Trial/Study Protocol

Reaching mEthadone users Attending Community pHarmacies with HCV

Trial/Study Acronym	**REACH HCV**
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PROTOCOL APPROVAL

Reaching mEthadone users Attending Community pHarmacies with HCV

Signatures

The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the trial/study/study in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Prof John F Dillon Chief Investigator	Signature	08/04/2020 Date
Prof Peter T Donnan Individual Responsible for Statistical Review	Signature	Date

LIST OF ABBREVIATIONS

AE	Adverse Events
BBV	Blood Borne Virus
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
CRF	Case Report Form
DAA	Directly Acting Antiviral
DBS	Dried Blood Spot
DMC	Data Monitoring Committee
DOT	Directly Observed Therapy
DNA	Deoxyribonucleic Acid
F# (e.g. F1, F4)	Markers on the fibrosis stages range (F0 – F4)
GP	General Practitioner
HBV	Hepatitis B Virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
HTA	Health Research Agency
ISF	Investigator Site File
LOD	Limit of Detection
LPLV	Last Patient Last Visit
NHS	National Health Service
OST	Opiate Substitute Therapy
PIL	Participant Information Leaflet
POC	Point Of Care
PWID	People Who Inject Drugs
QALY	Quality Adjusted Life Years
QC	Quality Control
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SMC	Scottish Medicines Consortium
SOP	Standard Operating Procedure
SIGN	Scottish Intercollegiate Guidelines Network
SVR	Sustained Viral Response
SVR12	Sustained Viral Response at 12 weeks post start of HCV treatment
TASC	Tayside Academic Health and Science Centre
TCTU	Tayside Clinical Trials Unit
TMF	Trial Master File
TMG	Trial Management Group
UK	United Kingdom

SUMMARY/SYNOPSIS

Trial Title	Reaching mEthadone users Attending Community pHarmacies with HCV – REACH HCV
Trial Design - UK	An international, multicentre, cluster randomised 2-arm trial of pharmacy outreach HCV diagnosis and DAA therapy versus conventional treatment pathways for HCV positive patients receiving daily OST in small volume community pharmacies in NHS Tayside and larger volume in NHS Wales and Australia. The pharmacies are geographically convenient to participants which suggests an outreach-based pathway as a solution to the HCV epidemic in this population. The trial will include up to 50 community pharmacies dispensing OST across 3 countries: Scotland, Wales and Australia. Each pharmacy will be randomised to one of two arms: Arm 1 (REACH arm): The community pharmacist will take the opportunity to explain the risks of contracting HCV from current or historical intravenous drug use. The OST patients will then meet with an outreach hepatology nurse specialist who will consent the patients and perform a diagnostic POC test along with venepuncture for safety laboratory blood tests and confirmatory HCV RNA. The outreach nurse will return at the next visit to confirm that the conditions for study eligibility have been met for patients who test positive for HCV, with the pharmacist to initiate medication supply using the Patient Group Direction (PGD). The outreach nurse will return after approximately 14 days to confirm negative results (or confer these by phone if required), supply medication for new patients with positive results (PCR positive but below limit of detection of POC test) and confirm follow up appointments where required. The RNA and POC test will also be administered for SVR12, at least 20 weeks from first dose (for 8 week treatment: 12 weeks post-treatment check). Arm 2 (Education-only arm): The community pharmacist will discuss the risks of contracting HCV through current or historical intravenous drug use. The community pharmacist will then advise on the nearest centre for testing and treatment, as is standard of care for the countries included in this study. If they are referred from a REACH pharmacy, they will present a reply slip and/or the PIS to the nurse who can then consent the participant and complete the study CRF. The participant's medication will be delivered to, and dispensed from, their community pharmacy.
Trial Design - Australia	All sponsorship and insurance activities will be undertaken by the Sponsor(s), [insert sponsors] in Australia. The University of Dundee and NHS Tayside, acting as co-Sponsor, have no responsibility or liability for trial activities conducted in Australia. These are subject to a separate sponsorship review in Australia. A multicentre, cluster randomised 2-arm trial of pharmacy outreach HCV diagnosis and DAA therapy versus conventional treatment pathways for HCV positive patients receiving daily OST in community pharmacies in

	Melbourne, Australia. The pharmacies are geographically convenient to participants which suggests an outreach-based pathway as a solution to the HCV epidemic in this population. The trial will include around 14 community pharmacies dispensing OST across Melbourne. Each pharmacy will be randomised to one of two arms: Arm 1 (REACH arm): The community pharmacist will take the opportunity to explain the risks of contracting HCV from current or historical intravenous drug use. The OST patients will then meet with an outreach hepatology nurse specialist who will consent the patients and perform a diagnostic POC test along with venepuncture for safety laboratory blood tests and confirmatory HCV RNA. The outreach worker nurse will return at the next visit to supply HCV medication for those patients who test positive. The outreach nurse will return after approximately 14 days to confirm negative results, dispense medication for new patients with positive results (PCR positive but below limit of detection of POC test) and confirm follow up appointments where required. The RNA and POC test will also be administered for SVR12, at least 20 weeks from first dose (for 8 week treatment: 12 weeks post-treatment check). Arm 2 (Education-only arm): The community pharmacist will discuss the risks of contracting HCV through current or historical intravenous drug use. The community pharmacist will then advise on the nearest centre for testing and treatment, as is standard of care for the countries included in this study. If they are referred from a REACH pharmacy, they will present a reply slip and/or the PIS to the nurse who can then consent the participant and complete the study CRF. The participant's medication will be delivered to, and dispensed from, their community pharmacy.	
Trial Population	Patients on OST across up to 50 community pharmacy sites.	
Sample Size	140 estimated to be equally split between countries (Scotland, Wales and Australia).	
Planned Trial/study Period	2 years.	
Clinical phase duration	1 year.	
Follow up phase duration	1 year.	
Primary	**Objectives** To evaluate whether the REACH pathway is more effective in increasing diagnosis and cure of HCV.	**Outcome Measures** Proportion of patients in a population of stable OST patients achieving SVR12 in the outreach pathway versus the standard of care pathway (ITT).
Secondary	**Objectives** To determine whether the REACH pathway compared with the education-only pathway leads to more people on OST who are confirmed HCV RNA positive being treated and cured.	**Outcome Measures** Percentage of patients achieving SVR12 from the patient population that tested positive for HCV in each arm (mITT).

	To evaluate whether the REACH pathway is more cost-effective than the education-only pathway, from the perspective of the NHS (UK) and Medicare (Australia).	The mITT population includes all enrolled subjects who tested positive for HCV.
	To determine whether the REACH pathway compared with the education-only pathway leads to more people on OST being tested for HCV.	ICER to consider the epidemiological impact of scaling up the intervention to all pharmacies in a specific setting in Australia, Scotland and Wales. Cost benefit calculations (e.g. cost per HCV diagnosis, cost per SVR, cost per HCV infection averted, Number needed to screen).
	To compare adherence and persistence to HCV therapy in the pharmacy setting to the education-only pathway.	Percentage of patients being tested for HCV in each arm
	To assess the impact of baseline blood tests on treatment decisions.	Proportion of patients adhering to therapy in each arm (defined as taking ≥ 85% of their tablets as reported in the DOT adherence log completed daily by the community pharmacist). Proportion of patients in whom changes in therapy are advised due to results of the baseline medical testing
Inclusion Criteria	• Patient is at risk of HCV due to current or historical intravenous drug use. • Patient has been on OST for at least 12 weeks prior to enrolment. • Not previously treated for HCV using glecaprevir/pibrentasvir.	
Exclusion Criteria	• Detailed in section 4.12	

1 INTRODUCTION

2 BACKGROUND & RATIONALE

Hepatitis C Virus (HCV) is a blood-borne virus that damages the liver and is a major public health concern in the UK and throughout the World. HCV is referred to as the 'silent epidemic' as most of those infected are unaware of it, and show no symptoms until presenting with incurable, fatal end-stage disease. At least 0.3% of the UK population (1) have been infected with and up to 1% in Scotland (2), with similar rates in Wales. Ongoing infection amounts to 15,000 incident cases a year across the UK. About 25% of the patients clear the infection spontaneously, whereas the remainder are chronically infected. In Scotland and Australia this is approximately 0.7% of the general population (3, 4) and 0.4% in Wales (5), and they are at risk of developing cirrhosis and hepatocellular carcinoma. The clinical challenge is to identify those infected and bring them into treatment before the disease advances. Highly effective, simplified treatments are now available to the NHS. These Directly Acting Antiviral (DAA) combinations achieve cure rates in excess of 95%, with once or twice daily tablets for 8-24 weeks (6). The effectiveness of these treatments is however dependent, at least in part, although less so than previously, on the genotype of the virus, stage of the disease, as well as adherence and persistence to treatment.

Hepatitis C is spread mainly through blood-to-blood contact. Currently, the greatest risk of acquiring the virus in developed countries and many developing countries is through injecting drug use. In the majority this will involve opiate use. On the road to recovery many will be placed on long term opiate substitution therapy (OST), commonly with methadone or buprenorphine. Internationally, OST is frequently dispensed by a community pharmacist on a daily or twice-weekly regimen. Consequently, the single-largest infected group diagnosed are those on opiate substitution therapy (OST) (3), with a prevalence of 40% amongst individuals on OST in the UK, in other countries with fewer needle exchange programmes and OST provision the prevalence is higher. The standard of care within NHS healthcare boards in Scotland and Wales is that people with a history of injecting drugs and those currently on methadone are at high risk of having HCV infection and should be offered HCV testing. Australia operates a similar policy that individuals at risk of contracting HCV are offered regular testing (7). Testing can be offered by GPs, drugs workers, drug agencies, social workers, community pharmacies and needle exchange sites. Once patients are diagnosed, they are referred to a hospital-based service to receive anti-HCV treatment. In this pathway, less than 10% of the OST population is tested per year, cumulative rates of testing are less than 50% of those on OST. Of those tested and positive for HCV, not more than 25% start treatment in one of the treatment centres and only around 70 to 80% successfully complete treatment (3). This suggests that only about 2-3% (3) of this vulnerable group are receiving adequate treatment per year. This illustrates major losses in HCV treatment reach and effectiveness, leading to unnecessary morbidity and mortality, preventable onward viral transmission, and major additional health care expenditures. Key barriers in the current

pathway are (i) low testing rates, (ii) poor linkage of those tested positively to treatment sites, (iii) suboptimal adherence and persistence to the treatment.
The paradox of the current situation is that so few HCV patients receive and complete anti-HCV treatment, while many are easy to locate, in pharmacies picking up OST on a regular basis. Hence, the provision of OST, usually methadone, presents a key opportunity to introduce a novel, potentially highly-cost-effective HCV management strategy: the testing and treatment of HCV infected patients receiving OST in community pharmacies.

2.1 RATIONALE FOR STUDY

To curb the HCV epidemic at a population level there is a requirement to identify a pathway of care that successfully treats HCV infections in the majority of patients on addictions therapy, a significant at-risk subgroup, many of whom are of advancing age and duration of infection and are increasingly likely to present with the complications of HCV infection, with the associated morbidity, mortality and health-related costs.
Patients on OST have a wide experience of stigma and discrimination from previous contacts with the health service and are reluctant to access care, especially in new environments. They have multiple barriers to travelling to hospital-based clinics, even if they knew about HCV and knew their HCV status. Recent work from our own group investigated how patients from a PWID background valued different aspects of HCV care, in terms of time they were prepared to wait (8). Their most valued preferences were to be treated in a familiar environment and to be treated with respect. In a community pharmacy, patients have a regular and familiar point of contact with the health care service that they highly value; they also have an incentive to attend and interact in this setting: to obtain OST.
A minority of pharmacies in NHS Tayside will dispense to large numbers of clients and it is logical to upskill or embed staff to focus on HCV diagnosis and treatment in such pharmacies. A strategy of upskilling staff in large volume OST pharmacies is being tested in an ongoing multi-centre cluster randomised controlled trial. However, the majority of pharmacies in NHS Tayside will have a small number of patients which, when considered together, represents a large pool of patients. Upskilling staff in such pharmacies would be inefficient as all the patients could have been treated before they gained competency in their skills and large numbers would have to be trained.
We anticipate the number of OST patients in the pharmacies involved in NHS Wales and Australia will be higher than those in NHS Tayside, but not to an extent that will impact on the number of participants or to necessitate the upskilling of pharmacy staff in these sites.
The large number of pharmacies each with a small part of a large cohort of patients who are resistant to referral and travel to other sites, would suggest an outreach-based pathway as a solution. Multiple visits to multiple sites would be an inefficient use of a skilled nurse's time. However, the advent of the HCV DAAs allows the rationalisation of much of the testing and monitoring for HCV therapy, and combining this with new developments in point of care (POC) testing for HCV RNA would allow a very streamlined care pathway with many fewer

visits. This could limit the number of blood tests required from each patient prior to treatment. Currently a patient requires; HBV and HIV screening, liver function tests, urea and electrolyte tests, full blood count, coagulation, fibrosis markers and liver immunology. Treatment with DAAs may not necessitate that these test results are within certain limits, given their safety and efficacy profile. Lowering the number of tests required relieves a great strain on both the patient and the laboratories performing the analysis.

3 TRIAL/STUDY OBJECTIVES & OUTCOMES

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
To evaluate whether the REACH pathway is more effective in increasing diagnosis and cure of HCV in patients on OST.	Proportion of patients in a population of stable OST patients achieving SVR12 in the REACH pathway versus education only pathway (ITT).	*End of study*

Table 2: Secondary Objectives and Outcome Measures

Secondary Objective:	Outcome Measure:	Time point of outcome measured
To determine whether the REACH pathway compared with the education only pathway leads to more people on OST who are confirmed HCV RNA positive being treated and cured.	Percentage of patients achieving SVR12 from the patient population that tested positive for HCV in each arm (mITT).	*End of study (1 year).*
To evaluate whether the REACH pathway is more cost-effective than the education-only pathway, from the perspective of the NHS (UK) and Medicare (Australia).	ICER to consider the epidemiological impact of scaling up the intervention to all pharmacies in a specific setting in Australia, Scotland and Wales. Cost benefit calculations (e.g. cost per HCV diagnosis, cost per SVR, cost per HCV infection averted, Number needed to screen).	*Lifetime horizon and between 10 and 20 years.*
To determine whether the REACH pathway compared with the education-only pathway leads to more people on OST being tested.	Percentage of patients being tested for HCV in each arm	*End of study (1 year).*
To compare adherence and persistence to HCV therapy in the pharmacy setting to the education only pathway.	Proportion of patients adhering to therapy in each arm (defined as taking ≥ 85% of their tablets as reported in the DOT adherence log completed daily by the community pharmacist).	*End of study (1 year).*
To assess the impact of baseline blood tests on treatment decisions.	Proportion of patients in whom changes in therapy are advised due to results of the medical testing.	*Study start.*

4 TRIAL/STUDY DESIGN

4.1 INTERVENTION

In the intervention pharmacies, the pharmacist dispensing OST would in the preceding weeks to opening as a study site have raised awareness about HCV infection and given information about HCV treatment to their OST patients. A trained, hepatology specialist nurse would arrive in each pharmacy, and on first visit to site would offer HCV RNA testing on a venepuncture sample of blood via GeneDrive (tubes for the additional bloods and confirmatory bloods would be taken at the same time). On their subsequent visit to site the

nurse would return and convey the diagnosis to each patient. Those who are positive would have a brief medical history taken, a check for contra-indications to HCV therapy, and then be offered therapy following assessment by the nurse. The Pharmacist would dispense the HCV therapy daily along with OST for 8 weeks (duration will be prolonged in line with product label if baseline tests suggest compensated cirrhosis or patients are GT3 TE) and the nurse would return to the pharmacy after at least 20 weeks (a minimum of 12 weeks post end of treatment) to check for SVR. Return visits may be required to capture SVR12 for all participants. In the meantime the nurse would have been visiting other pharmacies.

We propose to evaluate whether, using simpler and more effective HCV regimens, treatments can be safely initiated in community pharmacies by outreach nurses and then monitored by community pharmacists. We propose to utilise the existing, pharmacy environment that patients are already familiar with and are visiting on a regular basis to refine the pathway into HCV therapy. Pharmacists can co-administer OST with anti-HCV therapy, so that many medicines are taken under supervision (also known as partial or modified directly observed therapy, DOT) (9). The regular interactions allow for frequent reinforcement of behaviour and addressing concerns about side effects or treatment effectiveness; as opposed to the education-only pathway of treatment at a treatment centre that requires patients to familiarise themselves with new health care providers, frequent additional travelling (every 1-2 weeks, which costs time and money), fully autonomous medication consumption, and intermittent treatment supervision (every 1 or 2 weeks). The pharmacist role development (i.e. monitoring treatment, and the income generated through treatment fees) will also incentivise the pharmacists to raise awareness in the target group about HCV testing and treatment. The intervention will focus on stable OST patients who are much less likely to drop out of OST while on anti-HCV therapy and it will be important that we measure this potential drop-out rate, though previous trials in this population would suggest that prescription of HCV therapy is associated with a low rate of drop in OST cohorts (10).

The intervention will be evaluated against OST dispensing community pharmacies that would be randomised to standard of care awareness raising and signposting to testing for HCV.

4.2 TRIAL/STUDY DESCRIPTION

This is an international, multicentre, cluster randomised trial of pharmacy outreach HCV diagnosis and therapy versus conventional treatment pathways for HCV positive patients receiving daily OST in pharmacies. The unit of randomisation is pharmacies. The pathways are described below.

Education-only Pathway: In pharmacies randomised to the conventional care pathway, the staff training and educational materials on HCV testing and HCV treatment will be delivered by the trial staff to small groups of pharmacists. The pharmacist will, as recommended as good practice, opportunistically discuss with all attending OST patients the possibility of having HCV infection and getting tested and if positive, treated. Information will be provided

verbally and by offering standard leaflets about HCV and local services for testing and treatment. The pharmacist will record on a screening log which OST patients they have had a discussion with and provided with a PIS and reply slip. If the patient attends and presents the trial document(s) at one of the treatment centres; the treatment nurses will consent them, and test them for HCV. Should a participant attend without presenting study document(s) the study nurse will contact the pharmacy where participant receives their OST and confirm they have been noted on the screening log and have received at least a PIS and had over 24 hours to consider participation. Any HCV treatment prescribed would be dispensed by the OST-providing pharmacy as per standard practice and treatment follow up would be with the nurse as per the study treatment follow up. Adherence to the study drug will be recorded by the community pharmacist by noting the number of tablets dispensed alongside the patient's OST. For daily OST patients, non-attendance or refusal to take medication would be recorded. For patients who receive OST to take away these patients should be asked to return any untaken medication at their next visit. The study-related data collection will be undertaken by the treatment nurse and entered into the CRF by the study specialist nurse. Blood test results, including SVR12, will be reported to the patient by clinical letter and held with their electronic medical records.

The Pharmacy outreach pathway: In pharmacies randomised to the outreach pathway, the staff training and educational materials on HCV testing and HCV treatment will be delivered by the trial staff to small groups of pharmacists and pharmacy staff according to an established training programme. At the start of the pathway prior to attendance of the outreach nurse, pharmacists will discuss HCV infection and treatment with their OST patients. The outreach nurse would arrive in the pharmacy for a day and offer testing for HCV to OST recipients, patients would be consented to the study. From those agreeing to be tested, the nurse would perform conventional venepuncture taking blood for POC testing and additional tubes for subsequent full blood count, urea and electrolytes, liver function testing, including markers of liver fibrosis (Fib4, APRI, AST:ALT ratio), and viral parameters (HCV antibody and viral load, HIV and HBV screens to confirm no co-infection). In NHS Tayside, a baseline sample will also be stored at minus 80°C in a University of Dundee laboratory freezer, located within Ninewells Hospital, Dundee, to only be analysed in the event of a potential relapse to support differentiation of relapse from reinfection. These research samples will be destroyed at the end of the trial if they have not been analysed. For other sites, storage will be undertaken in line with prevailing local policy. The nurse will carry out a point of care (POC) test for HCV RNA using GeneDrive®, a PCR platform developed by Epistem (see below) as this takes 90 minutes it is anticipated the patients will not wait for the results and will be seen at a subsequent visit. The nurse would return to the pharmacy the next available day, meet those tested and convey their results, (or confer these by phone if required):

- Those who are HCV RNA positive would be offered anti-HCV therapy along with a study questionnaire and EQ5D-5L. If they accept therapy, the nurse will complete a

pre-treatment checklist of medical co-morbidities, medical history, and concomitant medication to look for drug-drug interactions. If there are no contraindications, therapy will be supplied by the nurse that day and dispensed in the pharmacy along with the patient's OST. The patients who decline study participation will be entered in the screening log. HCV+ patients who are unsuitable for the trial will be referred to local hospital services for assessment outside the study as standard clinical care. Their results will not be included in the study data or analyses.

- Patients who test negative following the POC test will be told that results are probably negative but that the result must be confirmed by labs (as the lower limit of detection is approximately 2,000 IU/mL) using their venous bloods taken for a RNA PCR. For those patients who are HCV PCR negative on the POC device, the nurse will revisit them in the pharmacy with the results of their venepuncture bloods to confirm their HCV status (or confer these by phone if required), any patients who are PCR positive but were below the limit of detection for the POC device will then be commenced on HCV therapy.

Both Pathways: In both pathways, patients deemed unsuitable for treatment with study drugs due to meeting 1 or more exclusion criteria and those with tests indicating co-infection with HIV or HBV will be excluded from the study and referred to the specialist hepatology service at the patient's nearest hospital. These patients will not contribute to the study data. The likely low percentage of patients who will meet exclusion criteria should not affect the sample size of the study. Patients with blood test results indicative of compensated cirrhosis will also be referred to secondary care, but treated within the study with a regimen which has been adjusted to their unique clinical requirements.

In NHS Tayside, a baseline sample of blood will be taken from all patients initiating HCV treatment and will be stored at minus 80°C in University of Dundee freezers at located at Ninewells Hospital, Dundee, to only be analysed In the event of a potential relapse, to support differentiation of relapse from reinfection. If these samples are not required for relapse/reinfection analysis they will be destroyed at the end of the study. For other sites, storage will be undertaken in line with prevailing local policy.

Prescription of medication: In Scotland and Wales, non-medic prescribing, i.e. prescriptions generated without a qualified physician seeing the patient is considered as standard practice across a range of conditions including HCV. This is covered in more detail in "Medicines, Ethics and Practice, The professional guide for pharmacists" of The Royal Pharmaceutical Society (11). For information, In Australia, a registered medical practitioner will sign-off HCV prescriptions remotely, following assessment for treatment conducted by a nurse.

Enrolled patients will be prescribed three combination tablets of 100mg glecaprevir and 40mg pibrentasvir (commercial name: Mavyret) for a total daily dose of 300 mg/120 mg, advised to be taken with food, based on the following criteria:

All genotypes will receive 8 weeks of Mavyret, if they are treatment-naïve (to both IFN-based or DAA-based therapies) and have an APRI score of ≤1.

Patients with APRI >1 will be evaluated with a further test. This will take place following commencement of therapy, by appointment in a clinic setting outside of their community pharmacy, (e.g. Fibroscan or Fibrotest). There will be no change to therapy if results are consistent with F0-F3; if results are consistent with F4, participants will have their treatment regimen extended by four weeks, to a total of twelve weeks.

Enrolled patients who have previously failed therapy with peg-IFN + ribavirin +/- sofosbuvir or sofosbuvir + ribavirin will be prescribed:

- Genotypes 1,2,4,5 and 6 will receive 8 weeks of Mavyret if their APRI score is ≤1. Patients with APRI >1 will be evaluated with a further test. This will take place following commencement of therapy, by appointment in a clinic setting outside of their community pharmacy, (e.g. Fibroscan or Fibrotest). There will be no change to therapy if results are consistent with F0-F3; if results are consistent with F4, participants will have their treatment regimen extended by four weeks, to a total of twelve weeks.
- Genotype 3: 16 weeks of Mavyret, (regardless of APRI score)

HCV RNA POC Detection: The POC device will be purchased at each site from Epistem who have developed a CE-IVD marked molecular diagnostic device, Genedrive®, a compact, low cost and highly sensitive POC molecular diagnostic platform. The Genedrive® device is a PCR-based platform, which incorporates a 'hybrid thermal engine' capable of performing ultra-fast PCR cycling. Single probes are used to detect a specific region of amplified target nucleic acid and precise melting curve analysis yields qualitative and quantitative target information. The device is suitable for use by operators after minimal training and provides a simple yes/no reading for unequivocal results. Genedrive® has been designed to enable 'Direct to PCR' analysis of different matrices without the requirement to undertake pre-extraction of nucleic acids, enabling rapid detection and diagnosis, all in under 90 minutes from sample collection (50 minutes for single nucleotide polymorphisms (SNPs), 90 minutes for viral detection). The platform also utilises Epistem's iD probesTM, a proprietary chemistry that provides robust melt-curve analysis for complex genotyping and qualitative and quantitative infectious disease detection. This device is now CE marked for HCV RNA detection in the EU.

4.3 TRIAL/STUDY FLOWCHART

See Appendix 3.

4.4 TRIAL/STUDY MATRIX

See Appendix 4.

4.5 TRIAL/STUDY ASSESSMENTS

Enrolled participants will receive three or four formal data collection visits, depending on pathway and will have regular between visit reviews and as needed if patients have concerns/problems, as per the standard of care in these countries, for the purpose of collecting information on any adverse events from their prescribed treatment and to check drug compliance.

The trial staff including the community pharmacists will be trained by the investigator in AE reporting. The management of AEs will be discussed with the trial specialist nurse or supervising physician. The trial staff will refer all patients for whom they deem it medically necessary as per standard medical practice to their primary medical care provider or emergency department.

4.6 TRIAL SITE RECRUITMENT

UK sites

Pharmacies will be invited to participate in the trial by local health board pharmacy representatives. The trial and related activities will be presented to them (pharmacy study information sheet) and they will be able to freely choose whether to take part. Pharmacies will receive the standard NHS-associated dispensing fees for dispensing HCV medication to trial participants.

If a pharmacy signs-up to take part as a site in the study, the activities they are expected to perform will be outlined in an NHS service specification.

N.B. Australian activity in this regard will be outlined in the Australian protocol, separate to this one.

PRE-SCREENING

Study and pathway specific information distributed to potential participants by community pharmacist.

REACH PATHWAY

Initial Screen
Informed consent obtained.
HCV RNA test administered by PoC device.
Safety blood laboratory tests (including full blood count, urea and electrolytes, liver function testing, including markers of liver fibrosis (Fib4, APRI, AST:ALT ratio), and viral parameters (HCV antibody and viral load, HIV and HBV screens to confirm no co-infection).
Study data collection.
Record concomitant medications.

Treatment Start		Consultation
Begin treatment, for those who tested positive on Poc device		Consultation for participants who tested negative on PoC Device initially.
Confirm consent.		HCV results conferred for patients who tested negative on PoC test. If negative for HCV confirmed, participant thanked for their time – study documents updated (completion of study form etc.).
HCV result by POC device from initial screen test conferred.	OR	If positive according to venous blood results, HCV PCR and genotype results from venous bloods used (historic genotype results within 5 years may be used where appropriate), **then:**
Inclusion/Exclusion criteria.		Inclusion/Exclusion criteria.
Study data collection (EQ5D-5L, demographics, stable housing, social care, medical history and injecting partner).		Study data collection.
Update concomitant medications.		Update concomitant medications.
Administer treatment dose.		Administer treatment dose.
Monitor and record adverse events.		Monitor and record adverse events.

Sustained Viral Response (SVR^{12})
Confirm Consent
HCV RNA test by PoC device for SVR^{12}
Study data collection (including but not limited to EQ5D-5L, demographics, stable housing, social care, medical history and injecting partner).
Update concomitant medications.
Monitor and record adverse events.

EDUCATION-ONLY PATHWAY

Initial Screen
Potential participant advised to attend local clinic running REACH trial for HCV care/test.
Participants evidences attendance at REACH pharmacy by trial documentation or phone call to pharmacy.
Informed consent obtained.
HCV RNA test administered by venous bloods.
Safety blood laboratory tests (including full blood count, urea and electrolytes, liver function testing, including markers of liver fibrosis (Fib4, APRI, AST:ALT ratio), and viral parameters (HCV antibody and viral load, HIV and HBV screens to confirm no co-infection).
Study data collection.
Record concomitant medications.

Treatment Start
Begin treatment, for those who tested positive on venous bloods
Confirm consent.
HCV result by venous bloods from initial screen test conferred.
Inclusion/Exclusion criteria.
Study data collection (EQ5D-5L, demographics, stable housing, social care, medical history and injecting partner).
Update concomitant medications.
Participant's result conferred to community pharmacist.
Participant's HCV prescription and medication transferred to community pharmacist
Pharmacist dispenses HCV treatment in line with participant's usual OST schedule and records adherence on log.

Sustained Viral Response (SVR^{12})
Confirm Consent
HCV RNA test by venous bloods for SVR^{12}
Study data collection (including but not limited to EQ5D-5L, demographics, stable housing, social care, medical history and injecting partner).
Update concomitant medications.
Monitor and record adverse events.

4.6 TRIAL/STUDY SAFETY ASSESSMENTS

For adverse event reporting see section 10 below.

Safety bloods to assess liver and kidney function including liver function tests (LFTs), urea and electrolytes (U&Es) Full blood count (FBC), and prothrombin time (PT) will be assessed prior to the onset of treatment to ensure that the participant can tolerate DAA therapy .

Female participants may be requested, but will not be required, to have a urine pregnancy test prior to beginning treatment to ensure that they are not pregnant. They must be willing to use a birth control method which is medically approved.

Medically approved birth control:

- Combined Oral Contraceptive Pill
- Intrauterine device – 'coil'
- Male condom

- Injected, patch or implant contraceptive
- Male partner vasectomy - sterilisation

4.7 TISSUE

Up to nine blood sample bottles (approximately 50 millilitres) will be taken by venepuncture to be used for; safety bloods, genotyping and initial HCV PCR, to validate the results of the POC test. Some of this blood will be stored for comparison in the event of a potential relapse to support differentiation of relapse from reinfection. Additionally, HCV RNA by PCR will be taken at SVR12. This will be analysed by local laboratories and stored as per local guidelines. Any samples that have gone unused at the completion of the study will be destroyed according to local guidelines.

4.8 INCIDENTAL FINDINGS

Any incidental findings (IF: previously undiagnosed condition) considered to be clinically significant will be reported to the participant's GP and/or consultant by the CI or Site PI, with the consent of the participant.

4.9 TRIAL/STUDY POPULATION

Current or historical intravenous drug users who have put themselves at risk of HCV and attend regularly for OST in a community pharmacy.

4.10 NUMBER OF PARTICIPANTS

Up to 140 participants may be recruited into active participation in the study from patients receiving OST at selected pharmacies across participating health boards in; Scotland, Wales and Australia. Each participating health board will form at least one 'hub' geographically mapped upon existing treatment centres currently providing conventional treatment pathways for HCV infection. Local community pharmacies providing OST within each hub area will be invited to participate. Participating pharmacies will be equally randomised to either conventional or REACH pathways, within each hub. The study population is all OST patients who are at risk of HCV based on current or historical injecting drug use in included pharmacies within the catchment area of 3 study hubs (1 in Scotland, 1 in Wales and 1 in Australia). Wales and Australia will be associated with 12-14 participating community pharmacies, giving 28 pharmacies; with Scotland recruiting up to 20 community pharmacies due to fewer eligible participants, resulting in a total of up to 48-50 participating pharmacies. This is a result of NHS Tayside's historically intensive community testing and treatment for HCV.

4.11 INCLUSION CRITERIA

- Over 18 years of age.
- Previous or current injecting drug user.
- Stable OST dose for greater than 12 weeks prior to study enrolment.
- Glecaprevir/pibrentasvir treatment naïve.
- Able to voluntarily sign and date an informed consent form prior to initiation of any screening or study specific procedures.
- Able to understand and adhere to study visit schedule and all other protocol requirements.

4.13 EXCLUSION CRITERIA

- Female who is pregnant, planning to become pregnant or breastfeeding or unwilling/unable to take appropriate birth control.
- Known current HIV infection.
- Known current HBV infection. Serological: patients with a positive HBsAg or isolated positive anti-HBC will be excluded from the study and followed up in secondary care.
- Previous treatment with glecaprevir/pibrentasvir.
- Currently taking any concomitant medication that has a warning of'do not co-administer' with glecaprevir and/or pibrentasvir as defined by the Liverpool Hep drug interactions website and product SmPC (12).
- Clinically significant abnormalities that make candidate unsuitable for this study in the opinion of the investigator including but not limited to:
    - Uncontrolled cardiac, respiratory, gastrointestinal, hematologic, neurologic, psychiatric or other medical disease or disorder, which is unrelated to existing HCV infection.
- History of either current or previous decompensated liver disease or symptoms/signs of decompensation e.g. ascites noted on physical exam, use of beta-blockers for portal hypertension, hepatic encephalopathy or oesophageal variceal bleeding.
- Candidate is deemed unsuitable to receive study drugs by the study investigator, for any reason according to clinical judgement.
- Unable or unwilling to provide informed consent.
- History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs.
- Drug-drug Interaction which may have safety concerns with any concomitant medication the patient is receiving including non-prescribed and/or recreational drugs.

Individuals will not be enrolled to the trial if they are participating in the clinical phase of another interventional trial/study or have done so within the last 60 days. Individuals who are participating in the follow-up phase of another interventional trial/study, or who are enrolled in an observational study, will be co-enrolled where the CIs of each study agree that it is appropriate.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Patients in OST attending participating pharmacies will be recruited following a discussion with their community pharmacist highlighting the risk of contracting HCV through current or previous intravenous drug use or patients with a previous known diagnosis would be systematically approached to participate in the trial. Those that agree to enter the trial would provide consent. For the study there would be no further adjustment of the groups so the trial will be testing the whole pathway of care.

For those patients attending a pharmacy within the REACH pathway a protocol-driven checklist for therapy suitability will be completed by the specialist nurse with medical review by the study investigators available for participants, where required, prior to commencing therapy.

5.2 CONSENTING PARTICIPANTS

Potential participants will be approached by their community pharmacist familiar with the trial methodology. They will be provided with information on the study verbally and via the Patient Information Sheet (PIS) and be given at least 24 hours to consider participation.

At their return visit for screening they will be interviewed by the outreach nurse trained in obtaining informed consent in clinical trials and asked to sign an informed consent form, once they are satisfied that they have had adequate explanation from the outreach nurse explaining the trial to them.

For the education only pathway consent will be taken when the participant attends at the local clinic with evidence they were referred by a pharmacy within the trial.

Where a participant requests to speak with a physician from the study team the consent process will not be completed until the participant has spoken to the physician and had all their questions answered to their satisfaction.

The ICF and all participant facing documents will be made available in Welsh for any and all participants within NHS Wales who request this service.

For adults who lose capacity their previous wishes will remain legally binding and this will remain valid unless the protocol changes significantly. If this occurs and further consent is required from a participant who has lost capacity, the appropriate person will be asked for their consent. In all cases the CI or delegate will consult with carers and take note of any signs of objection or distress from the participant – the participant will be withdrawn if they raise objection. Where appropriate the participant will be withdrawn from any further clinical intervention and agreement will be sought from a carer to allow data collection.

The informed consent process will be conducted in compliance with TASC SOP07: Obtaining Informed Consent from Potential Participants in Clinical Research.

5.3 SCREENING FOR ELIGIBILITY

All OST patients attending the participating pharmacies will be assessed for eligibility, with those currently already on HCV treatment or who meet the exclusion criteria being deemed ineligible to participate.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Ineligible or non-recruited participants will be thanked for their interest in the trial and be given a clear explanation as to why they are ineligible for the trial.

5.5 RANDOMISATION

5.5.1 Randomisation

Up to 50 pharmacies centred on 3 hubs 1 in Scotland, 1 in Wales and 1 in Australia will be enrolled to this study. Within each hub, 50% of pharmacies will be randomised to the outreach pathway and 50% randomised to the education-only pathway. The randomisation will be carried out using the online facility: https://www.graphpad.com/quickcalcs/randomize2/, where group A is the REACH pathway and group B the Education-only. Those pharmacies allocated to conventional care will direct patients to their existing hub centre which provides the current conventional treatment pathway. The duration of therapy is short so the chances of a patient changing methadone provider during the trial is low. However, if it does occur, we will be informed as it happens by the pharmacist. As this is a national service Trial Staff will transfer the trial medication to the new pharmacist for dispensing, it is standard care to provide HCV medication and OST at the same time from pharmacies.

5.5.2 Intervention Allocation

Participants will then be allocated to conventional HCV treatment or to the outreach pathway depending on the pathway to which their pharmacy was randomised.

5.5.3 Withdrawal procedures

Participants will be informed that they have the right to withdraw from the study at any time. The right to refuse to participate without reasons will be respected. After the participant has entered the study they remain under the care of a supervising physician, and the local blood-borne virus services whose clinicians are free to give alternative treatment to that specified in the protocol at any stage if it is considered that it is in the participant's best interest, but reasons for doing so will be recorded. In such cases the participants remain within the study for the purposes of follow-up and data analysis. All participants will be free to withdraw at any time from the study without giving reasons and without prejudicing further treatment.

For participants who withdraw and do not wish to receive study related interventions, then no further contact will be made by the study team. They will continue with their OST in line with their prevailing care plan in place with their pharmacist.

Where participants are withdrawn from treatment for safety reasons due to adverse drug reactions they will continue to be followed up for as long as is necessary until the adverse event has resolved. Those who withdraw can ask for data to be destroyed.

6 DATA COLLECTION & MANAGEMENT

6.1 DATA COLLECTION

The data will be principally collected by the staff appointed to the study and supported by other study appointed staff. The data sources will include the CRF, medical notes (if followed up in standard care pathway) and laboratory reports.

Patient-specific data will be collected during treatment and at fixed points thereafter as detailed in the study matrix. Due to the nature of the study population most data recording and study interventions will be directly supervised. The majority of the information related to concurrent and previous drug use will be entered directly into the CRFs without this information being routinely recorded in clinical data sources.

6.2 DATA MANAGEMENT SYSTEM

Data management will be conducted in compliance with TASC SOPs on Data Management, including TASC SOP53 Data Management Systems in Clinical Research.

Health Informatics Centre (HIC) will be commissioned to provide a customised online database for data entry for the data management system (DMS), as approved by Sponsor.

The DMS will be based on the protocol and CRF for the trial and individual requirements of the investigators. The CRF will collect only information that is required to meet the aims of the trial and to ensure the eligibility and safety of the participant. The trial database will be compliant with TASC SOP53 Data Management Systems in Clinical Research.

The database is managed in line with all applicable principles of medical confidentiality and UK law on data protection, namely, the Data Protection Act 1998, which brought UK law into line with the EU Data Protection Directive. The Data Controller will be the University of Dundee and the Data Custodian will be the CI.

The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the trial team.

7 STATISTICS AND DATA ANALYSIS

7.1 SAMPLE SIZE CALCULATION

As the pharmacist pathway is a specific population-based intervention for diagnosis and treatment, the number of patients on OST treatment at each pharmacy is the known factor, HCV status of individuals within the pharmacy will be unknown at time of study set up so the number of patients on OST in pharmacy will be the target for trial set up.

Studies show some international variability in the rate of patients on OST who are HCV positive, with an average being around 40% prevalence (13, 14). We have based the power calculation for the study on the assumption that each pharmacy will have approximately 4 HCV positive OST patients (assuming on average 10 patients on OST at each pharmacy and 40% prevalence) who could be identified and considered for treatment.

The study is powered on the rates of SVR12. Approximately 3% of HCV positive OST patients enter HCV therapy per year via education-only pathways, with 2.5% of the total eligible population achieving SVR per annum. The study will be powered on the difference in proportions of those HCV positive on OST who achieve SVR. Currently this is estimated to be 2.5% and we expect to achieve 25%. For a parallel group design the number required per arm would be n = 48 and so 96 in total with 90% power and two-sided alpha of 0.05. Allowing for clustering by assuming four patients per pharmacy and an intra-cluster correlation of 0.05, then the inflation factor is 1.15 and gives a total of 112. If we assume 20% drop out then the total number required is 140 and with four patients per pharmacy on average this would require 35 pharmacies. Given the cluster randomised design, it is possible to lose a whole pharmacy and so we will aim to recruit up to 50 pharmacies, allowing for potential loss of a pharmacy or fewer eligible participants in NHS Tayside. Estimation was based on software nQuery Advisor v7 and confirmed by an independent statistician using GPower. The randomisation of the pharmacies will be stratified by associated hub centre.

7.2 PROPOSED ANALYSES

Analysis of the trial will follow the principles outlined in the ICH E9 'Statistical Principles for Clinical Trials' and carried out by the UKCRC registered Tayside Clinical Trials Unit (TCTU). Prior to data lock an agreed Statistical Analysis Plan (SAP) will be finalised covering the pre-specified statistical analysis.

The primary outcome of SVR12 will be assessed as a binary outcome for subjects and so will utilise logistic regression modelling. The outcome will be analysed on an intention to treat (ITT basis). The numerator will be the number of subjects achieving SVR at 12 weeks and the denominator will be total number of patients on OST as this pathway tests and is dependent the uptake of testing, the rate of initiation onto treatment and the efficacy of treatment. Additionally results will be expressed as a proportion of the known HCV infected subjects on OST. The estimated number of infected patients will be based on national survey data and the empirical rate discovered in the trial (allowing for patients who refuse testing). In order to account for the clustered nature of the trial a mixed-effects logistic regression model will be performed with the parameter indicator of trial arm in the model and a random parameter to account for within-cluster correlation. As all patients will have either achieved SVR12 or not and we will assume that drop-outs/lost to follow-up are failures, there will be no missing data in the primary outcome. Extra-binomial variability or over-dispersion as well as number of zeros will be examined in the logistic model and if present alternative modelling such as negative binomial models and zero-inflated negative binomial models will be considered. This

will also be adjusted by prior therapy and genotype; the two factors are interdependent determining length of therapy.

Multiple logistic regression modelling will explore the patient and pharmacy characteristics associated with the primary/secondary outcomes (including, but not limited to; age, gender, deprivation, employment, comorbidity, and the psycho-social variables, geographic location, type of pharmacy service and size of OST population).

Secondary binary outcomes will be analysed in the same procedure, initially as intention to treat with all eligible patients as the denominator and then to explore the steps in the pathway by modified ITT (mITT) analysis, in particular to analyse on treatment success. The mITT population contains all enrolled subjects who tested positive for HCV:

a) Percentage of patients achieving SVR12 in each arm (mITT population).

c) Proportion who start HCV treatment within the duration of the study in each arm (mITT population)

d) Proportion of those initiating treatment that complete the treatment course (≥85% adherence) (mITT population).

Descriptive analyses will be performed to evaluate patient- and pharmacy-level baseline characteristics for the overall population and appropriate subgroups.

Health Economic evaluation

The cost-effectiveness of HCV case finding is contingent on uptake of HCV treatment (15). The decision whether to delay treatment until severe disease develops, or to treat PWID now, and the overall cost-effectiveness of treating PWID depends on the prevention benefit of HCV treatment (i.e. secondary infections averted through treating someone with HCV) (14). In order to account for the 'prevention benefit' of treatment, a dynamic HCV transmission model is required that can track disease transmission as well as follow liver disease progression. Standard NICE models of treatment cost-effectiveness just consider health benefits of patients treated. However, recent NICE models of Needle Exchange Provision and HCV case finding used dynamic HCV transmission models to enable them to also capture the prevention benefit in their cost-effectiveness projections (16).

In this analysis, we will adapt an existing dynamic, deterministic model of HCV transmission, progression and HCV treatment amongst community PWID in order to evaluate the impact of the intervention (REACH pathway) compared to standard of care testing and treatment (15). All PWID can acquire and transmit HCV, with those on OST having a lower likelihood of transmitting and acquiring HCV. Participants will be followed up to track their continued disease progression (assuming no re-infection risk). The risk of individual PWID acquiring HCV is proportional to the setting-specific HCV prevalence, which in England and Scotland is approximately 40% chronic prevalence, but also can vary by site (17) which will be incorporated.

A Bayesian parameter sampling and model calibration process will be used to take account of uncertainty in key factors (e.g. injecting duration, HCV disease progression rates, health

utilities, death rates and HCV prevalence) to generate HCV epidemic profiles consistent with each study site. The model will then be run with and without the intervention to project the degree to which the intervention results in additional benefits. These runs will also account for uncertainty in the intervention outputs as obtained from the trial. The economic analysis will be performed from a UK National Health Service and Australian Medicare perspective with health utilities (in quality-adjusted life years, QALYs) attached to each model compartment, and costs attached where relevant. Costs and QALYs will be discounted 3.5% per annum, with a 100-year time horizon (to accrue individual and population benefits). The drug costs will be based on NHS list price, but the analysis will also be performed, at drug cost of 50% and 25% of list price to reflect actual discounted price in the health service.

We will use existing utility estimates for HCV disease and treatment stages and PWID (18, 19), but will update them as new data appears, we will have the data from EQ5D-5L and change in behaviours and domestic status to add to the analysis. We will incorporate the potential impact of disutility on diagnosis, which can be fully regained with treatment SVR. Transition rates between disease stages will be taken from previous UK economic evaluations (20-23). Chronic HCV prevalence will be estimated from routine surveillance and laboratory testing of PWID (13, 24). Data on HCV testing, treatment uptake and SVR, and the costs of the intervention and standard of care will be collected by the study (see above). Data on the coverage of OST and pharmacy OST will be obtained from the setting. The effect of the intervention on HCV infections averted and QALYs saved will be projected by the model. Results will be presented as mean incremental cost-effectiveness ratio (ICER). Probabilistic uncertainty analyses will be used to estimate the uncertainty around the ICER, accounting for uncertainty in the intervention outcomes as well as other cost, behavioural and epidemiological inputs. The probability that the intervention is cost-effective will be estimated for different willingness-to-pay thresholds (£20,000 or £30,000 per QALY as used by NICE, and £13,000 in line with a recent estimate of where the UK Willingness To Pay (WTP) should lie, other thresholds can be modelled (25). Cost-effectiveness acceptability curves will be constructed and univariate sensitivity analyses undertaken, with analysis of covariance (ANCOVA) methods being used to summarize the proportion of the variability in the incremental costs and QALYs explained by the uncertainty in input parameters. Univariate sensitivity analyses will consider such things as changes in the: time horizon (50/200 years); discount rates (3.5% costs/1.5% QALYs); PWID HCV chronic prevalence (national average/ site specific); changes to the treatment costs; and coverage of the intervention. We will also explore the effect of assuming no prevention benefit (but allowing for re-infection), by permanently fixing the force of infection, independent of numbers of infected individuals. The model will also be used to consider the epidemiological impact of scaling up the intervention to all pharmacies in Dundee, Cardiff and Melbourne over a 10 and 20 year timeframe.

7.3 MISSING DATA

The nature of this study is to assess the applicability of this model in the real world, so incomplete data that impacts the primary outcome will be assumed to be consistent with failure of therapy. However every effort will be made to obtain missing blood test results and as the primary outcomes are not time point critical a wider latitude for admissibility of data will be employed.

7.4 TRANSFER OF DATA

No patient identifiable data will be transferred from any participating site. Data will be stored in site pharmacies or the standard care nurse led services office and identified by study number, with a separately held key to link study number to identifiers that could be used for record linkage.

Hard copies of the study CRF will be delivered from Wales to University of Dundee by secure courier. Electronic data can be transferred from NHS Wales to NHS Tayside using the secure NHS webmail system.

Hard copies of the study CRF in Australia will be retained by the Australian trial team, stored and archived according to their local approved procedures and responsibilities. CRF data integrity will be checked in line with local approved procedures.

Anonymised trial data will be entered at each site directly into the HIC web-based data management system.

8 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

8.1 TRIAL MANAGEMENT GROUP

The trial will be co-ordinated by a Trial Management Group (TMG), consisting of e.g. the grant holder Chief Investigator (CI), Hub Principal Investigators (PIs), Study Manager, research nurses and clinical staff who will meet regularly.

8.2 DATA MONITORING COMMITTEE

Not required as this is a study with a licensed product with the intervention being the pathway of care.

8.3 INSPECTION OF RECORDS

The CI, PIs and all institutions involved in the study will permit study-related monitoring, audits, and REC review. The CI agrees to allow the Sponsor or, representatives of the Sponsor, direct access to all study records and source documentation.

9 GOOD CLINICAL PRACTICE

9.1 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the principles of good clinical practice (GCP).

In addition to Sponsorship approval, a favourable ethical opinion will be obtained from the appropriate REC and appropriate NHS R&D approval(s) will be obtained prior to commencement of the study.

9.2 CONFIDENTIALITY AND DATA PROTECTION (UK SITES)

The CI and trial staff will comply with all applicable medical confidentiality and data protection principles and laws with regard to the collection, storage, processing and disclosure of personal data.

The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality or equivalent.

All trial records and personal data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with access limited to appropriate trial staff only. Computers used to collate personal data will have limited access measures via user names and passwords.

Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

The CI and trial staff will not disclose or use for any purpose other than performance of the trial, any personal data, record, or other unpublished, confidential information disclosed by those individuals for the purpose of the trial. Prior written agreement from the Sponsor will be required for the disclosure of any said confidential information to other parties.

Access to collated personal data relating to participants will be restricted to the CI and appropriate delegated trial staff.

Where personal data requires to be transferred, an appropriate Data Transfer Agreement will be put in place.

Published results will not contain any personal data that could allow identification of individual participants.

9.3 INSURANCE AND INDEMNITY (UK SITES)

The University of Dundee and Tayside Health Board are Co-Sponsoring the study in Scotland and Wales. University of Dundee and Tayside Health Board are not providing insurance and indemnity for the Australian activities in the trial.

Insurance – The University of Dundee will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the study.

Tayside Health Board will maintain its membership of the Clinical Negligence and Other Risks Insurance Scheme ("CNORIS") which covers the legal liability of Tayside in relation to the study.

Indemnity The Co-Sponsors do not provide study participants with indemnity in relation to participation in the Study but have insurance for legal liability as described above.

10 ADVERSE EVENTS

10.1 DEFINITIONS

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • Or is otherwise considered serious

Suspected adverse reaction:

Adverse drug reactions concern noxious and unintended responses to a medicinal product. 'Responses to a medicinal product' means that a causal relationship to a medicinal product and adverse event is at least a reasonable possibility/suspected.

10.2 RECORDING AND REPORTING AE

All AEs and/or SAEs will be recorded on the AE Log in the CRF and will be assessed for severity by the CI or delegate. AEs/SAEs will be recorded from the time a participant consents to join the study until the participant's last study visit.

The Investigator will make a clinical judgment as to whether or not an AE is of sufficient severity to require the participant's removal from the study. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant should, if required, be offered an end of study assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. SAEs will be followed up until 30 days after participant's last visit.

The CI or delegate will ask about the occurrence of SAEs and hospitalisations at every visit during the study. **SAEs which are both unexpected and related to study participation** will be submitted on an HRA NCTIMP Safety Report form to the REC by the CI, within 15 days of becoming aware of the SAE, and copied to the Sponsor Research Governance Office.

Worsening of the condition under study will not be classed as an AE, but will be defined as an outcome. Pre-specified outcome(s) will not be classed as an AE but as an outcome. Elective admissions and hospitalisations for treatment planned prior to randomisation, where appropriate, will not be considered as an AE. However AEs/SAEs occurring during such hospitalisations will be recorded.

Due to the large amount of comorbid disease and very high levels of illness and AEs that are expected to be present in this population, we will record as AEs/SAEs, but not report as SAEs to Sponsor or REC, in the following categories:

- Hospitalisation for assault or accidental injury
- Hospitalisation for pre-planned surgery
- Worsening of pre-existing co-morbidity
- Hospitalisation for abscesses due to drugs use
- Infectious complications of drug use
- Hospitalisation for wound management due to drugs use
- Any death or hospitalisation due to new cardiovascular events
- Any death or hospitalisation due to new diagnosis or treatment of cancer
- Any death or hospitalisation due to infection
- Any admission for elective or planned investigation or treatment
- Any death or hospitalisation for deteriorating renal function, high or low potassium levels
- Any hospitalisation due to nausea, vomiting, constipation or diarrhoea

2. Reporting of suspected adverse reactions:

UK SITES:

In accordance with the Regulatory Agency guidance for Healthcare Professionals in the UK and Australia, Trial Staff will be responsible for reporting all suspected adverse reactions associated with Mavyret (or any other suspect product) during the course of this study to the MHRA (UK) via a Yellow Card.

Australia:

For information – In Australia suspected adverse reactions will be reported to the Department of Health, Therapeutic Goods Administration (www.tga.gov.au) via the blue card adverse reaction reporting form. In addition, any significant additional information obtained following the reporting of the initial report will be reported to the MHRA.

3. Reporting of potential safety concerns / signals

If any Trial Staff identifies any potential new safety concerns or signals that may be possibly related to Mavyret, Trial Staff will inform AbbVie within 15 calendar days for further analysis. Equally, if AbbVie becomes aware of significant new safety information for the product, the sponsor and investigator will be informed in a timely manner.

4. Safety data provision to AbbVie:

At the end of the study, all safety data that has been collected by the sponsor (at a minimum suspected adverse reactions reported to the MHRA) will be provided to AbbVie in the form of a summary line listing and/or final study report.

10.3 TOXICITY MANAGEMENT

The management of specific AEs and laboratory parameters is described in the **Operations Manual**. This includes the following laboratory abnormalities:

If a subject experiences a post-baseline increase in ALT to > 5 × ULN which is also > 2 × baseline value, the subject should have a confirmatory ALT measurement performed.

If, the ALT increase is confirmed to be > 5 × ULN which is also > 2 × baseline value, the recommendations below should be followed:

- Complete hepatic questionnaire.
- Evaluate for alternate etiology of ALT elevation; document in the source, update the medical history and concomitant medications, and obtain Anti-hepatitis A virus immunoglobulin M (HAV IgM), Anti-hepatitis A virus immunoglobulin G (HAV IgG), Anti-HBc IgM, Anti-HBc Total, Anti-HBs, HBV DNA, HBsAg, Anti-hepatitis E virus immunoglobulin M (HEV IgM), Anti-hepatitis E virus immunoglobulin G (HEV IgG) and HEV RNA, and other additional tests, as appropriate.
- Manage the subject as medically appropriate.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and international normalized ratio (INR) within 1 week. Repeat liver chemistries as indicated until resolution.

Discontinue study drug if any of the following is observed at any time:

- ALT level is ≥ 20 × ULN in the absence of an alternate etiology.
- Increasing direct bilirubin or INR or onset of symptoms/signs of hepatitis.
- At the discretion of the investigator.

Alternate management of ALT increases is permitted with approval of the CI or PI.

10.4 PRODUCT COMPLAINT

A Product Complaint is any complaint related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose colour/markings do not match the labelling, labelling discrepancies/inadequacies in the labelling/instructions (example: printing illegible), missing components/product, or packaging issues.
Product Complaints concerning the product must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product Complaints occurring during the study will be followed up to a satisfactory conclusion.

11 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in CTIMPs and Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.
Any safety reports additional to SAE reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS, DEVIATIONS AND BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.
In the event that a CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.
In the event that a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately.

12.2 STUDY RECORD RETENTION

Archiving of study documents will be for five years after the end of study.

12.3 END OF STUDY

The end of study is defined as last patient last visit LPLV. The Sponsor, CI and/or the SC have the right at any time to terminate the study for clinical or administrative reasons.
The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.
A summary report of the study will be provided to the Sponsor and REC within 1 year of the end of the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared.

13.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

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15 APPENDIX 1: TRIAL MANAGEMENT GROUP

Chair: To be appointed

Members

Prof John Dillon (Chief Investigator)

Andrew Radley (Coordinating Pharmacist NHST)

Frances Rooney (Director of Pharmacy)

Ann Eriksen (Executive Lead SH&BBV MCN)

Dr Sarah Inglis Clinical Trial Manager

Prof Peter Donnan (Statistician)

Dr Brendan Healy (Principle Investigator)

Prof Margaret Hellard (Principle Investigator)

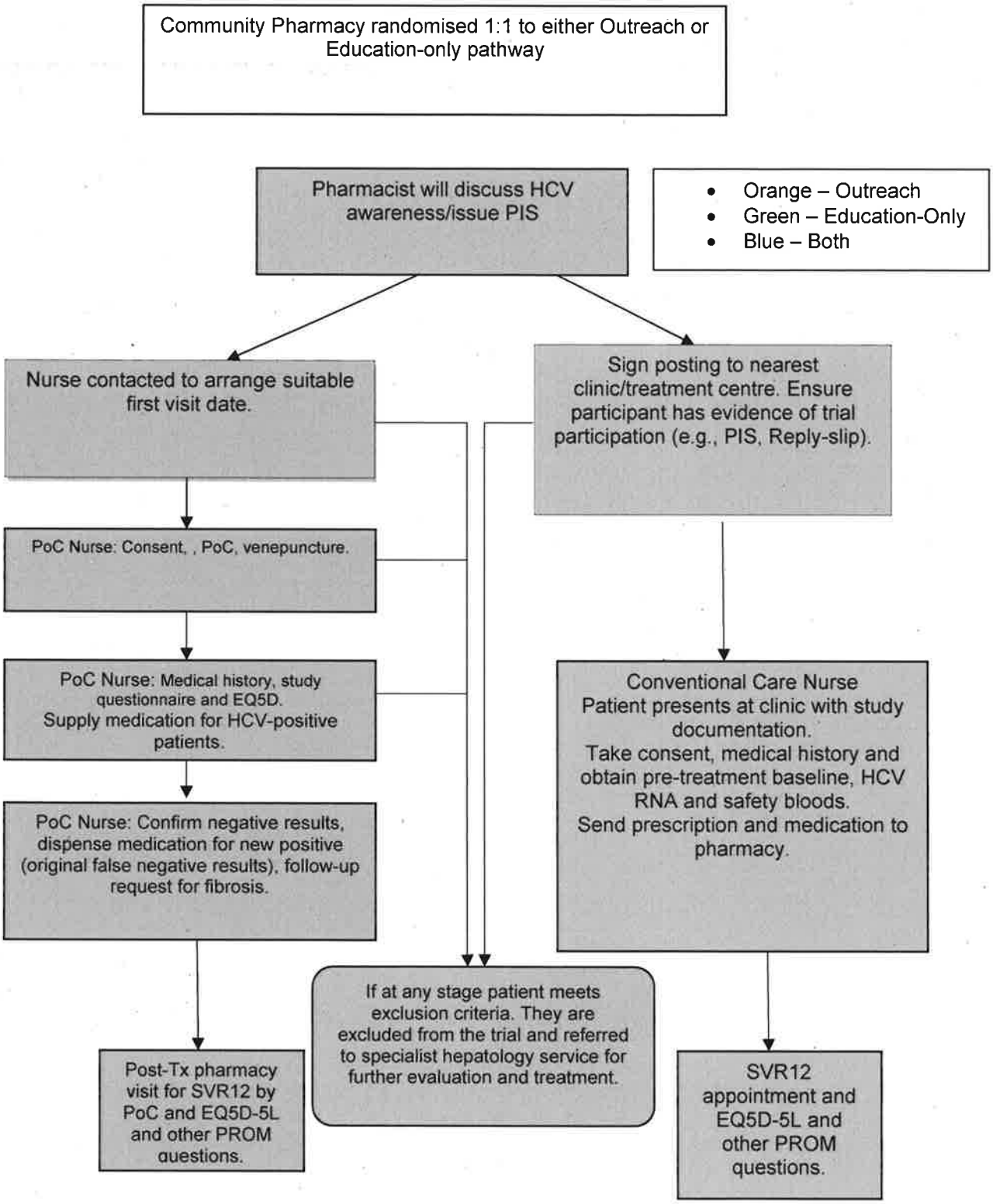
Dr Joseph Doyle (Principle Investigator)

SPECIFIC ROLES OF TMG

The TMG's role will include, but not be restricted to, the following:

- To provide advice, through its Chair, to the Chief Investigator(s), the Trial Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial
- To provide advice to the investigators on all aspects of the trial
- maintain confidentiality of all trial information that is not already in the public domain
- make decisions as to the future continuation (or otherwise) of the study
- monitor recruitment rates and encourage the TMG to develop strategies to deal with any recruitment problems
- review regular reports (eg follow-up rates) of the trial from the trials unit (sent on behalf of the Trial Management Group (TMG))
- receive letters of feedback from the DMC and consider their recommendations
- censure sites that are deviating from the protocol
- oversee the timely reporting of trial results
- comment on the trial and economic analysis plan
- comment on the publication policy
- comment on the main trial manuscript
- approve external requests for release of data or subsets of data including clinical data
- monitor compliance with previous TSC recommendations

16 APPENDIX 2: study flow chart



17 APPENDIX 3: STUDY SCHEDULE MATRICES

STUDY SCHEDULE MATRIX: REACH PATHWAY

	Potential participant visiting pharmacy for OST	Initial Screen	Treatment Start and/or Consultation	SVR12
PIS / Study Information	X			
Informed Consent		X		
Check Inc/Exc Criteria			X	
Demographics		X		X
HCV RNA by POC		X		X
Safety and staging bloods		X		
HCV Results confirmation			X	
Dispense HCV Therapy			X	
Adverse Event Assessment			X	X
Study Questionnaire			X	X
EQ5D-5L			X	X

STUDY SCHEDULE MATRIX: EDUCATION-ONLY PATHWAY

	Potential participant visiting pharmacy for OST	Initial HCV screen	Treatment Start	SVR12
PIS / Study Information	X			
Informed Consent		X		
Check Inc/Exc Criteria			X	
Demographics		X		X
HCV RNA by conventional testing		X		X
Safety and staging bloods		X		
HCV Results confirmation			X	
Dispense HCV Therapy			X	
Adverse Event Assessment			X	X
Study Questionnaire			X	X
EQ5D-5L			X	X