A multi-centre, practice-level, stepped wedge cluster randomized controlled trial to compare point-of-care HCV RNA testing, dried blood spot testing, and standard of care to enhance treatment uptake among people with HCV who have recently injected drugs attending needle and syringe programs: the TEMPO study

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1.0 Protocol synopsis

Title	A multi-centre, practice-level, stepped wedge cluster randomized, controlled trial to compare point-of-care HCV RNA testing, dried blood spot testing, and standard of care to enhance treatment uptake among people with HCV who have recently injected drugs attending needle and syringe programs: the TEMPO study
Protocol registration no.	NCT04014179
Background and rationale	Viral hepatitis is the 7th leading cause of mortality globally, having surpassed the number of annual deaths due to HIV, malaria, and tuberculosis[1]. Globally, 71 million people are living with HCV virus (HCV), with 6.1 million having recently injected drugs[2], and an additional burden among former people who inject drugs (PWID). In Australia, the majority of existing (80%) and new (90% of 9,000 annually) cases are in PWID[3,4]. The advent of simple, well-tolerated, direct-acting antiviral (DAA) HCV therapies with cure rates >95% is one of the most exciting medical advances in decades[5]. Successful therapy leads to improved quality of life and reduced morbidity/mortality[6], providing an opportunity to reverse the rising burden of advanced liver disease. The World Health Organization (WHO) has set a goal to eliminate HCV as a global public health threat by 2030, with targets to increase HCV diagnoses and treatment, and reduce new infections and liver-related mortality[7]. However, among the 71 million people with HCV worldwide, less than 20% have been diagnosed and less than 10% have received treatment[8]. In Australia, HCV DAA treatment uptake initially exceeded expectations (2016: 32,400 treated; 14% with HCV). But, the number of people initiating therapy has continued to decline (2017: 21,370; 2017: ~2,000/month; 2018: ~1,400/month). Improving HCV testing and treatment to reduce disease burden is a key aim of global and national HCV strategies[9,10]. Globally, HCV testing and diagnosis remains inadequate[11]. Current testing algorithms involve detection of HCV antibodies to confirm exposure, followed by HCV RNA testing to detect active infection. This two-step pathway requires up to 5 visits to practitioners and off-site phlebotomists, leading to a drop-off in those receiving a diagnosis of active infection[12]. Standard of care HCV testing is also limited by a lack of on-site phlebotomists (requiring off-site referral) and poor venous access (a major problem among people who inject drugs). In Australia, 81% have had an antibody-based HCV diagnosis, but only 47% have been tested for active infection[12]. As highlighted in the *4th National HCV Strategy*, a Priority Action is to "improve referral and access to high quality support services at the time of diagnosis for people with HCV to initiate a pathway to care". In a systematic review of interventions to improve HCV care among PWID led by our group[13], key interventions to enhance HCV testing

	(on-site testing; and dried blood spot testing), linkage to care (facilitated referral for HCV assessment) and treatment (integrated HCV care) were identified. Studies were limited by small sample sizes, and the lack of randomized controlled trials or comparative studies in the DAA era. Well-designed studies evaluating interventions to enhance HCV testing/treatment among PWID are needed. Dried blood spot testing can enhance HCV testing and linkage to care[13,14]. Benefits of dried blood spots include: 1) avoiding the need for phlebotomy; 2) enables testing for HCV antibodies (exposure) and RNA (active infection); 3) easy to transport/store; 4) can test for other viruses (e.g. HIV); 5) sample collection can be performed by peers or self-collection[11]. Also, dried blood spot testing has excellent sensitivity and specificity for the detection of active HCV [15]. Point-of-care HCV testing has also been demonstrated to increase testing and linkage to care[14]. Our group led the first evaluation of a finger-stick point-of-care HCV RNA assay[16,17] as part of a clinical observational study in drug treatment clinics and needle and syringe programs (NSPs), enabling same-day diagnosis of active infection (HCV RNA) in one hour (sensitivity and specificity, 100%)[17]. The findings have informed regulatory approval submissions in Europe and Australia. The next step is to translate this novel discovery into routine clinical practice. There is an unprecedented opportunity to evaluate whether finger-stick point-of-care HCV RNA testing could be integrated into routine practice to enhance HCV testing and treatment among PWID. Settings for HCV care for PWID include hospitals, primary care, drug treatment clinics, and prisons[18]. But, there is a need to link less service-connected PWID to HCV care. In Australia, there is broad NSP access (3,627 NSPs; 98 primary sites)[19] and PWID regularly attend NSPs to collect injecting equipment. NSPs offer an opportunity to engage with PWID who may not be engaged in health services. Further, on-site testing improves linkage to HCV treatment[13]. As highlighted in the *National HCV Strategy*, "Peer support programs offering education may improve engagement in HCV assessment/treatment[20]" and "The role of peer educators to increase testing should be explored. Such services should be linked to peer-based drug-user organisations…and NSPs." The TEMPO study will compare point-of-care HCV RNA testing, dried blood spot testing, and standard of care as strategies to enhance HCV treatment uptake among people with HCV and recent injecting drug use attending NSP services.
Study objectives	**Primary objective** To compare the proportion of HCV RNA positive participants who initiate HCV treatment at 12 weeks following enrolment between those who receive point-of-care HCV RNA testing, dried blood spot testing, and standard of care.

	Secondary objective(s) Among those who receive point-of-care HCV RNA testing, dried blood spot testing, and standard of care: 1. To compare the time to HCV DAA treatment initiation among those who initiate treatment. 2. To compare the proportion of HCV RNA positive participants who initiate HCV DAA treatment at 24 weeks following enrolment. 3. To compare the proportion of HCV RNA positive participants who initiate HCV DAA treatment at 12 months (52 weeks) following enrolment. 4. To compare the proportion of participants who complete HCV DAA treatment. 5. To compare the proportion of participants who achieve an SVR (defined as HCV RNA below the lower limit of quantitation at post treatment week 12). 6. To compare the proportion of participants who are HCV RNA negative at 12 weeks. 7. To compare the proportion of participants who are HCV RNA negative at 24 weeks. 8. To compare the proportion of participants who are HCV RNA negative at 12 months (52 weeks). 9. To evaluate the incidence of HCV reinfection following successful HCV therapy. 10. To compare the cost-effectiveness of these different testing strategies.
Participant population	It is anticipated that approximately 3,300 participants (assuming an HCV RNA prevalence of 20%) will be screened for HCV infection using either dried blood spot testing, point-of-care testing or standard of care testing. Screening in the intervention arm will continue until a total of 220 HCV RNA positive participants (~20 participants per site) are enrolled in the intervention arm (either dried blood spot and point-of-care). In the delayed intervention arm, 220 HCV RNA positive participants (~20 participants per site) will be enrolled in the control (standard of care) phase and then clusters/sites will be switched to intervention (either dried blood spot and point-of-care) – at which screening will continue until a total of 220 HCV RNA positive participants (~20 participants per site) are enrolled. Hence a total of 660 HCV RNA positive participants. **Identification and inclusion criteria for clusters** NSPs must meet the following criteria to participate in the study: a. Be a primary NSP site, defined as, providing services to PWID staffed by specialist workers b. Have the capacity for on-site nursing support or externally, and HCV treatment provision c. Provide services to > 60 people per week.

	Potential eligible NSP sites will be identified from existing service centres in Australia and will complete site feasibility assessment to ensure the inclusion criteria are met. NSP sites may have prior experience or are active in surveillance and clinical studies, but it is not mandatory to have clinical research experience. **Inclusion criteria for participants** Attendees of the NSP service are eligible for inclusion if the following criteria are met: a. Provided written informed consent b. ≥ 18 years of age c. Recent injecting drug use – defined as self-reported use within the previous six months. **Exclusion criteria for participants** a. Is unable or unwilling to provide informed consent or abide by the requirements of the study. **Eligibility criteria for treatment** Participants who have a quantifiable HCV RNA will be assessed for treatment eligibility. Those in the point-of-care arm will be able to complete the treatment work-up on the day of HCV screening. Those in the control arm and dried blood spot arm will have treatment work-up as per standard of care once the HCV RNA test results are received from the laboratory. **Inclusion criteria for treatment** Participants are eligible for HCV DAA treatment if all of the following inclusion criteria are met: a. Quantifiable HCV RNA at screening b. An assessment of liver cirrhosis status is performed in the intervention arm, i.e. point-of-care and dried blood spot arm: i) If pathology is available to determine an APRI in the previous 12 months, and is <1.0, then a FibroScan is not required. OR ii) If pathology is not available for APRI, and no FibroScan is available, then phlebotomy can be taken at baseline and treatment commenced. Once pathology is returned, if >1.0 then an ultrasound can be organised. In these cases (unknown stage of disease) would be preferable to use SOF/VEL, given standard duration. c. In the opinion of the Investigator, the participant is suitable for treatment within an NSP-based setting. **Exclusion criteria for treatment**

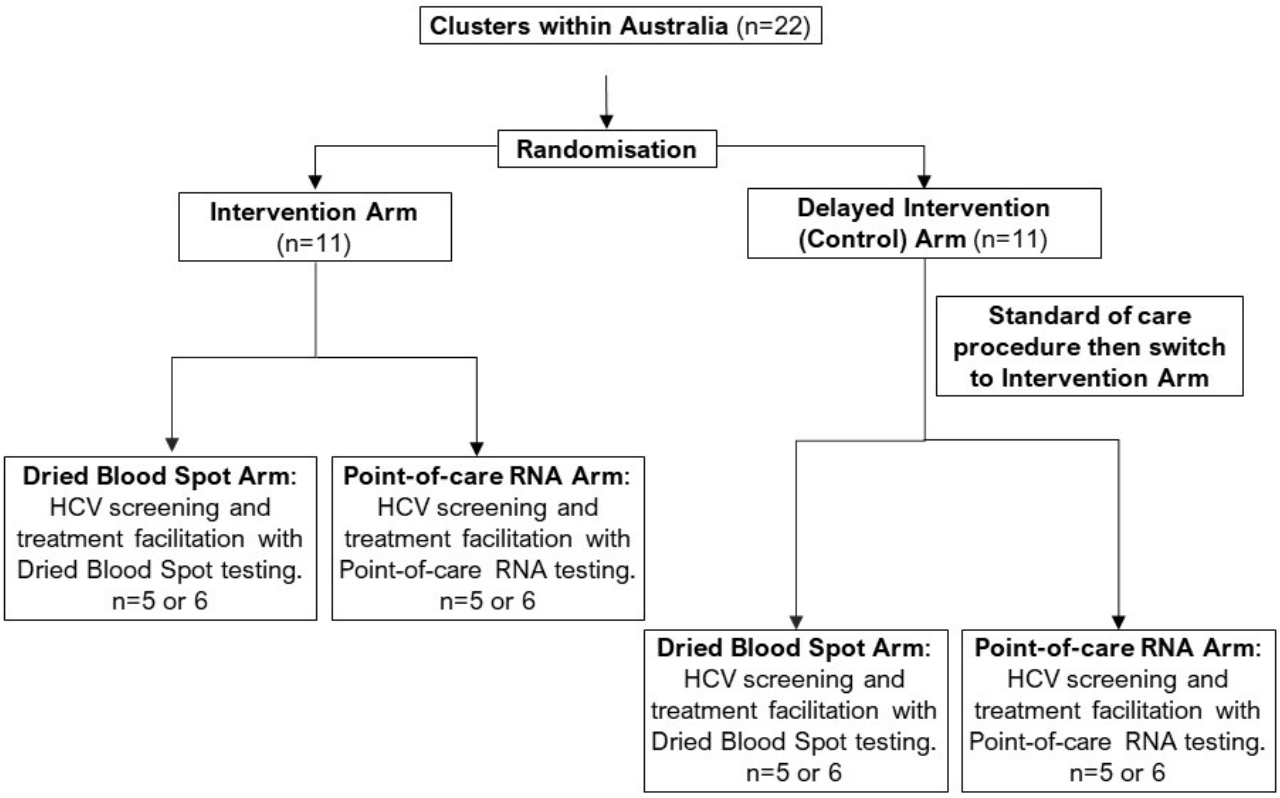
	a. In the opinion of the Investigator, any factors or reasons which could preclude management within an NSP-based setting b. Any clinically significant condition or history known to contraindicate the use of the prescribed DAA treatment medication or would not be suitable for management within an NSP-based setting c. Any medication contraindicated to the prescribed HCV DAA treatment regimen (as detailed in the product information) d. HIV co-infection* e. Active hepatitis B co-infection* f. Is female and is pregnant or breastfeeding. *Participants who meet all other eligibility criteria but have HIV or active hepatitis B co-infection can be eligible for treatment if their HCV treatment is co-managed with a specialist.
Study design	The study is a multi-centre, practice-level, stepped wedge cluster randomized controlled trial. The clusters will be primary needle syringe programs (which provide services to people who inject drugs and have capacity to provide HCV treatment) located in Australia. Twenty-two NSPs [the clusters] will be randomly allocated to receive the intervention immediately (11 clusters) versus standard of care with delayed intervention (11 clusters). The immediate intervention arm will be randomized 1:1 to receive point-of-care HCV RNA testing (5 or 6 clusters)* or HCV RNA testing from dried blood spots (5 or 6 clusters)*. The delayed intervention arm will have a period of standard of care (based on the number of enrolled participants) and switch to receiving the intervention. The delayed intervention arm will then be randomized 1:1 to receive point-of-care HCV RNA testing (5 or 6 clusters)* or HCV RNA testing from dried blood spots (5 or 6 clusters)*. As such, at the end of the study, there will be 11 clusters randomized to point-of-care HCV RNA testing or 11 clusters to HCV RNA testing from dried blood spots. *Based on randomisation, there will be 5 sites using point-of-care and 6 sites using dried blood spots, or vice versa with 6 sites using point-of-care and 5 sites using dried blood spots.
Treatment of participants	At enrolment, participants will be referred for testing (standard of care), tested for HCV infection with dried blood spot, or tested with an HCV RNA point-of-care, depending on cluster randomisation. Participants who are eligible for treatment will be prescribed an approved pan-genotypic DAA HCV treatment at the discretion of the Investigator. The dose, form, strength, regimen and duration of treatment will be as per the approved product information for the prescribed regimen.
Study procedures	Refer to the Schedule of Assessments.
Statistics	**Hypothesis** Compared to standard of care, an intervention consisting of either dried blood spot testing or point-of-care HCV RNA testing will lead

	to an increased proportion who initiate HCV treatment at 12 weeks following enrolment among people with HCV who have recently injecting drug use attending NSP services. Compared to dried blood spot testing, point-of-care HCV RNA testing will lead to an increased proportion who initiate HCV treatment at 12 weeks following enrolment among people with HCV who have recently injecting drug use attending NSP services. **Primary outcome** The proportion who initiate HCV treatment at 12 weeks from enrolment. **Sample size** *Control versus intervention:* The sample size for comparing control versus intervention was calculated by using a stepped wedge cluster randomized controlled trial design (two steps) accounting for estimates of outcomes in the control arm (p1), the average of intervention arms (p2), the mean cluster size (m), the intracluster correlation coefficient (ICC) for the proportion initiating treatment (rho), and study power. Given an HCV RNA prevalence of 20% (based on data from the Australian NSP survey), it is estimated that 100 participants will need to be screened to enable a mean cluster size (m) of 20 participants. For the comparison of control and intervention, we assumed 22 NSP sites/clusters (3,300 tested, 660 HCV RNA detectable), two steps, a mean cluster size (m) of 20 people who are HCV RNA positive, HCV treatment uptake of 10% over 12 weeks in the control group (p1), an intracluster correlation coefficient of ρ=0.05 (to provide a more conservative variation in treatment uptake) and 90% power. Under these assumptions, we are powered to detect a difference of HCV treatment uptake of 20% between control and intervention arms [e.g. 30% in intervention arm (p2)] with α=0.05. *Dried blood spot versus point-of-care HCV RNA testing:* The sample size for comparing dried blood spot testing to point-of-care HCV RNA testing was calculated by using a cluster randomized controlled trial design accounting for estimates of outcomes in dried blood spot testing arm (p1) and the point-of-care HCV RNA testing arm (p2), the mean cluster size (m), the intracluster correlation coefficient (ICC) for the proportion initiating treatment (rho), and study power. Given an HCV RNA prevalence of 20% (based on data from the Australian NSP survey), it is estimated that 100 participants will need to be screened to enable a mean cluster size (m) of 20 participants. For the comparison of control and intervention, we assumed 22 NSP sites/clusters (3,300 tested, 660 HCV RNA detectable), a mean cluster size (m) of 20 people who are HCV RNA positive, HCV treatment uptake of 20% over 12 weeks in the dried blood spot testing (p1), an intracluster correlation coefficient of ρ=0.05 (to provide a more conservative variation in treatment uptake) and 90% power. Under these assumptions, we are powered

	to detect a difference of HCV treatment uptake of 25% between control and intervention arms [e.g. 45% in point-of-care HCV RNA testing arm (p2)] with α=0.05. In the intervention and control arms, the total number tested will be 3,300 [total infected, n=660; total treated, n=165 (n=22 in the control arm, n=44 in the dried blood testing arm, and n=99 point-of-care HCV RNA testing arm)]. **Randomisation** Clusters will be randomised using a computer-generated randomisation scheme, minimised based on cluster characteristics (geographic location and urban vs rural classification). **Statistical analysis** Analysis will follow the CONSORT guidelines for cluster randomised trials[21]. The analysis of the primary outcome will occur when all participants have completed 12 weeks of follow-up or have been permanently lost to follow-up. Participant and cluster flow will be summarised, showing the numbers of clusters and participants randomised and included, and numbers of participants across clusters who complete follow-up with a primary outcome. The primary endpoint will be the proportion of participants who initiate HCV treatment within 12 weeks. Participants who initiate HCV treatment will be traceable, so participants lost to follow-up before initiating HCV treatment will be included in Intention to Treat analyses as having not initiated treatment. Randomised groups will be compared using repeated measures logistic regression methods, clustered on site, fitted using GEE methods with robust standard errors. Secondary analyses will include the proportion linked to care, time to HCV treatment initiation, the proportion initiating HCV treatment by 24 weeks of follow-up, the proportion initiating HCV treatment by the end of follow-up, HCV treatment completion, and response to HCV treatment.

1.1 Study Flow Chart

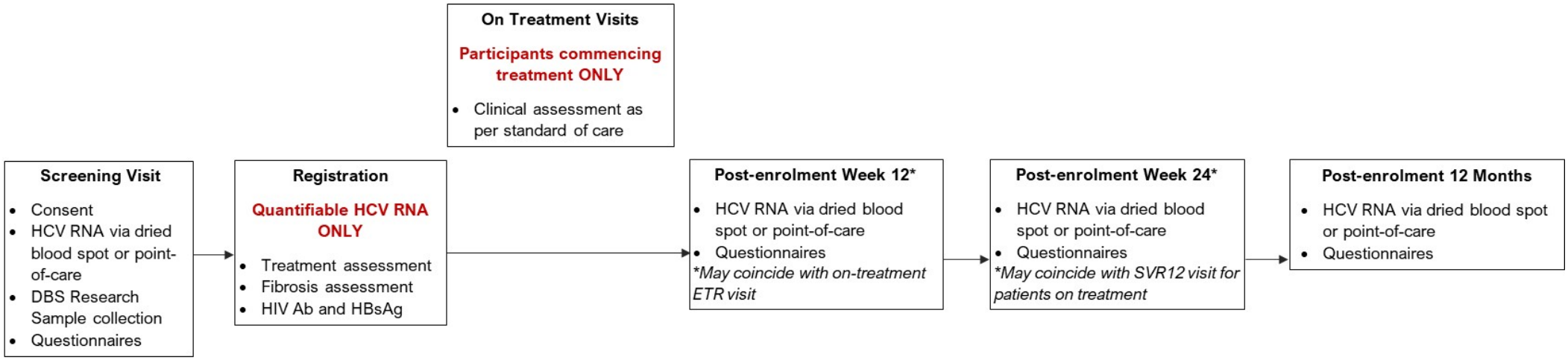
Study Flow Chart – Cluster/Site Level



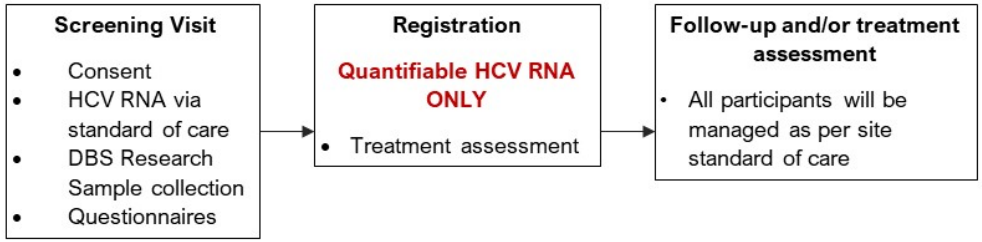
Based on randomisation, there will be 5 sites using point-of-care and 6 sites using dried blood spots, or vice versa with 6 sites using point-of-care and 5 sites using dried blood spots.

1.2 Study Flow Chart – Participant Level

Intervention Arm



Control Arm



1.3 Participant Schedule of Assessments

1.3.1 Intervention Arm

	All participants	**Participants with a quantifiable HCV RNA**			
Study Visit	**Screening**	**Registration**	**Follow-up Visit 1**	**Follow-up Visit 2**	**Follow-up Visit 3**
Study Weeks	0	0	12	24	52
Visit Window (weeks, min to max)	0	N/A	10 to 14	14 to 34	34 to 56
Informed consent	X				
Behavioural questionnaire (Screening version)	X				
Behavioural questionnaire (Follow-up version)			X	X	X
EQ-5D-5L	X		X	X	X
Health economics questionnaire	X		X	X	X
HCV RNA[1]	X		X	X	X
HCV RNA result notification[2]	X	X			
HCV treatment work-up (as per standard of care)[3]		X			
HIV serology		X[4]			
HBV serology		X[4]			
FibroScan® / APRI		X[5]			
Research Samples					
Dried blood spot	X				

Key	
1	HCV RNA via point-of-care or dried blood spot. Participants with a *non-quantifiable and detected* result are recommended for further testing for confirmation.
2	Point-of-care arm: HCV RNA result will be delivered on the same day of testing where possible. Dried blood spot arm: HCV RNA result will be delivered within two weeks of testing. Refer to section 10.2 for additional details.
3	Treatment work-up for enrolled participants with a quantifiable HCV RNA who wish to commence anti-HCV DAA therapy. To be conducted on day of the HCV RNA test where possible.
4	For participants with a quantifiable HCV RNA who initiate HCV treatment, their HIV and HBV status will be determined using rapid tests. Excluded for those with a recent known status.
5	Measure of liver cirrhosis by either a FibroScan (if available at site) or an APRI result from a phlebotomy for participants with a quantifiable HCV RNA who initiate HCV treatment.

1.3.2 Delayed Intervention (Control) Arm

	All participants	**All participants will be managed as per site standard of care[5]**		**Once clusters/sites are switched, follow procedures for the Intervention Arm.**	
		Participants with a quantifiable HCV RNA	**All other participants**		
Study Visit	**Screening[4]**	**Registration[5]**	N/A		
Study Weeks	0	0	N/A		
Visit Window (weeks, min to max)	0	N/A	N/A		
Informed consent	X				
Behavioural questionnaire (Screening version)	X				
EQ-5D-5L	X				
Health economics questionnaire	X				
Testing acceptability questionnaire[1]	X				
HCV RNA and/or Ab[2]	X	X			
HCV result notification[3]	X	X			
Treatment[4]		X			
Research Samples					
Dried blood spot	X				

Key	
1	Testing acceptability questionnaire will be completed in the control arm only.
2	Participant will be referred for HCV testing (standard of care).
3	Standard of care arm: The result will be delivered as per site local procedure. Refer to section 10.2 for additional details.
4	For participants with a quantifiable HCV RNA who do not initiate treatment in the control arm (standard of care), they can be re-screened in the delayed intervention arm 3 months after their date of screening.
5	Data will be collected on participants with a quantifiable HCV RNA and those who initiate HCV treatment.

2.0 Background and rationale

Viral hepatitis is the 7th leading cause of mortality globally, having surpassed the number of annual deaths due to HIV, malaria, and tuberculosis[1]. Globally, 71 million people are living with hepatitis C virus (HCV), with 6.1 million having recently injected drugs[2], and an additional burden among former people who inject drugs (PWID). In Australia, the majority of existing (80%) and new (90% of 9,000 annually) cases are in PWID[3,4]. The advent of simple, well-tolerated, direct-acting antiviral (DAA) HCV therapies with cure rates >95% is one of the most exciting medical advances in decades[5]. Successful therapy leads to improved quality of life and reduced morbidity/mortality[6], providing an opportunity to reverse the rising burden of advanced liver disease.

The World Health Organization (WHO) has set a goal to eliminate HCV as a global public health threat by 2030, with targets to increase HCV diagnoses and treatment, and reduce new infections and liver-related mortality[7]. However, among the 71 million people with HCV worldwide, less than 20% have been diagnosed and less than 10% have received treatment[8]. In Australia, HCV DAA treatment uptake initially exceeded expectations (2016: 32,400 treated; 14% with HCV). But, the number of people initiating therapy has continued to decline (2017: 21,370; 2017: ~2,000/month; 2018: ~1,400/month). Improving HCV testing and treatment to reduce disease burden is a key aim of global and national HCV strategies[9,10].

Globally, HCV testing and diagnosis remains inadequate[11]. Current testing algorithms involve detection of HCV antibodies to confirm exposure, followed by HCV RNA testing to detect active infection. This two-step pathway requires up to 5 visits to practitioners and off-site phlebotomists, leading to a drop-off in those receiving a diagnosis of active infection[12]. Standard of care HCV testing is also limited by a lack of on-site phlebotomists (requiring off-site referral) and poor venous access (a major problem among people who inject drugs). In Australia, 81% have had an antibody-based HCV diagnosis, but only 47% have been tested for active infection[12]. As highlighted in the *4th National HCV Strategy*, a Priority Action is to "improve referral and access to high quality support services at the time of diagnosis for people with HCV to initiate a pathway to care".

In a systematic review of interventions to improve HCV care among PWID led by our group[13], key interventions to enhance HCV testing (on-site testing; and dried blood spot testing), linkage to care (facilitated referral for HCV assessment) and treatment (integrated HCV care) were identified. Studies were limited by small sample sizes, and the lack of randomized controlled trials or comparative studies in the DAA era. Well-designed studies evaluating interventions to enhance HCV testing/treatment among PWID are needed.

Dried blood spot testing can enhance HCV testing and linkage to care[13,14]. Benefits of dried blood spots include: 1) avoiding the need for phlebotomy; 2) enables testing for HCV antibodies (exposure) and RNA (active infection); 3) easy to transport/store; 4) can test for other viruses (e.g. HIV); 5) sample collection can be performed by peers or self-collection[11]. Also, dried blood spot testing has excellent sensitivity and specificity for the detection of active HCV [15].

Point-of-care HCV testing has also been demonstrated to increase testing and linkage to care[14]. Our group led the first evaluation of a finger-stick point-of-care HCV RNA assay[16,17] as part of a clinical observational study in drug treatment clinics and needle and syringe programs (NSPs), enabling same-day diagnosis of active infection (HCV RNA) in one hour (sensitivity and specificity, 100%)[17]. The findings have informed regulatory approval submissions in Europe and Australia. The next step is to translate this novel discovery into routine clinical practice. There is an unprecedented opportunity to evaluate whether finger-stick point-of-care HCV RNA testing could be integrated into routine practice to enhance HCV testing and treatment among PWID.

Settings for HCV care for PWID include hospitals, primary care, drug treatment clinics, and prisons[18]. But, there is a need to link less service-connected PWID to HCV care. In Australia, there is broad NSP access (3,627 NSPs; 98 primary sites)[19] and PWID regularly attend NSPs to collect injecting equipment. NSPs offer an opportunity to engage with PWID who may not be engaged in health services. Further, on-site testing improves linkage to HCV treatment[13]. As highlighted in the *National HCV Strategy*, "Peer support programs offering education may improve engagement in HCV assessment/treatment[20]" and "The role of peer educators to increase testing should be explored. Such services should be linked to peer-based drug-user organisations…and NSPs."

The TEMPO study will compare point-of-care HCV RNA testing, dried blood spot testing, and standard of care as strategies to enhance HCV treatment uptake among people with HCV and recent injecting drug use attending NSP services.

3.0 Hypotheses

Compared to standard of care, an intervention consisting of either dried blood spot testing or point-of-care HCV RNA testing, will lead to an increased proportion who initiate HCV treatment among people with HCV and recent injecting drug use attending NSP services.

Compared to dried blood spot testing, point-of-care HCV RNA testing will lead to an increased proportion who initiate HCV treatment at 12 weeks following enrolment among people with HCV who have recently injecting drug use attending NSP services.

4.0 Study objectives

4.1 Primary objective

To compare the proportion of HCV RNA positive participants who initiate HCV treatment at 12 weeks following enrolment between those who receive point-of-care HCV RNA testing, dried blood spot testing, and standard of care.

4.2 Secondary objective(s)

Among those who receive point-of-care HCV RNA testing, dried blood spot testing, and standard of care:

1. To compare the time to HCV DAA treatment initiation among those who initiate treatment.
2. To compare the proportion of HCV RNA positive participants who initiate HCV DAA treatment at 24 weeks following enrolment.
3. To compare the proportion of HCV RNA positive participants who initiate HCV DAA treatment at 12 months (52 weeks) following enrolment.
4. To compare the proportion of participants who complete HCV DAA treatment.
5. To compare the proportion of participants who achieve an SVR (defined as HCV RNA below the lower limit of quantitation at post treatment week 12).
6. To compare the proportion of participants who are HCV RNA negative at 12 weeks.
7. To compare the proportion of participants who are HCV RNA negative at 24 weeks.
8. To compare the proportion of participants who are HCV RNA negative at 12 months (52 weeks).
9. To evaluate the incidence of HCV reinfection following successful HCV therapy.
10. To compare the cost-effectiveness of these different testing strategies.

5.0 Study setting

This study will be conducted at 22 primary NSP in Australia. It is estimated that each site will consent and screen 100-120 participants for HCV infection, of which an estimated 20-30 HCV RNA positive participants per site will enrol (based on an HCV RNA prevalence of 20%). Depending on recruitment rate, some sites may enrol more than 20 HCV RNA positive participants.

6.0 Participant population

It is anticipated that approximately 3,300 participants (assuming an HCV RNA prevalence of 20%) will be screened for HCV infection using either dried blood spot testing, point-of-care testing or standard of care testing.

Screening in the intervention arm will continue until a total of 220 HCV RNA positive participants (~20 participants per site) are enrolled in the intervention arm (either dried blood spot and point-of-care). In the delayed intervention arm, 220 HCV RNA positive participants (~20 participants per site) will be enrolled in the control (standard of care) phase and then clusters/sites will be switched to intervention (either dried blood spot and point-of-care) – at which screening will continue until a total of 220 HCV RNA positive participants (~20 participants per site) are enrolled. Hence a total of 660 HCV RNA positive participants.

7.0 Eligibility criteria

7.1.1 Identification and inclusion criteria for clusters

NSPs must meet the following criteria to participate in the study:

a. Be a primary NSP site, defined as, providing services to PWID staffed by specialist workers
b. Have the capacity for on-site nursing support or externally, and HCV treatment provision
c. Provide services to > 60 people per week.

Potential eligible NSP sites will be identified from existing service centres in Australia and will complete site feasibility assessment to ensure the inclusion criteria are met. NSP sites may have prior experience or are active in surveillance and clinical studies, but it is not mandatory to have clinical research experience.

7.1.2 Inclusion criteria for participants

Attendees of the NSP service are eligible for inclusion if the following criteria are met:

a. Provided written informed consent
b. ≥ 18 years of age
c. Recent injecting drug use – defined as self-reported use within the previous six months.

7.1.3 Exclusion criteria for participants

Attendees of the NSP service are not eligible for inclusion if any of the following exclusion criteria are met:

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

7.1.4 Eligibility criteria for treatment

Participants who have a quantifiable HCV RNA will be assessed for treatment eligibility. Those in the point-of-care arm will be able to complete the treatment work-up on the day of HCV screening. Those in the control arm and dried blood spot arm will have treatment work-up as per standard of care once the HCV RNA test results are received from the laboratory.

Treatment uptake is expected to be higher at 12 weeks following enrolment in the point-of-care arm (45%) compared with the dried blood spot arm (20%) or control arm (10%).

7.1.4.1 Inclusion criteria

Participants are eligible for HCV DAA treatment if all of the following inclusion criteria are met:

a. Quantifiable HCV RNA at screening
b. An assessment of liver cirrhosis status is performed in the intervention arm, i.e. point-of-care and dried blood spot arm:

i) If pathology is available to determine an APRI in the previous 12 months, and is <1.0, then a FibroScan is not required.

OR

ii) If pathology is not available for APRI, and no FibroScan is available, then phlebotomy can be taken at baseline and treatment commenced. Once pathology is returned, if >1.0 then an ultrasound can be organised. In these cases (unknown stage of disease) would be preferable to use SOF/VEL, given standard duration.

c. In the opinion of the Investigator, the participant is suitable for treatment within an NSP-based setting.

7.1.4.2 Exclusion criteria

Participants are not eligible for HCV DAA treatment if any of the following exclusion criteria are met:

a. In the opinion of the Investigator, any factors or reasons which could preclude management within an NSP-based setting
b. Any clinically significant condition or history known to contraindicate the use of the prescribed DAA treatment medication or would not be suitable for management within an NSP-based setting
c. Any medication contraindicated to the prescribed HCV DAA treatment regimen (as detailed in the product information)
d. HIV co-infection*
e. Active hepatitis B co-infection*
f. Is female and is pregnant or breastfeeding.

*Participants who meet all other eligibility criteria but have HIV or active hepatitis B co-infection can be eligible for treatment if their HCV treatment is co-managed with a specialist.

8.0 Study design

8.1 Summary of study design

The study is a two-arm, practice-level, stepped wedge cluster randomized controlled trial. The clusters will be primary NSPs (which provide services to people who inject drugs and have capacity to provide HCV treatment services) located in Australia.

Twenty-two NSPs [the clusters] will be randomly allocated to receive the intervention immediately (11 clusters) versus standard of care with delayed intervention (11 clusters) (Figure 1). The immediate intervention arm will be randomized 1:1 to receive point-of-care HCV RNA testing (5 or 6 clusters)* or HCV RNA testing from dried blood spots (5 or 6 clusters)*. The delayed intervention arm will have a period of standard of care (based on the number of enrolled participants) and switch to receiving the intervention. The delayed intervention arm will then be randomized 1:1 to receive point-of-care HCV RNA testing (5 or 6 clusters)* or HCV RNA testing from dried blood spots (5 or 6 clusters)*. As such, at the end of the study, there will be 11 clusters randomized to point-of-care HCV RNA testing or 11 clusters to HCV RNA testing from dried blood spots.

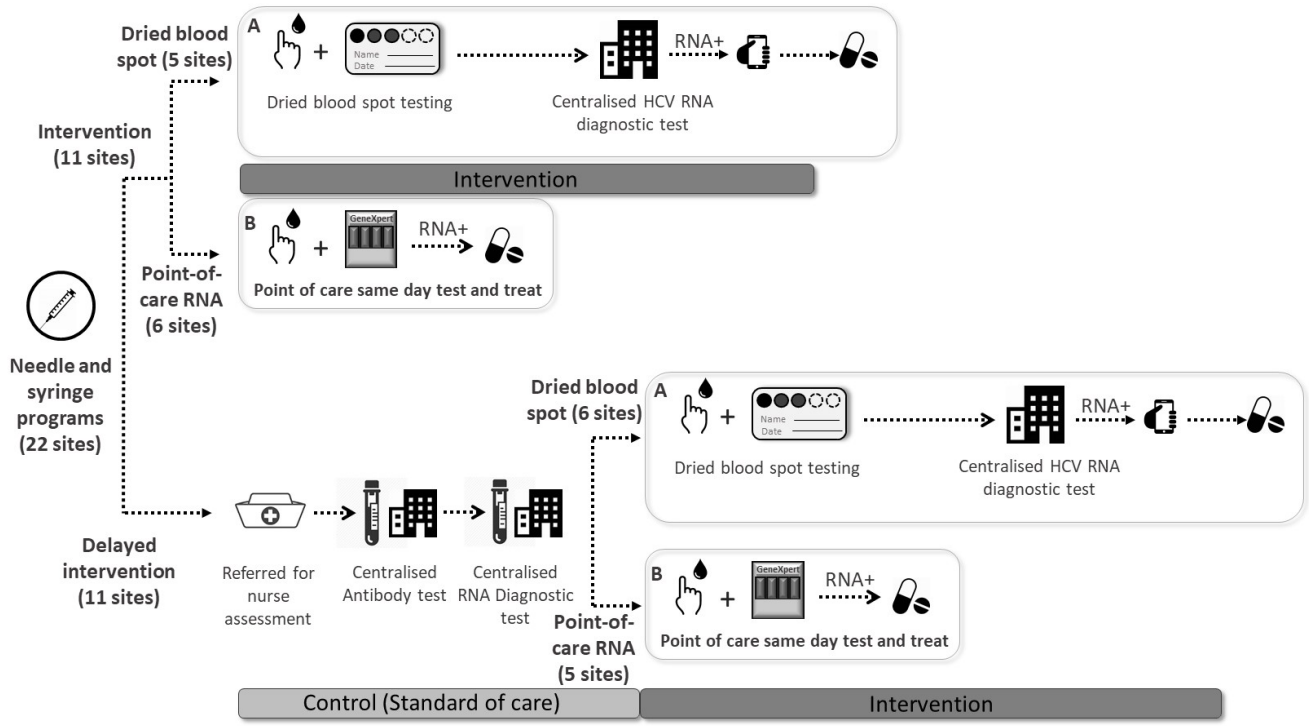


Figure 1 TEMPO cluster randomisation

Clusters will be randomized using a computer-generated randomization scheme minimised based on cluster characteristics.

*Based on randomisation, there will be 5 sites using point-of-care and 6 sites using dried blood spots, or vice versa with 6 sites using point-of-care and 5 sites using dried blood spots.

Eligible NSP attendees will be screened, enrolled and treated as detailed in Figure 2.

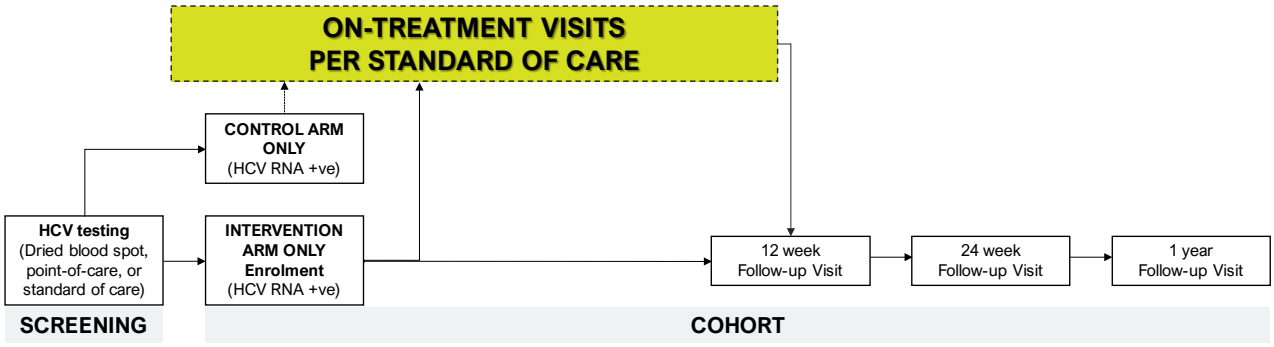


Figure 2 TEMPO study scheme

At enrolment, participants will be referred for testing (standard of care), tested for HCV infection with dried blood spot, or tested with an HCV RNA point-of-care, depending on cluster randomisation.

HCV RNA negative participants will have no further assessments or visits as part of the study protocol. Participants who are HCV RNA positive will be enrolled in the cohort. Screening in the intervention arm will continue until a total of 220 HCV RNA positive participants (~20 participants per site) are enrolled in the intervention arm (either dried blood spot and point-of-care). In the delayed intervention arm, 220 HCV RNA positive participants (~20 participants per site) will be enrolled in the control (standard of care) phase and then clusters/sites will be switched to intervention (either dried blood spot and point-of-care) – at which screening will continue until a

total of 220 HCV RNA positive participants (~20 participants per site) are enrolled. Hence a total of 660 HCV RNA positive participants will be enrolled in the study.

Participants with a quantifiable HCV RNA will be assessed for treatment based on standard eligibility criteria for government reimbursement of therapy. If eligible, they will be treated as per standard of care with a government approved pan-genotypic HCV DAA treatment. Participants will be encouraged to take the first dose on the day of treatment work-up where possible. On-treatment and post-treatment testing and monitoring will be based on the site investigator as per standard clinical practice.

All HCV RNA positive participants will be followed up at 12 weeks, 24 weeks, and 12 months post HCV RNA test.

9.0 Treatment of participants

9.1 Treatment

Participants (with a quantifiable HCV RNA) who are eligible for treatment will be prescribed a government approved pan genotypic DAA HCV treatment (e.g. glecaprevir/pibrentasvir 300mg/120mg, sofosbuvir/velpatsvir 400mg/100mg, or sofosbuvir/velpatasvir/voxilaprevir 400mg/100mg/100mg), at the discretion of the Investigator. The dose, form, strength, regimen and duration of treatment will be as per the approved product information for the prescribed regimen.

Dispensing

Participants who initiate treatment through the study will be prescribed through a government approved scheme. Participants will collect their medication from a local community pharmacy. Quantities dispensed to participants from the pharmacy and dosing regimen (e.g. daily observed, self-dosed etc.) will be based on the government guidelines and the Investigator's discretion respectively. Details on the HCV treatment administration, including the treatment regimen and date of the first treatment dose and the last treatment dose will be recorded for all HCV RNA positive participants.

9.2 Prior and concomitant medications

Allowed and excluded medications prior to, during the study and post-treatment will be based on the product information of the prescribed HCV DAA therapy as only government approved medicines are used in this study. The treating Investigator will review the participants medical history and review all medication the participant is taking for potential drug-drug interactions. The hep-drug interactions website may be used as a tool: https://www.hep-druginteractions.org/.

10.0 Study procedures

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

Questionnaires	Behavioural survey, Abbreviated behavioural survey, Health outcomes survey (EQ-5D-5L), Health economics survey, Testing acceptability survey
HCV RNA	HCV RNA via point-of-care, dried blood spot or standard of care*
HIV serology	HIV Ab (point-of-care and dried blood spot arm only)**
HBV serology	HBsAg (point-of-care and dried blood spot arm only)**
Fibrosis assessment	FibroScan or APRI score (point-of-care and dried blood spot arm only)
Dried blood spot	Dried blood spot research sample collection

*For standard of care, participants will be referred for HCV testing, including HCV Ab and/or RNA.
**At time of treatment initiation and excluded for those with a recent known status.

10.1 Screening visit

The following procedures will be completed at the screening visit:

- Informed consent
- Screening behavioural questionnaire
- Health outcomes survey (EQ-5D-5L) and health economics questionnaire
- Testing acceptability questionnaire (control arm only)
- HCV RNA using dried blood spot or point-of-care
    - Dried blood spot: A finger-stick capillary whole blood sample will be collected on a dried blood spot card, air dried for 4 hours and then posted to St Vincent's Hospital Centre for Applied Medical Research (AMR) laboratory for HCV testing. If an invalid or error result is obtained, a repeat test will be performed via venepuncture.
    - Point-of-care: A finger-stick capillary whole blood sample will be collected for the GeneXpert. Results are generated in approximately 1 hour and provided to the participants on the same day (where possible). If an invalid or error result is obtained, a repeat point-of-care test will be performed (same day where possible).
- HCV testing using standard of care - the participant will be referred for HCV testing via standard of care.
- Research blood sample – dried blood spot
- HIV and HBV serology using a rapid test for participants with a quantifiable HCV RNA in the intervention arm who initiate HCV treatment. Excluded for those with a recent known status.
- Fibrosis assessment for HCV RNA positive participants in the intervention arm only.
- Participant reimbursement

10.2 HCV RNA test notification

Participants at sites randomized to standard of care or dried blood spots will be notified once their results are returned from the testing laboratory whilst those at sites randomized to point-of-care will be notified of their results on the same day (where possible).

Negative results from dried blood spot HCV RNA testing will be delivered through a text message. Participants with a positive result from dried blood spot HCV testing will be notified through a text message to contact the study site team to facilitate the participant to return to the site for HCV RNA results and linkage to care. Positive HCV RNA results will be delivered in person by the site study team.

To facilitate participant notification of results, contact details (phone number and/or email, if available) will be collected through an electronic data capture system. Up to 3 secondary contact

details (phone number and/or email) will be collected in case the study team cannot reach the study participant on their main contact details.

10.3 Registration

Consecutive HCV RNA positive participants will be enrolled in the cohort.

In the intervention arm, screening will continue until a total of 220 HCV RNA positive participants (~20 participants per site) are enrolled in either dried blood spot and point-of-care. Only HCV RNA positive participants i.e., participants with a quantifiable HCV RNA will be followed up after enrolment at 12 weeks, 24 weeks and 1 year.

In the delayed intervention arm, 220 HCV RNA positive participants (~20 participants per site) will be enrolled in the control (standard of care) phase and managed as per site standard of care. Sites will then be switched to intervention (either dried blood spot and point-of-care) – at which screening will continue until a total of 220 HCV RNA positive participants (~20 participants per site) are enrolled. Only HCV RNA positive participants i.e., participants with a quantifiable HCV RNA in the point-of-care or dried blood spot arm will be followed up post-enrolment at 12 weeks, 24 weeks and 1 year.

Hence a total of 660 HCV RNA positive participants.

HCV RNA negative participants will not complete any further visits as part of the study protocol.

10.4 Treatment

Participants with a quantifiable HCV RNA will be assessed for treatment eligibility. If eligible, they will be offered treatment via standard clinical practice as recommended by the Australian recommendations for the management of HCV virus infection: a consensus statement (latest version). Participants will attend at a minimum, a visit prior to treatment and a Week 8-12 post-treatment (SVR).

There are no study specific assessments required during the HCV treatment. The following participant information will be collected through participant medical records/notes for study data:

- Planned duration of treatment
- HCV treatment regimen prescribed
- HCV treatment start and end date
- Treatment outcome (sustained virological response at 12 weeks after the last dose of treatment)

If a participant fails treatment, additional information may be recorded: reason for treatment failure, reinfection risks and reasons for missed doses (if known).

If determined by the doctor to be eligible for treatment initiation a government approved prescription for a pan-genotypic HCV DAA treatment will be provided to the participant (or faxed to their pharmacy). The dose, form, strength, regimen and duration of treatment will be as per the approved product information for the prescribed regimen.

10.5 Follow-up phase

All HCV RNA positive participants i.e., participants with a quantifiable HCV RNA in the intervention arm only will return for follow-up visits at 12 weeks, 24 weeks and 12 months (52 weeks) post-test. The following procedures will be conducted at follow-up visits:

- Follow-up behavioural questionnaire
- Health outcomes survey (EQ-5D-5L) and health economics questionnaire

- HCV RNA (either dried blood spot or point-of-care)
- Participant reimbursement

10.6 Re-screening

For participants with a quantifiable HCV RNA who do not initiate treatment in the control phase (standard of care) of the delayed intervention arm, they can be re-screened in the intervention phase 3 months after their date of screening.

10.7 Study questionnaires

All participants will complete behavioural questionnaires, health economics, health outcomes survey (EQ-5D-5L) and testing acceptability questionnaire at Screening. Subsequently, all HCV RNA positive participants in the intervention arm will complete study questionnaires at Follow-up visits 1, 2 and 3.

10.7.1 Behavioural questionnaire

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

- Demographics (including Indigenous Status)
- Drug and alcohol usage
- Injecting risk behaviours
- HCV testing and treatment
- HIV and drug treatment history
- Experience with overdose and naloxone
- Experience with hospitalisations and police
- Treatment acceptance and willingness (prior to treatment commencement only)
- NSP utilisation
- Acceptability of HCV testing

An abbreviated behavioural questionnaire (follow-up) will be administered at Follow-up visits 1, 2 and 3.

10.7.2 Health Economics surveys

10.7.2.1 Health economics questionnaire

This questionnaire will collect information on the use of health and social care services, medication, and expenses incurred as a result of HCV over the previous 3 or 12 months. This questionnaire will be completed at Screening, Follow-up visit 1, Follow-up visit 2 and Follow-up visit 3.

10.7.2.2 Health outcomes survey (EQ-5D-5L)

The EQ-5D-5L 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.

10.7.3 HCV testing acceptability questionnaire

Participants in the control arm will participate in a discrete choice experiment to assess preferences for different HCV testing attributes. They will be asked ten questions, each comprising five scenarios with two potential options. Participants will indicate their preference for one option or “none”.

Sample size

All participants in the control arm (estimated ~1100 people) will be asked to participate in the discrete choice experiment. It is anticipated that this will provide an accurate estimation of the preferences for different testing options. This will also provide a sufficient sample to understand the attributes of testing which most influence testing decision making through conjoint analysis.

Statistical analysis
Conjoint analyses will also be used to understand the attributes of testing which most influence decision making around HCV testing options. The characteristics of groups of participants which influence preferences for testing options will also be evaluated. Data will be analysed using Lighthouse Studio 9.11.0 and Stata 15[22].

Data collection
Data for the discrete choice experiment will be collected using Sawtooth. Sawtooth is an online survey software that can be used on tablets and laptops. All data collected using the Sawtooth software is server dedicated to the project. The server is located in Australia.

10.7.4 Data linkage study in Australia (optional)

All study participants will be invited to consent to link their data collected from TEMPO with routinely collected data from a range of population databases and registers.
Two types of data linkage will be performed:

1) Health and incarceration data linkage
2) Medicare Benefits Schedule/Pharmaceutical Benefits Scheme (MBS/PBS) data linkage

The collection of participant names, date of birth, sex, full address and post code (and for MBS/PBS; Medicare number) in TEMPO is essential for accurate data linkage. Participant data will be linked to a variety of health variables including information on HCV notifications, HIV/AIDS notifications, use of hepatitis services, use of prescription medication (including HCV 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). MBS/PBS data will be collected from Services Australia. 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. A separate consent for MBS/PBS linkage will be signed by participants who wish to opt into the MBS/PBS data linkage. Participants not wishing to have their data used in either of the data linkage studies may still enrol in the TEMPO study.

10.8 Withdrawal of study participants

Study participants may withdraw from the study for reasons including, but not limited to, the following:

- investigator or participant wish to stop therapy
- discontinuation of the study at the request of the sponsor, regulatory agency or Human Research Ethics Committee (HREC)/Institutional Review Board (IRB)

Participants who cease HCV treatment will, wherever possible, continue to be followed up according to the protocol study plan. Participants may revoke consent for follow-up without jeopardizing their relationship with either their doctor or the Sponsor. If a participant revokes consent then, if possible, all assessments scheduled for the final visit should be completed.

11.0 Recording and reporting adverse events (AEs)

11.1 Adverse Event definition (including adverse drug/device reactions)

The medications for this study are supplied via the Pharmaceutical Benefit Scheme (PBS) in Australia. Adverse events will not be collected as part of this clinical trial. Adverse Drug Reactions will be reported to the Therapeutic Goods Administration (TGA) in Australia as per standard practice for government approved medications.

11.2 Serious Adverse Event (SAE) definition (including Serious Adverse Drug Reactions)

The medications for this study are supplied via the PBS in Australia. Serious adverse events will not be collected as part of this clinical trial. Serious Adverse Drug Reactions will be reported to the TGA in Australia as per standard practice for government approved medications.

11.3 Suspected Unexpected Serious Adverse Reaction

The Project Team in collaboration with the Medical Officer will review and identify all Serious Adverse Drug Reactions which fit the criteria of a Suspected Unexpected Serious Adverse Reaction (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) and where the nature and severity is not consistent with known information (e.g. the Investigator's Brochure for an unapproved investigational product or Product Information for an approved product).

11.4 Reporting requirements

11.4.1 Serious Adverse Drug Reactions

Serious Adverse Drug Reactions will be reported to the TGA in Australia as per standard practice for government approved medications and an electronic copy submitted to the Sponsor project team via tempo@kirby.unsw.edu.au. HCV medications manufactured by Gilead which are prescribed to enrolled participants, the Sponsor will forward these reports to Gilead within 24 hours of being notified.

11.4.2 Suspected Unexpected Serious Adverse Reaction

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.

12.0 Packaging, labelling, storage and accountability of treatment

The medications for this study are supplied via the PBS in Australia. The packaging, labelling and accountability of prescribed medication will be as per PBS guidelines.

13.0 Biological samples

13.1 Laboratory supplies and sample processing

Laboratory supplies for collection of research specimens, dried blood spots and point-of-care testing will be supplied by the Kirby Institute.

13.2 Dried blood spot (DBS) cards

A DBS sample will be collected at screening and at time points specified in the Schedule of Assessments. Samples will be collected by sites, dried (4 hours minimum but preferably overnight). Each DBS sample card must be sealed in a foil zip locked bag which is then sealed in a clear zip locked bag with a humidity can and desiccants. Care must be taken to ensure that individual DBS sample cards do not touch prior to being dry. DBS sample cards will be used for study endpoint analysis. HCV antibody and/or RNA will be measured using in-house and commercial assays. This data may be shared with the state health authorities. 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, to examine the prevalence of mixed infection, to look at clusters and networks in communities and factors associated with relapse including resistance-associated substitutions (RAS) and to perform phylogenetic analyses to examine molecular epidemiology. For HCV phylogenetic analysis, only viral RNA is extracted, amplified and sequenced. No human genetic analysis is being proposed. There is no potential to identify human genetic traits.

13.3 HIV antibody point-of-care testing

For HCV positive participants in the intervention arm, a qualitative HIV antibody testing may be performed using the Alere™ HIV Combo: a point-of-care, 20-minute immunoassay for the qualitative detection HIV-1 p24 antigen (Ag) and antibodies (Ab) to HIV-1 and HIV-2. A capillary (whole blood) sample will be collected from the participant and applied to the Sample Pad followed by a Chase Buffer. The device provides a visual indicator of the results to display positive, negative or invalid results. As determined by the prescribing clinician, point-of-care testing results may be repeated/confirmed with standard laboratory immunoassays via venepuncture.

This test is approved by the Australian Government TGA and registered as a Medical Device – IVD Class 4 by Inverness Medical Innovations Australia Pty Ltd T/A Alere (Queensland, Australia) and manufactured by Alere Medical Co Ltd (Chiba-ken, Japan). This device will be provided to sites by the Sponsor and must be stored in storage conditions of 2 - 30°C.

13.4 HBV surface antigen point-of-care testing

For HCV positive participants in the intervention arm, a qualitative hepatitis B surface antigen testing may be performed using the Alere Determine™ HBsAg (either Determine HBsAg or Determine HBsAg 2, depending on availability) – a rapid 15-minute point-of-care invitro qualitative immunoassay for detection of hepatitis B surface antigen. This test is currently not approved by the TGA. A 50µL whole blood sample will be collected from participants via a finger-stick and added to the Alere Determine test pad with the Alere Determine™ Chase Buffer (Chase Buffer prepared in phosphate buffer). The device provides a visual indicator of the results to display positive, negative or invalid results. As determined by the prescribing physician, point-of-care testing results may be repeated/confirmed with standard laboratory immunoassays via venepuncture. This device will be provided to sites by the Sponsor and must be stored in storage conditions of 2 - 30°C.

13.5 HCV RNA point-of-care testing

At screening and at time points specified in the Schedule of Assessments, HCV RNA detection will be performed using the validated Xpert® HCV Viral Load Fingerstick point-of-care assay with finger-stick whole-blood samples, as previously validated by our group[24]. A whole blood sample will be collected from participants via a finger-stick and collected into a 100µL minivette collection tube. Immediately after collection, 100µL of capillary whole blood will be placed directly into the

Xpert® HCV Viral Load Fingerstick cartridge (Cepheid, USA; lower limit of quantification of 10IU/mL) for on-site HCV RNA testing. HCV Viral Load testing of capillary whole blood will be done on a clinic-based GeneXpert R2 6-colour, two or four module machines operated by the site study team as per the manufacturer's instructions (time to result is 60 minutes).

Quality assurance and training will be provided by the Sponsor on the use of the device. The Xpert HCV VL Fingerstick cartridge will be provided to sites for use in the study with the GeneXpert. The cartridges must be stored in conditions of 2 – 28°C. Whole blood specimens will be collected for the cartridges can be stored in temperatures of 5 - 35°C for up to maximum of 15 minutes. Specimens collected must be analysed in the GeneXpert within 15 minutes.

13.6 Shipping of biological samples

DBS sample cards will be express posted to the St Vincent's Hospital Centre for AMR laboratory within 1 week of collection for testing or the Kirby Institute for storage at -80°C. DBS cards will be supplied with a marked biohazard foil zip lock bag, desiccants and a humidity monitor card (SMD – Humitector).

13.7 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 HCV related research. Additional consent will not be sought for permission to store any remaining DBS samples after analyses for study endpoints have been completed for future HCV related research. Participants can withdraw their samples from storage for future HCV related research at any time by completing the revocation of consent.

14.0 Statistics

14.1 Hypothesis

Compared to standard of care, an intervention consisting of either dried blood spot testing or point-of-care HCV RNA testing will lead to an increased proportion who initiate HCV treatment at 12 weeks following enrolment among people with HCV who have recently injecting drug use attending NSP services.

Compared to dried blood spot testing, point-of-care HCV RNA testing will lead to an increased proportion who initiate HCV treatment at 12 weeks following enrolment among people with HCV who have recently injecting drug use attending NSP services.

14.2 Primary outcome

The proportion who initiate HCV treatment at 12 weeks from enrolment.

14.3 Sample size

Control versus intervention: The sample size for comparing control versus intervention was calculated by using a stepped wedge cluster randomized controlled trial design (two steps) accounting for estimates of outcomes in the control arm (p1), the average of intervention arms (p2), the mean cluster size (m), the intracluster correlation coefficient (ICC) for the proportion initiating treatment (rho), and study power. Given an HCV RNA prevalence of 20% (based on data from the Australian NSP survey), it is estimated that 100 participants will need to be screened to enable a mean cluster size (m) of 20 participants. For the comparison of control and intervention, we assumed 22 NSP sites/clusters (3,300 tested, 660 HCV RNA detectable), two steps, a mean cluster size (m) of 20 people who are HCV RNA positive, HCV treatment uptake of 10% over 12 weeks in the control group (p1), an intracluster correlation coefficient of ρ=0.05 (to provide a more

conservative variation in treatment uptake) and 90% power. Under these assumptions, we are powered to detect a difference of HCV treatment uptake of 20% between control and intervention arms [e.g. 30% in intervention arm (p2)] with α=0.05.

Dried blood spot versus point-of-care HCV RNA testing: The sample size for comparing dried blood spot testing to point-of-care HCV RNA testing was calculated by using a cluster randomized controlled trial design accounting for estimates of outcomes in dried blood spot testing arm (p1) and the point-of-care HCV RNA testing arm (p2), the mean cluster size (m), the intracluster correlation coefficient (ICC) for the proportion initiating treatment (rho), and study power. Given an HCV RNA prevalence of 20% (based on data from the Australian NSP survey), it is estimated that 100 participants will need to be screened to enable a mean cluster size (m) of 20 participants. For the comparison of control and intervention, we assumed 22 NSP sites/clusters (3,300 tested, 660 HCV RNA detectable), a mean cluster size (m) of 20 people who are HCV RNA positive, HCV treatment uptake of 20% over 12 weeks in the dried blood spot testing (p1), an intracluster correlation coefficient of ρ=0.05 (to provide a more conservative variation in treatment uptake) and 90% power. Under these assumptions, we are powered to detect a difference of HCV treatment uptake of 25% between control and intervention arms [e.g. 45% in point-of-care HCV RNA testing arm (p2)] with α=0.05.

In the intervention and control arms, the total number tested will be 3,300 [total infected, n=660; total treated, n=165 (n=22 in the control arm, n=44 in the dried blood testing arm, and n=99 point-of-care HCV RNA testing arm)].

14.4 Randomisation

Clusters will be randomised using a computer-generated randomisation scheme, minimised based on cluster characteristics (geographic location and urban vs rural classification).

14.5 Statistical analysis

Analysis will follow the CONSORT guidelines for cluster randomised trials[21]. The analysis of the primary outcome will occur when all participants have completed 12 weeks of follow-up or have been permanently lost to follow-up. Participant and cluster flow will be summarised, showing the numbers of clusters and participants randomised and included, and numbers of participants across clusters who complete follow-up with a primary outcome. The primary endpoint will be the proportion of participants who initiate HCV treatment within 12 weeks. Participants who initiate HCV treatment will be traceable, so participants lost to follow-up before initiating HCV treatment will be included in Intention to Treat analyses as having not initiated treatment. Randomised groups will be compared using repeated measures logistic regression methods, clustered on site, fitted using GEE methods with robust standard errors. Secondary analyses will include the proportion linked to care, time to HCV treatment initiation, the proportion initiating HCV treatment by 24 weeks of follow-up, the proportion initiating HCV treatment by the end of follow-up, HCV treatment completion, and response to HCV treatment.

15.0 Data Safety and Monitoring Board (DSMB)

A Data Safety Monitoring Board will not be used for this study as treatment is being prescribed and supplied according to government regulatory indications.

16.0 Operator Training, Quality Assurance, and Quality Control Program

An Operator Training, Quality Assurance, and Quality Control Program for the point-of-care testing and dried blood spot testing for HCV RNA will be developed in collaboration with the International Centre for Point-of-Care Testing, Flinders University; St. Vincent's Hospital, and the Australasian

Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). The aim of the program is to develop clinical education and operator training with an analytical quality component for the point-of-care testing and dried blood spots in the TEMPO study. The program will involve pre-requisite training, theoretical and practical training, and assessments of operator knowledge and competency in the use of the point-of-care testing and/or dried blood spots in a non-laboratory setting.

17.0 Data collection, source documents and record retention

If required, 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.

17.1 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.

Questionnaires (behavioural questionnaires, health economics, EQ-5D-5L and testing acceptability) will be completed electronically through a tablet and/or via a desktop computer. Participants will self-complete the questionnaires under the supervision of site staff. Site staff will provide instructions on tablet/computer use and ensure data collection is possible.

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 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 and/or request de-identified data 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 enrolling 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.

17.2 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.

18.0 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 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) (e.g. study nurse). 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. 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).

19.0 Confidentiality of data

19.1 Confidentiality of participant records

The Kirby Institute has a personal data confidentiality policy and procedure. Identifying data, when collected is stored on a password protected secure network and only authorised members of the project team will have access to the data. Participant confidentiality will be maintained at all times. In this study identifying data will be collected and used as follows:

Participants will have their full name, phone number and/or email address collected by the site staff and sent to the sponsor via an electronic case report form. These contact details will be used for the purpose of study related notifications only (for example, HCV results notifications and upcoming study visit reminders). The name and phone number and/or email address of up to 3 secondary contacts will be collected in case the study team cannot reach the study participant directly. These contact details will not be used for any other purposes. No other identifying information will be collected.

It may be necessary for the sponsor's representatives, the IRB 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.

19.2 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.

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.

20.0 Governance

This national research protocol is funded by a NHMRC Partnership Grant, Gilead Sciences, Maridulu Budyari Gumal Sydney Partnership for Health, Education, Research and Enterprise (SPHERE), and South Western Sydney Local Health District.

The GeneXpert device and cartridges have been provided by Cepheid. The study is sponsored by the UNSW Sydney 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.

21.0 Financing and insurance

Enrolled participants will receive reimbursement for their study visits to compensate for the time involved.

Financing and insurance details (e.g. indemnity cover, during the course of the study, and compensation in the event of study-related injury) are described in the Clinical Trial Research Agreement between the Site and Sponsor.

22.0 Quality Control (QC) and Quality Assurance (QA)

By signing this protocol, 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.

As part of quality assurance, authorised staff from Cepheid may visit participating sites to perform installation, maintenance, training or other QA activities on the Xpert machines. Principal Investigators at participating sites with a GeneXpert on premises, will permit access to the GeneXpert instrument on site if required.

23.0 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).

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25.0 Abbreviations List

Abbreviation/Acronym		Description
Ab	-	Antibody
AE	-	Adverse event
Ag	-	Antigen
ASHM		Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
CI	-	Chief investigator
CRF	-	Case report form
DAA	-	Direct acting antiviral
DBS	-	Dried blood spot
DSMB	-	Data safety monitoring board
EC	-	Ethics committee
ETR	-	End of treatment
GEE	-	Generalised estimating equation
HCV	-	Hepatitis C virus
HIV	-	Human immunodeficiency virus
ICC	-	Intraclass correlation coefficient
IRB	-	Institutional review board
IVD	-	In vitro diagnostics
MBS	-	Medicare benefits schedule
NHMRC	-	National Health and Medical Research Council
NSP	-	Needle syringe program
PBS	-	Pharmaceutical benefits scheme
PWID	-	People who inject drugs
QA	-	Quality assurance
QC	-	Quality control
RAS	-	Resistance associated substitution
RNA	-	Ribonucleic acid
SAE	-	Serious adverse event
SVR	-	Sustained virological response
TGA	-	Therapeutic Goods Australia
VL	-	Viral load
WHO	-	World Health Organisation

26.0 Appendices

26.1 Evaluation of operator training, quality assurance and quality control program for point-of-care and dried blood spot testing for hepatitis C (HCV) infection.

Title	Evaluation of an operator training, quality assurance, and quality control program for point-of-care and dried blood spot testing for hepatitis C (HCV) infection.
Background and Rationale	The advent of simple direct-acting antiviral hepatitis C (HCV) therapies with cure rates >95% is one of the greatest medical advances in decades, having led to a reversal in liver-related mortality. In Australia, treatment uptake has declined between 2016 (32,000 treated) and 2019/20 (2019: 11,500; 2020: estimated 8,000). Progress towards HCV elimination has been impeded by COVID-19, affecting the delivery of national and state-based HCV strategies. Scale-up of HCV testing and treatment will be required to achieve elimination by 2030. Current diagnostic pathways require multiple visits to a practitioner, reducing the proportion who receive a diagnosis. In Australia, 81% of people have had HCV antibody testing (indicative of exposure), but only 47% have had HCV RNA testing (indicative of active infection and the need for HCV treatment). Mathematical modelling suggests that HCV RNA testing needs to increase by at least 50% annually to achieve elimination in Australia by 2030. Dried blood spot testing can enhance HCV testing and linkage to care[13,14]. Benefits of dried blood spot testing include: 1) avoiding the need for phlebotomy; 2) enables testing for HCV antibodies (exposure) and RNA (active infection); 3) easy and stable to transport/store; 4) allows testing for other viruses (e.g. HIV) and 5) sample collection can be performed by peers or self-collection[11]. In addition, dried blood spot testing has high sensitivity and specificity for the detection of active HCV[15]. Point-of-care HCV testing has also been demonstrated to increase testing and linkage to care[14]. As part of a clinical observational study in drug treatment clinics and needle and syringe programs (NSPs), our group led the first evaluation of a finger-stick point-of-care HCV RNA assay[16,17]which enabled same-day diagnosis of active infection (HCV RNA) in one hour (sensitivity and specificity, 100%)[17]. These findings have informed regulatory in vitro diagnostic (IVD) approval submissions in Europe and Australia. The next step is to translate this novel discovery into routine clinical practice. There is an unprecedented opportunity to evaluate whether finger-stick point-of-care HCV RNA testing could be integrated into routine practice to enhance HCV testing and treatment among people who inject drugs (PWID). The Kirby Institute, Flinders University, and St. Vincent's Hospital have a strong track record of implementing point-of-care and dried blood spot testing for sexually transmitted infections (STIs), HCV, and SARS-CoV-2 (COVID-19), thus providing an sound foundation on which to scale-up GeneXpert HCV and dried blood spot testing in Australia. One of the most critical aspects in the implementation of new point-of-care and dried blood spot testing programs is the development of a program which includes clinical education, operator training and competency assessment, and appropriate risk and quality management. A standardised training program will be developed through the Kirby Institute, Flinders

	University International Centre for point-of-care testing, St. Vincent's Hospital, and the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Flexible training resources will be developed specifically for operator use in the required clinical settings. The training program will be delivered to operators using well established training pathways via remote learning platforms, such as GoToMeeting, website tutorials, and other online resources. The training will include pre-analytical (e.g. specimen collection, cartridge preparation, analytical (e.g. test operation including use of software and middleware) and post-analytical components (results interpretation and recording, waste disposal, and environmental decontamination) required to accurately perform patient tests. The HCV point-of-care testing program will also implement a quality system, consistent with best practice and regulatory standards and based upon successful existing programs currently in place for infectious disease point-of-care testing. This program provides an excellent opportunity to prospectively evaluate the effectiveness of the operator training with regard to knowledge improvement, practical competency and professional conduct for performing point-of-care and dried blood spot testing for HCV infection. This data will be useful in the assessment of training effectiveness across different trainee occupations and will be utilised to improve training processes for scale-up of point-of-care and dried blood spot testing.
Study Objectives	This study aims to address several objectives among people participating in point-of-care and dried blood spot testing for HCV infection clinical education, operator training, external quality assurance, and internal quality control programs, including: 1) To evaluate changes in self-reported knowledge about point-of-care and dried blood spot testing for HCV infection; 2) To evaluate changes in self-reported competency in performing point-of-care and dried blood spot testing for HCV infection; 3) To evaluate the concordance of quality control and external quality assurance testing with the expected results in the program; 4) To evaluate the proportion of operators who participate and complete the quality control and external quality assurance program; 5) To evaluate the proportion of tests with error or invalid results; 6) To evaluate the proportion of error/invalid test with a successful repeat point-of-care test.
Study Setting	This study will be conducted at services (either needle and syringe programs or health services) in Australia. It is envisaged that each site will consent and train a maximum of 4 participants for participation in an operator training, quality assurance, and quality control programs for point-of-care and dried blood spot testing for HCV infection.
Participant population	Depending on the exact number of operators undertaking and completing training at each site, it is anticipated that 100-150 operators will be enrolled and will participate in an operator training, quality assurance, and quality control program for point-of-care and dried blood spot testing for HCV infection. Participants/operators will consist of nurses, physicians, needle and syringe program staff, peer-support workers, other health workers and other staff who have an interest to be appropriately trained.
Eligibility criteria	Operators at the service are eligible for inclusion if the following criteria are met: 1) Provide written informed consent 2) ≥18 years of age 3) Staff member who will be performing point-of-care or dried blood spot testing for HCV infection.

Study design	This is an observational study of people who initiate commence and complete training through this "Operator Training, Quality Assurance, and Quality Control Program" that will be developed in collaboration by Flinders University, The Kirby Institute, UNSW Sydney, St. Vincent's Hospital and the Australian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). The Program will consist of online pre-requisite learning modules (developed by ASHM), 2) theoretical operator training (developed by Kirby Institute, Flinders University, and St. Vincent's Hospital); 3) practical operator training and 4) competency assessment using quality assurance/quality control (developed by Kirby Institute, Flinders University, ASHM, and St. Vincent's Hospital). The online prerequisite learning modules will cover: 1) epidemiology, risk factors, and natural history of HCV infection; 2) the importance of why point-of-care and dried blood spot testing for hepatitis C are needed to enhance linkage to care and treatment uptake; 3) markers of HCV infection and the different types of HCV tests; 4) how samples for HCV testing can be collected and where HCV sample testing may occur; 5) the advantages and disadvantages of different diagnostic tools (point-of-care and dried blood spot) and their availability in Australia. The Operator Training and Quality Assurance/Quality Control will cover online theoretical training will include: 1) specimen collection, 2) sample preparation, 3) general device overview and use 4) test cartridge preparation, 5) test orders, 6) interpretation and actioning of patient results, 6) internal quality control testing, 7) external quality assurance testing, 8) device maintenance and troubleshooting and 9) result notification. Operators completing theory training will be required to pass an online quiz prior to proceeding to practical competency assessment. Practical competency assessment of the operator performing a negative and positive quality control test will be observed via teleconferencing. Operators will be deemed competent for a period of 2 years, once satisfactory QC testing has been observed. Operator competency certificates will be issued with a unique operator login. At enrolment, participants will complete a self-administered, online survey. The survey will collect information on demographic characteristics (age, gender), the type of service at which participants are employed, role in service, personal experience with HCV testing and treatment for HCV (e.g. numbers tested and treated), knowledge of hepatitis C infection, and knowledge of HCV point-of-care testing and dried-blood-spot testing. A 5-point Likert scale will be utilised to measure participants' HCV-related competence in (i) ensuring people at risk for HCV are regularly screened, (ii) interpreting test results and diagnose HCV, (iii) collection of a fingerstick sample, (iv) performing dried blood spot HCV testing, (v) performing point-of-care HCV testing, (vi) operating the GeneXpert machine. Participants graded own competence in the six five categories by selecting either (1) Not at all confident, (2) Slight knowledge, skills or competence, (3) Average

competence amongst peers, (4) Confident and competent, (5) Very confident and competent.

All participants will complete a self-administered, online survey following each stage of the operator training process, including completion of the: online pre-requisite learning modules, theoretical operator training, practical operator training and at 6 months post-training completion; and quality assurance/quality control.

Study Procedures

Study Visit	Screening (Enrolment)	Pre-requisite Learning	Theoretical Training	Practical Training	6-month Post-training Review
Informed consent	X				
Survey (Screening version)	X				
Survey (Follow-up version)		X	X	X	X

To evaluate the quality system participation rate and the concordance of quality control and external quality assurance testing with the expected results in the program, data will be collected at defined intervals from the GeneXpert devices, evaluated for concordance with the expected result and recorded on a quality control or quality assurance spreadsheet.

We will use data from the point-of-care connectivity systems to measure the uptake of point-of-care testing, error rates (proportion of point-of-care tests with an error code), invalid rates (proportion of point-of-care tests with an invalid result) and successful re-tests (proportion of errors/invalid, with a successful repeat point-of-care test). These data will be provided back to operators as part of the process for improved performance in a summary feedback report.

Study analysis

The population attending HCV education and training sessions will be characterised using descriptive analyses. The frequency and proportion of each participant who responded to surveys at each stage of the operator training process, including online pre-requisite learning modules, theoretical operator training, practical operator training; and quality assurance/quality control will also be evaluated.

We will evaluate knowledge and self-perceived competency related to HCV management and treatment. Competency scores will be re-categorised into a binomial 0/1 response, where 0 indicates little or no competency and includes: (1) Not at all confident, (2) slight knowledge, skills, or confidence, and (3) Average competence amongst peers, and 1 indicates confidence and competence including responses: (4) Confident and competent, and (5) Very confident and competent. Using a McNemar's test for binomial paired data, we will test for a significant change in competency (from baseline (pre-training) to follow-up (6 months post-training) and significance of this change for self-reported participant ability in (i) ensuring people at risk for HCV are regularly screened, (ii) interpreting test results and diagnose HCV, (iii) collection of a finger-stick sample, (iv) performing dried blood spot HCV

	testing, (v) performing point-of-care HCV testing, (vi) operating the GeneXpert device among participants who answered all four surveys. Factors associated with poor self-perceived (little/no competency) will be assessed using logistic regression analyses. We will also assess if knowledge or self-perceived competence leads to improved practice (e.g. lower proportion with error or invalid test results).