWID with recent injecting drug use or receiving OST and chronic HCV genotype 1 or 4 infection and evaluate demographic and clinical predictors of non-response. The secondary objective of this project is to evaluate the rate of HCV reinfection up to three years following treatment among PWID with recent injecting drug use.

A prospective, observational cohort design will be used to enrol patients with chronic HCV and recent injecting drug use (injecting drug use in the previous six months) attending tertiary, drug and alcohol and primary health care services. Persons with chronic HCV genotype 1 or 4 and recent injecting drug use (in the previous 6 months) or receiving OST will receive therapy with elbasvir/grazoprevir.

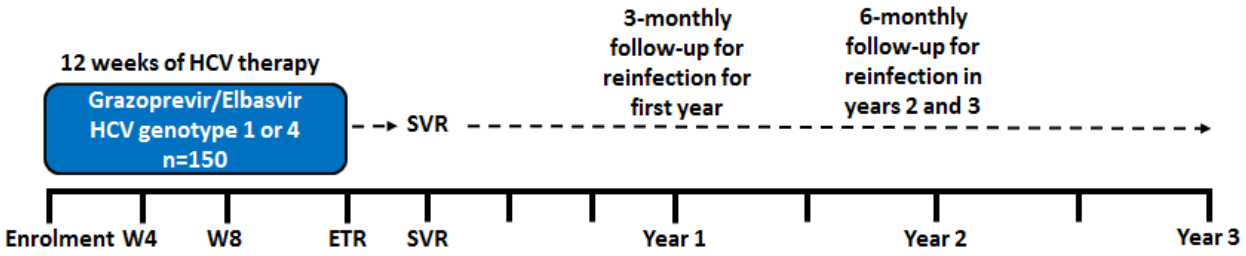

Figure 1. Cohort Study Schema

The study consists of a treatment phase (12 weeks) and a follow-up phase (up to 3 years) where participants will be followed every 3 months for the first year and every 6 months in years 2-3 to evaluate treatment response and reinfection.

5. Treatment of participants

It is estimated that a total 150 participants with HCV genotype 1 or 4 will be treated (approximately 100 in 2017 and 50 in 2018). All participants will be treated with a ribavirin-free regimen of elbasvir/grazoprevir for 12 weeks (all treatment-naïve) as per the recommended indication.

Therapy with elbasvir/grazoprevir will be administered within indication utilising PBS drug therefore a Clinical Trials Notification (CTN) is not required.

5.1 Dosage and administration

Elbasvir/grazoprevir is to be administered once daily with or without food. Each subject must be given instructions to maintain approximately the same daily dosing interval between study drug doses. Subjects should be instructed to swallow the study medication tablet whole. Subjects should be instructed to only remove the tablet immediately prior to dosing.

For a missed dose of study medication, subjects should be instructed to take the missed dose of study medication as soon as possible during the same day. However, no more than the daily dose of elbasvir/grazoprevir should be taken on any calendar day. Subjects should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

Participants will be required to complete a monthly adherence questionnaire and unused medication will be returned for a pill count.

Elbasvir/grazoprevir is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C) due to the expected significantly increased grazoprevir plasma concentration and increased risk of alanine aminotransferase (ALT) elevations.

5.2 Elbasvir/grazoprevir prior and concomitant medications

Elbasvir/grazoprevir is contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong inducers of cytochrome P450 3A (CYP3A), and efavirenz. See Table 2 for details.

Table 2: Drugs that are contraindicated with elbasvir/grazoprevir

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comment*
Anticonvulsants	Phenytoin Carbamazepine	May lead to loss of virologic response to elbasvir/grazoprevir due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by strong CYP3A induction.
Antimycobacterials	Rifampin	May lead to loss of virologic response to elbasvir/grazoprevir due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by strong CYP3A induction.
Herbal Products	St. John's Wort (*Hypericum perforatum*)	May lead to loss of virologic response to elbasvir/grazoprevir due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by strong CYP3A induction.
HIV Medications	Efavirenz†	May lead to loss of virologic response to elbasvir/grazoprevir due to significant decreases in elbasvir and grazoprevir plasma concentrations caused by CYP3A induction.
HIV Medications	Atazanavir Darunavir Lopinavir Saquinavir Tipranavir	May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition.
Immunosuppressants	Cyclosporine	May increase the risk of ALT elevations due to a significant increase in grazoprevir plasma concentrations caused by OATP1B1/3 inhibition.

*This table is not a comprehensive list of all drugs that inhibit OATP1B1/3 or strongly induce CYP3A.

†Efavirenz is included as a strong CYP3A inducer in this table, since co-administration reduced grazoprevir exposure by ≥80%.

Should any participant need to initiate treatment with an excluded concomitant medication during the study, the Medical Monitor, A/Prof Gail Matthews must be consulted prior to the initiation of any excluded medication. In the event that an excluded medication is initiated prior to discussion with A/Prof Gail Matthews, she must be made aware of the use of the excluded medication as soon as possible. A/Prof Gail Matthews' contact details are listed on the cover of this protocol.

6. Study procedures

6.1 Visits and Procedures

The following assessments must be conducted at study visits as per the schedule of assessments:

Vital signs & physical measurements	Sitting systolic and diastolic blood pressure, heart rate, body weight[a], height[a]
Fibroscan	Within 12 months prior to screening
Biochemistry	Creatinine, glucose, sodium, chloride, and potassium
Liver Function Tests	ALT, AST, GGT, total bilirubin, albumin, alkaline phosphatase, total protein
Full Blood Count	Haemoglobin, haematocrit , White Blood Cells, platelets, neutrophils
HCV RNA	Must be quantitative at Screening (within 12 weeks prior to Screening) and Week 4
HCV Genotype	Within 12 weeks prior to screening
HBV Serology	Anti-HBc, HBsAg and Anti-HBs testing (within 6 months prior to Screening)
HIV Serology	HIV antibody (within 6 months prior to Screening)
HCG Pregnancy Test	For women of childbearing potential, a negative urine (or serum) HCG test at screening, baseline, weeks 4, 8, week 12 (ETR) and week 14 (home test allowed at week 14)
Questionnaires	Behavioural survey, abbreviated behavioural survey, adherence questionnaire and EQ-5D
Finger-stick point-of-care HCV RNA testing (POC)	At sub-study sites only

[a] at screening only

The following assessments and procedures must be performed at each visit as specified below:

Initial screening period (Week -6 to Week 0)

- Informed consent
- Medical history
- Vital signs and physical measurements
- Quantitative HCV RNA and genotype (Local Laboratory)
- LFTs, FBC and biochemistry
- HIV & HBV serology
- Fibroscan
- Pregnancy test (females of child bearing potential only)
- Concomitant medication
- Study questionnaires (Behavioural and EQ-5D)
- Research specimen collection (EDTA plasma & whole blood)
- Finger-stick point-of-care HCV RNA testing (Sub-study sites only)

Baseline visit (Week 0)

- Vital signs and physical measurements
- LFTs, FBC and biochemistry
- Pregnancy test (females of child bearing potential only)
- Serious Adverse Events
- Concomitant medication
- Study questionnaires (Abbreviated Behavioural)
- Research specimen collection (EDTA plasma & whole blood)
- Finger-stick point-of-care HCV RNA testing (Sub-study sites only)

On-Treatment Visits

Week 4 (+/- 7 days)

- Quantitative HCV RNA (Local laboratory)
- Pregnancy test (females of child bearing potential only)
- Serious Adverse Events
- Research specimen collection (EDTA plasma)
- Study questionnaire (Adherence)
- Finger-stick point-of-care HCV RNA testing (Sub-study sites only)

Week 8 (+/- 7 days)

- LFTs – ALT only
- Pregnancy test (females of child bearing potential only)
- Serious Adverse Events
- Research specimen collection (EDTA plasma)
- Study questionnaire (Adherence)

End of Treatment (ETR) - Week 12 (+/-14 days)

- Qualitative HCV RNA (where available, otherwise quantitative), (Local laboratory)
- LFTs, FBC and biochemistry
- Pregnancy test (females of child bearing potential only)
- Serious Adverse Events
- Concomitant medication
- Study questionnaires (Abbreviated Behavioural, Adherence, and EQ-5D)
- Research specimen collection (EDTA plasma)

Post Treatment Follow-up Visits

Post Treatment Week 12 (SVR12) - Week 24 (+/- 14 days)

- Qualitative HCV RNA (Where available, otherwise quantitative) (Local laboratory)
- LFTs, FBC and biochemistry
- Pregnancy test (females of child bearing potential only) (at 14 days post end of treatment – home test allowed)
- Serious Adverse Events (up to week 16 (SVR4) only)
- Study questionnaires (Abbreviated Behavioural and EQ-5D)
- Research specimen collection (EDTA plasma)
- Finger-stick point-of-care HCV RNA testing (Sub-study sites only)

Post Treatment Weeks 36 (FU1), 48 (FU2), 60 (FU3), 84 (FU4), 108 (FU5), 132 (FU6) and 156 (FU7) (+/- 14 days)

- Qualitative HCV RNA (Where available, otherwise quantitative) (Local laboratory)
- Study questionnaires (Abbreviated Behavioural)
- Research specimen collection (EDTA plasma)
- Finger-stick point-of-care HCV RNA testing (Sub-study sites only)

If a patient has suspected viral relapse or HCV reinfection HCV RNA sequencing will be performed. No additional sample is required.

Monitoring of HBV reactivation

At screening, all patients will be tested for evidence of current (Hepatitis B surface antigen positive) and prior (anti-Hepatitis B core antibody positive) HBV infection before initiation of treatment. Patients with current HBV infection will be excluded. Patients with evidence of prior HBV infection only will be enrolled.

Patients with evidence of prior HBV infection will be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. LFTs will be performed 4-weekly during treatment. In the setting of a clinically significant ALT elevation or symptoms and signs of acute hepatitis, HBV DNA testing will be performed to assess for reactivation. Appropriate management for HBV infection will be initiated by the site investigator as clinically indicated.

Sites should advise patients of the risk of HBV reactivation and instruct patients on the signs and symptoms of reactivation (such as lethargy, nausea, jaundice). Patients should be encouraged to report any signs or symptoms.

6.2 Study Questionnaires

All subjects will undertake a number of study questionnaires at screening, baseline, and selected follow-up visits.

The Behavioural Questionnaire

The study staff will assist participants to complete this questionnaire. The behavioural survey will collect information on the following:

- Demographics
- HIV and drug treatment history
- Drug and alcohol usage
- Treatment acceptance and willingness (prior to treatment commencement only)
- Attitudes and behaviours associated with HCV reinfection
- Injecting risk behaviours (including information about injecting sharing partners and equipment sharing)

An abbreviated behavioural questionnaire (follow-up) will be administered at subsequent time points during the study.

Health Outcomes Survey (EQ-5D)

The EQ-5D health questionnaire 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.

Adherence Survey

Adherence to elbasvir/grazoprevir will be assessed by a four-weekly structured self-report adherence questionnaire and four-weekly pill count.

6.3 Linkage of data (optional)

Participants are invited to consent to link their data collected during the DARLO-C study with routinely collected data from a range of population Health and Incarceration databases and registers.

The collection of participant names, date of birth, sex, and post code in DARLO-C is essential for accurate data linkage. Participant data will be linked to a variety of health variables including information on hepatitis C notifications, HIV/AIDS notifications, use of hepatitis services, use of prescription medication (including hepatitis C treatment), OST, incarceration, hospitalizations, emergency department use, cancer, and mortality through the New South Wales Centre for Health Record Linkage (www.cherel.org.au), and the Australian Institute of Health and Welfare (www.aihw.gov.au). Linkage will be both retrospective and prospective, with the time period covered dependent on the properties of the specific data set. Approval from the NSW Population and Health Services Research Ethics Committee, and all other required Human Research Ethics Committees will be sought prior to any data linkage being performed.

Participants are given the option to opt out of the health and incarceration data linkage component of this study on the Participant Consent Form. Participants not wishing to have their data used in the data linkage studies may still enroll in DARLO-C.

7. Recording and reporting Adverse Events (AEs)

7.1 Definitions of Adverse Events, Adverse Reactions and Serious Adverse Events

7.1.1 Definitions of Adverse Events, Adverse Reactions and Serious Adverse Events

The medications for this study are supplied via the PBS. Adverse events and adverse drug reactions will be reported to the Therapeutic Goods Administration as per standard practice for PBS prescribed medications. Only serious adverse events will be reported as detailed below.

7.1.2 Definition of Serious Adverse Events (Including Serious Adverse Drug Reactions)

The definition of a SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

  (Note: the term “life-threatening” in the definition of “serious” refers to an event/reaction in which the participant was at risk of death at the time of event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)

- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Results in a medically important event or reaction (includes infections from contaminated medicinal product/s). Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not require hospitalization, or development of drug dependency or drug abuse.
- Is an overdose of study medication (whether accidental or intentional)
- Cancer (that is not the condition under the study)*

All Serious Adverse Events, regardless of causal relationship to the investigational product, must be forwarded to **Merck Worldwide Product Safety** via fax (+1 215 993-1220) within 2 working days of the investigator becoming aware of the event and no later than 3 calendar days.
Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the outcomes listed in the definition above.

Serious adverse events are collected from screening through to 4 weeks post end of treatment (SVR4).

7.2 Assessment of Serious Adverse Events

7.2.1 Assessment of Causality for Study Drugs and Procedures

The investigator or designee must assess each adverse event for the following:

Relationship

Unlikely: An adverse event that is unlikely to be related to the use of the drug or procedures

Possibly: An adverse event that might be related to the use of the drug or procedures

Probably: An adverse event that is likely to be related to the use of the drug or procedures

7.2.2 Assessment of Severity

The investigator or designee must assess each adverse event for the following:

Severity

Mild: Discomfort noticed but no disruption of normal daily activity

Moderate: Discomfort sufficient to reduce or affect normal daily activity

Severe: Incapacitating with inability to work or perform normal daily activity

Life threatening: Represents an immediate threat to life

7.3 Reporting Requirements

7.3.1 Adverse Events

An adverse event means any unfavourable and unintended change in the structure, function, or chemistry of the body temporally associated with any use of the Merck product whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a pre-existing condition which is temporally associated with the use of the product, is also an adverse experience.

Adverse events and adverse drug reactions will be reported to the Therapeutic Goods Administration as per standard practice for PBS prescribed medications.

7.3.2 Serious Adverse Events

All serious adverse events (SAEs) should be reported within TWO (2) WORKING DAYS of becoming aware of the event to the Kirby Institute and Merck by fax on the Serious Adverse Event Reporting Form. The appropriate Serious Event form should be used. Reports should be followed promptly by detailed, written follow-up reports when all information is not included in the initial report. Follow-up reports should be reported within TWO (2) WORKING DAYS also. The immediate and follow up reports should identify participants by unique code numbers assigned to study participants rather than personal identification. The investigator must also comply with all applicable ethical and regulatory requirement/s relating to the reporting of serious adverse events.

Any serious adverse event that is ongoing at the post-study follow-up visit must be followed until resolution or until the event stabilizes (for those events that will not resolve).

For deaths, the Principal Investigator will supply the sponsor and the IRB/IEC with any additional requested information (e.g. death certificate, autopsy reports and medical reports).

Merck (Attn: Worldwide Product Safety; FAX +1 215 993-1220) will be provided with copies of all serious adverse experiences regardless of causality to use of a Merck product within two working days. Additionally, any pregnancy occurring in association with use of a Merck Product will be reported (Attn: Worldwide Product Safety; FAX +1 215 993-1220).

A copy of all 15 Day Reports is submitted as required by local regulators by the investigator. This submission will be cross referenced according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, a copy of these reports will be submitted to Merck (Attn: Worldwide Product Safety; FAX +1 215 993-1220) at the time of submission to local regulator.

SAE reports must be submitted to **BOTH the Kirby Institute AND Merck:**

Kirby Institute:	Fax:	+61 2 9385-9214.
Merck Worldwide Product Safety:	Fax:	+1 215 993 1220

7.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Project Team in collaboration with the Medical Officer will review and identify all serious events which fit the criteria of a SUSAR and requiring expedited reporting to relevant parties.

The definition of a SUSAR is a serious adverse event which is both suspected as being related to the drug (i.e. has a reasonable suspected causal relationship) and is unexpected) whereby the nature and severity is not consistent with known information (e.g. the Investigator's Brochure).

The sponsor must expedite the reporting of all SUSARs to all concerned investigators/institutions, IRB/IEC/s, and regulatory authorities within the reporting timeframe. Reports must comply with the applicable regulatory requirements and ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Researchers must inform the IRB/IEC and regulatory authorities of all SUSARs that occur during the study that may affect the conduct of the study or the safety of the participants or their willingness to continue participation in the study. Researchers must inform the IRB/IEC as soon as possible of any new information from other published or unpublished studies which may have an impact on the continued ethical acceptability of the study or which may indicate the need for amendments to the study protocol.

All SAEs and SUSARs will be reported to the approving Human Research Ethics Committee as per local policy.

Coding

Serious Adverse Events will be assigned preferred terms and categorised into system organ classes according to the Medical Dictionary for Drug Regulatory Affairs (MedDRA) classification of the WHO terminology.

8. Packaging, labeling, storage and accountability of clinical trial supplies

All study drugs will be supplied via PBS following PBAC listing. The drugs should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist.

Medications must be stored, and dispensed according to PBS regulations as per standard practice.

8.1 Formulation

The elbasvir/grazoprevir (50mg/100mg) tablets are beige, oval-shaped, film-coated, debossed with "770" on one side and plain on the other. In addition to the active ingredients the tablets also contain the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, sodium chloride, sodium lauryl sulfate, and vitamin E polyethylene glycol succinate.

8.2 Packaging and Labelling

The tablets are packaged into a carton (NDC 0006-3074-02) containing two (2) 14-count child-resistant dose packs for a total of 28 tablets.

8.3 Storage and handling

Elbasvir/grazoprevir packs should be stored in the original packs at controlled room temperature until required for administration. Elbasvir/grazoprevir should be stored at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

Subjects should be counselled to store elbasvir/grazoprevir blister packs at room temperature not in the refrigerator.

All drug products should be stored in a securely locked area, assessable only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied.

9. Biological samples

9.1 Laboratory supplies and sample processing

Laboratory supplies for collection of research specimens (plasma and whole blood) will be supplied by the Kirby Institute.

The following blood samples will be collected as time point specified in the schedule of assessments:

1. 10 mL EDTA plasma for HCV RNA testing and future HCV related research (20 mL will be collected at Screening and Baseline visits);
2. 4mL whole blood for human genomic DNA analysis collected at the screening and baseline visits only.

Samples will be collected by sites and then processed and stored at -70°C at the site local laboratory for bulk shipment to the Kirby Institute laboratory. Detailed sample processing instructions will be provided in the laboratory manual.

EDTA plasma samples will be used for study endpoint analysis. HCV viral load will be measured using in-house and commercial assays. Sequencing of the viral genome will also be performed as a more accurate means of genotyping. Data generated from the sequencing may also be used to distinguish relapse from reinfection and to examine the prevalence of mixed infection.

HCV sequencing/resistance testing

Sanger sequencing will be performed on a pre-treatment sample on all participants. Complementary RNA will be generated using SuperScript® VILO™ cDNA Synthesis Kit (Life Technologies, Carlsbad, CA) with random hexamers. Sequencing of NS5A will be performed on all participants. A fragment of the HCV genome covering Core, Envelope-1, hypervariable region-1 and beginning of Envelope-2 (E2) will be amplified using a method previously described. Sequencing of NS3/4, NS5A, NS5B, and full-length next generation sequencing may also be performed. Purified amplicons will be sequenced using the Sanger method and sequence chromatograms processed using RECall: a fully automated sequence analysis pipeline. Subtypes will be determined using the Oxford HCV Automated Subtype Tool. Reverse transcription, PCR and sequencing reaction and thermal cycling conditions will be performed as previously described. Further, Sanger sequencing and next generation sequencing will be performed among samples with persistent infection at risk of HCV mixed infection (e.g. treatment non-response). Lastly, Sanger sequencing and next generation sequencing will be performed among samples with HCV recurrence to distinguish HCV reinfection from viral relapse (detectable HCV RNA following HCV virological suppression).

HCV RNA point of Care testing (sub-study sites only)

Point of care testing for HCV RNA detection will be performed at each visit at selected sub study sites using the Xpert® HCV Viral Load assay for samples collected by finger-stick capillary whole-blood as described below. This point of care testing will be undertaken in addition to the standard of care (local laboratory).

The capillary whole-blood sample is collected from participants via a finger-stick [MiniCollect® Safety Lancet (Order Number 450429), Greiner Bio-One, Monroe, Frickenhausen, Germany] using procedures recommended by the World Health Organization[31] and collected into a 100µL minivette collection tube [Minivette® POCT 100µl (Order number 17.2111.100), Sarstedt, Nümbrech, Germany].

9.2 Shipping of biological samples

Samples must only be shipped to the Kirby Institute laboratory on the instruction from the Study Coordinator.

It is the responsibility of each site Principal Investigator to ensure that all site staff handling, packaging, and/or shipping biological samples understand and comply with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods and/or diagnostic specimens.

9.3 Future use of biological samples

After the samples have been analysed for the study endpoints as specified in the protocol, remaining samples will be stored for use in future Human Research Ethics Committee approved hepatitis C related research. Additional consent will not be sought for this storage and future use. It is not optional. Subjects not wishing to have their samples stored or used in future hepatitis C related research will not be eligible to participate in this study.

10. Statistics

The statistical team and investigators at the Kirby Institute will be responsible for analysing the study data.

Primary Objective: **To evaluate the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment (SVR12) following elbasvir/grazoprevir therapy among PWID with recent injecting drug use or receiving OST and chronic HCV genotype 1 or 4 infection and evaluate demographic and clinical predictors of non-response.**

Hypothesis: Elbasvir/grazoprevir therapy will lead to SVR12 >90% among PWID with recent injecting drug use or receiving OST and chronic HCV genotype 1 or 4 infection.

Outcome: The primary endpoint for this aim is the proportion of participants with a treatment response (measured by SVR, undetectable HCV RNA 12 weeks after the completion of therapy).

Statistical analysis: The proportion of people with a response to HCV therapy will be evaluated. Factors associated with treatment response (as measured by SVR) will be assessed by univariate and multivariate logistic regression analyses. Factors hypothesized to be associated with HCV treatment response will be assessed including: sociodemographic factors (housing and education), injecting behaviours (recent injecting drug use prior to and during therapy and type of drug injected), and clinical factors (opioid substitution treatment, HCV genotype, fibrosis stage).

Sample Size: Assuming an overall SVR of 90% (135 of 150), the 95% confidence interval around this estimate will be 84.0% to 94.3%. This study will have robust power to examine the effect of treatment setting on SVR: e.g. 80% power to detect an odds ratio of 0.39 or 2.59 or more extreme (with alpha=0.05) for a variable that is 50% prevalent.

Secondary Objective: Estimate incidence and predictors of HCV reinfection after successful elbasvir/grazoprevir.

Hypothesis 2.1: The incidence of HCV reinfection following successful elbasvir/grazoprevir therapy will be <8 per 100 p-yrs among people with recent injecting drug use or receiving OST.
Hypothesis 2.2: HCV reinfection will be associated with ongoing ≥daily injecting drug use, and needle and syringe borrowing. OST and high-coverage access to needle and syringes will be associated with reduced HCV reinfection.

Outcome: Incidence of HCV reinfection following successful elbasvir/grazoprevir therapy.

Statistical analysis: Rates of HCV reinfection will be calculated using person-time of observation. The estimated date of reinfection will be calculated as the midpoint between the dates of the last undetectable HCV RNA test and the first detectable HCV RNA test at the time of HCV reinfection. Time at risk will commence at the date of undetectable HCV RNA at end of treatment and end at the first of estimated date of re-infection, death, loss-to-follow up or end of study. Confidence intervals for rates will be calculated using a Poisson distribution.

Cox proportional hazards analyses (or other appropriate regression models) will be used to estimate crude and adjusted hazard ratios and corresponding 95%CI to evaluate factors associated with reinfection. Factors hypothesised to be associated with reinfection include demographic factors (age, sex), injecting behaviours (current injecting drug use, daily injecting, type of drug injected, injecting equipment borrowing), use of needle and syringe programs, and opioid substitution treatment with time-updated co-variates.

Sample Size: Overall, based on previous reports of HCV reinfection among current PWID[32], and assuming loss to follow-up is 20% per year, it is estimated that the overall reinfection rate will be 8/100 p-yrs (95%CI 5.3, 11.4; 337 p-yrs of follow-up; 27 reinfections). Overall (135 with successful therapy, 27 reinfections), we will have 80% power to detect a hazards ratio (HR) of 2.94 or greater (with alpha=0.05) for a variable 50% prevalent (e.g. ongoing injecting drug use).

Collateral research

Evaluation of HCV phylogenetics

All participants enrolled in this study with available plasma samples at screening or baseline (HCV RNA detectable) will be sequenced for HCV RNA for evaluation of HCV phylogenetics.

Evaluation of HCV re-infection

All participants with an ETR will be followed for up to three years post-ETR to assess HCV reinfection. Participants with viral recurrence (detectable HCV RNA following HCV virological suppression, reinfection rate: 8/100 person years, estimated n=27 x 2 samples=54 total samples) will be identified and available follow-up plasma samples assessed for re-infection.

The sensitivity and specificity of the Xpert® HCV Viral Load point-of-care test for detection of HCV RNA in plasma samples collected via venepuncture and capillary whole-blood samples collected by finger-stick will be assessed using both detectable and quantifiable thresholds (limit of quantification >10 IU/mL) for each assay compared to the local laboratory HCV RNA assay in plasma as the gold standard. A Bland-Altman difference plot will be generated to assess bias and agreement measurements, including limits of agreement, between the quantification of HCV by Xpert® HCV Viral Load both sample types, compared to the local laboratory HCV RNA assay in plasma.

11. Data Safety and Monitoring Board (DSMB).

A Data Safety Monitoring Board will not be used for this study as the drug is being prescribed and supplied according to indication via the PBS.

The study Medical Monitor, A/Prof Gail Matthews will oversee all serious adverse events for DARLO-C. A/Prof Matthews is independent of the study project management team and Protocol Steering Committee. A/Prof Matthews is also a clinician at St Vincent's Hospital which is one of the recruiting sites. Should an SAE occur in a patient under A/Prof Matthews's care the project team will seek an independent review of the SAE from a suitably qualified independent Infectious Diseases Specialist or Hepatologist.

12. Data collection, source documents and record retention

The Principal Investigator and the institution where the study will be conducted will permit study-related monitoring, audits, ethics committee review and regulatory inspection providing direct access to source documents.

Data will be collected on study specific electronic or paper copy case record forms. The Principal Investigator is responsible for ensuring the data collected are complete, accurate and recorded in a timely manner.

12.1 Submission of data

Electronic CRFs: 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 will visit sites to conduct source document verification. The number of visits will depend upon study complexity and recruitment rate; however, the monitor will conduct a minimum of two source data verification visits during the study. These should occur shortly after randomization of the first participant(s) and following completion of all study visits.

The Principal Investigator is responsible for retaining all 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.

12.2 Linkage of data

Study data will be periodically linked with public registries, for example the National Notifiable Diseases Database, hospital morbidity databases, cancer and death registries. Ethics approval from the Population Health Ethics Committee, and all other required Human Research Ethics Committees will be obtained prior to any linkage study being performed.

12.3 Retention of Data Linkage Records

All datasets relating to the project will be held at CHeRel and AIHW for at least 12 months following the last update so that the linkage can be recreated should a problem with the linkage be identified at the

time of analysis. The electronic data files will be retained by the Kirby Institute for 7 years after the publication of the study results. At the end of this period, the Kirby Institute Information Technology staff will follow standard operating procedures to delete the archived electronic records.

12.4 Archiving

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

13. Ethics committee/regulatory approval and informed consent

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

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/IEC 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/IEC reporting requirements for all adverse events, annual updates and end of study reports and must agree to abide by any IRB/IEC 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).

14. Confidentiality of data

14.1 Confidentiality of participant records

By signing the Clinical Trial Agreement, the site Principal Investigator agrees that the sponsor, IRB/IEC or regulatory authorities may consult and/or copy study documents to verify information in the case report form. By signing the consent form the participant agrees to these processes. The following wording may be included in the protocol.

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/IEC 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 Personal Information for Data Linkage

The Kirby Institute has a strict participant data confidentiality policy. An independent Data Custodian will be appointed for this study to manage the identifiable data required for data linkage. The Data Custodian will not be involved in the conduct of the study, and in most cases, will be a Data Manager. The role of the Data Custodian is to ensure that identifiable information is collected, used, accessed, stored and destroyed in line with HREC approval and in accordance with the participant data confidentiality policy and the NHMRC National Statement on Ethical Conduct in Research Involving Humans (2007). The Data Custodian will be responsible for the exchange of information with data linkage services, and for provision of de-identified linked records back to the person/s who requested the data linkage. Once the linked data file is received by the Data Custodian at the Kirby Institute, all study data will be transferred to a secure network protected by a firewall and individual files will also be password-protected. All results will be published in a form that will not allow individuals to be identified, that is, in tabular, aggregate form only; no individual results will be disclosed.

14.2 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.

15. Governance

The study is sponsored by UNSW and coordinated through the Kirby Institute. It is funded by the University of New South Wales (UNSW) and Merck Sharpe and Dohme. The Kirby Institute has established governance and implementation structures which use resources efficiently to deliver program objectives on schedule.

16. 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.

17. 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.

18. List of References

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19. Abbreviations List

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
DAA	Direct Acting Antiviral
End of treatment	Date of last dose of treatment
ETR	End of Treatment Response, undetectable HCV RNA at the completion of treatment
FBC	Full Blood Count (haemoglobin, WCC including differentials, platelets)
HCV	Hepatitis C Virus
IDUs	Injection Drug Users
IEC	Institutional Ethics Committee (Human Research Ethics Committee)
INR	International Normalized Ratio
IRB	Institutional Review Board (Human Research Ethics Committee)
LFTs	Liver Function Tests – albumin, ALT, AST, alkaline phosphatase, GGT, total bilirubin, total protein
LLOQ	Lower Limit Of Quantification
GGT	Gamma Glutamic Transpeptidase
Hgb	Haemoglobin
OST	Opioid Substitution Therapy
PEG-IFN	Pegylated interferon alfa 2a
PWID	People Who Inject Drugs
POC	Point of Care
RAS	Resistant Associated Substitutions
Reinfection	Detection of infection with an HCV strain which was distinct from the primary infecting strain among participants with either spontaneous or treatment-induced HCV virological suppression (≤15 IU/ml on Roche TaqMan).
SVR12	Sustained Virological Response, HCV RNA undetectable 12 weeks post-treatment
SVR24	Sustained Virological Response, HCV RNA undetectable 24 weeks post-treatment
Undetectable HCV RNA	HCV RNA results that are <15 IU/ml (non-quantifiable), but “detectable” will be considered as undetectable HCV RNA
WCC	White Cell Count