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Reaching mEthadone users Attending Community pHarmacies with HCV: an international cluster randomised controlled trial protocol (REACH HCV)

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ABSTRACT

Introduction Hepatitis C virus (HCV) is a global public health threat, and novel models of care are required to treat those currently or previously at highest risk of infection, particularly persons who inject drugs (PWID; ever injected), as conventional healthcare models do not have the reach to deliver cure of HCV to disadvantaged, disproportionately affected communities. In Western Europe and Australasia, it is estimated that HCV affects between 0.4% and 1.0% of the regions' populations, accordingly, it affects between 0.4% and 0.7% of the populations of countries in this study (Scotland, Wales and Australia). Reaching mEthadone users Attending Community pHarmacies with HCV (REACH HCV) will evaluate community pharmacy-based diagnostic outreach and HCV treatment against conventional HCV testing and treatment pathways for clients receiving opioid substitution therapy (OST) in community pharmacies.

Methods and analysis REACH HCV is an international multicentre cluster randomised controlled trial with sites in Scotland, Wales and Australia. The sites are community pharmacies which are randomised equally to one of two pathways: the pharmacy intervention pathway or the education-only (control) pathway. Participants are recruited from OST clients in these pharmacies.

In the pharmacy intervention pathway, participants receive a rapid point-of-care HCV PCR test in their pharmacy by a study outreach nurse. If positive, direct-acting antivirals (DAAs) are delivered to participants via their pharmacist in line with their OST schedule.

In the education-only pathway, pharmacists counsel OST clients on HCV and refer them to the nearest nurse-led clinic or general practitioner offering HCV testing according to standard care protocols. If positive, DAAs are delivered as in the intervention pathway.

The primary endpoint for both pathways is sustained viral response at 12 weeks post-treatment . Secondary outcomes are: cost-efficacy by pathway; participants tested by pathway; adherence to therapy by pathway and impact of blood test results on treatment decisions.

A statistical analysis plan will be finalised prior to data lock. Analysis will be by intention to treat (ITT) to show superiority. Modified ITT analysis will also be undertaken to explore the steps in the pathways.

Ethics and dissemination The trial received ethical favourable opinion from the East of Scotland Research Ethics Committee 2 (19/ES/0025) for UK sites and approval from the Alfred Hospital Ethics Committee (148/19) for Australian sites and complies with principles of Good Clinical Practice. Final results will be presented in peer-reviewed journals and at relevant conferences.

Trial registration number ClinicalTrials.gov Registry NCT03935906.

Protocol version V.4.0—19 March 2020.

Strengths and limitations of this study

- Pragmatic test-and-treat trial based in community pharmacies which decentralises hepatitis C virus (HCV) care.
- Complements health policy encouraging primary care providers to engage in HCV through care.
- All aspects of the HCV cascade of care located on site in the intervention arm.
- The trial population is stable opioid substitution therapy clients, limiting the results' applicability at-risk groups who lead a less predictable lifestyle.

INTRODUCTION

Background

Viral hepatitis is a serious public health threat which contributes substantially to the global burden of liver-related health complications. Of the 1.4 million deaths attributable to viral hepatitis annually, 48% are due to hepatitis C virus (HCV), which is spread through blood-to-blood contact.[1] There are an estimated 71.1 million viraemic HCV infections globally, representing a worldwide disease burden of about 1% of the population.[2] In Western Europe and Australasia, it is estimated that HCV viraemia affects between 0.4% and 1.0% of the regions' populations.[2] In line with that, chronic HCV affects between 0.4% and 0.7% of the populations of countries (Scotland,

Wales and Australia) in this study.[3–6] A common HCV transmission route in high-income countries like these is injection drug use.

While recovering from substance use, including injecting drug use, many individuals will be prescribed a course of managed opioid substitution therapy (OST), typically by a general practitioner (GP), which is dispensed by a community pharmacist. Around 40% of individuals receiving OST could be infected with HCV,[7] therefore test and treat initiatives in this population are required to progress towards WHO HCV elimination targets.[1] Recent data estimates HCV antibody prevalence of between 49% and 57% among persons who inject drugs (PWID) in Scotland, Wales and Australia.[8–10]

Recommended standard care in jurisdictions in this trial is to offer those with a history of injecting drug use regular HCV testing,[11 12] often through drug treatment services or GPs, but there is significant variation in the availability and the offer of testing. Typically individuals reactive for HCV are referred to a secondary care-led viral hepatitis service. Under this model, approximately 50%–66% of PWID attending needle exchanges in our jurisdictions self-report as aware of their HCV status or having been tested in the last 12 months,[9 10] although few had initiated treatment. These figures indicate HCV testing among PWID could be improved and suggests new models should be explored which integrate HCV care into new environments.

Studies have supported the provision of testing and treatment for HCV via community pharmacies.[7 13 14] However, research assessing HCV care in community settings suggest that only between 15% and 18% of individuals testing positive for HCV then commence treatment,[8 15] with further population-level observations noting an only 12% treatment uptake.[16] This suggests a significant disparity between confirmation of infection in community settings and commencing treatment.

Despite the evidence noted[7 13 14] for up-skilling community pharmacy staff to test and treat for HCV, in some instances it may not be resource-efficient to do so; for example, in pharmacies with few OST clients, staff will struggle to maintain competence in testing. Further, in the time it takes train staff to competence, an outreach nurse could feasibly have tested the client cohort.

Rationale

This trial will address the need to increase HCV testing rates among PWID, and linkage to treatment for those testing HCV positive, by the provision of a novel pathway of care for persons in receipt of OST in community pharmacies using an outreach nurse to test and assess individuals, and then provide direct-acting antiviral (DAA) treatment. The aims of this trial support the implementation of national HCV policy in the UK and Australia[17–20] by embedding all elements of the HCV care cascade in a community setting, thereby testing whether that model increases HCV testing coverage and improves linkage to care.

PWID are subject to significant societal and systems-wide stigma linked to their drug use,[21] which disincentivises them from presenting to health services for screening and treatment of HCV,[22] and embedding full HCV care in community settings offers an opportunity to negate that. Recent work explored the most valued attributes of a service delivering HCV care. OST clients' most valued preferences were to be treated in a familiar environment and to be treated with respect.[23] In a community pharmacy, individuals have a regular and familiar point of contact with the healthcare service that they highly value; they also have an incentive to attend and interact in this setting due to OST. Co-locating test and treat services within community pharmacies has been identified as a valuable addition to HCV care by PWID in receipt of OST.[24] The strength of the patient-pharmacist relationship offers a clear rationale for co-locating HCV testing and treatment in community pharmacies for those receiving OST.[24 25]

The safety and efficacy profile of DAAs[26] can allow the rationalisation of supply and management of treatment in less complex cases of infection. Combining DAA treatment with point-of-care (PoC) testing which enables straight-to-PCR analysis in a short time could produce a streamlined pathway of care which reduces waiting time for diagnostic results, and decreases the number of required on-treatment visits for patients. This trial is designed to have minimal on-treatment monitoring for participants, while also leveraging the support of their community pharmacy to promote adherence.

Objectives

The primary objective is to compare the efficacy of the pharmacist-intervention pathway with the education-only pathway for proportion of participants achieving a cure following DAA treatment for HCV. The outcome measure is sustained viral response at 12 weeks post-treatment (SVR^{12}), which is measured 12 weeks post-HCV treatment completion.

Secondary outcomes are cost-effectiveness by pathway; participants tested by pathway; adherence to therapy by pathway and impact of blood test results on treatment decisions.

METHODS

Trial setup

Sponsorship for sites in the UK is provided via a joint agreement between Tayside Health Board and the University of Dundee; for Australian sites, this is provided by the Alfred Hospital. Overall administration of the trial is provided by Tayside Clinical Trials Unit (TCTU), a UK Clinical Research Collaboration (UKCRC)-registered clinical trials unit.[27] Trials conducted by TCTU are subject to independent ad-hoc audit by the study sponsor and its representatives, as well as relevant regulatory authorities (eg, the Medicines and Healthcare products Regulatory Agency (MHRA)). Protocol modifications

are communicated to relevant authorities by the TCTU trial coordinator or delegated individual. There is a Trial Management Group (TMG) in place for the trial comprised of the study investigators, TCTU management and coordinating staff, and National Health Service care network staff. The role of the TMG includes, but is not limited to:

- To provide advice on all appropriate aspects of the trial.
- To provide advice to the study investigators.
- To adjudicate on future continuation (or otherwise) of the trial.
- To monitor recruitment and strategise if required.
- To review and consider issues relating to data management and integrity.
- To review and consider proposals for interim analyses.
- To review and consider site deviations/breaches of protocol.
- To oversee timely publication of results.
- To review approve external requests for data or subsets of data.

Trial design

This trial is an international, multicentre, cluster-randomised two-arm unblinded trial of pharmacy outreach PoC HCV diagnosis and DAA treatment versus conventional test-and-treat pathways for clients receiving OST in community pharmacies in Scotland, Wales and Australia. There are two pathways the pharmacy-intervention pathway and education-only (control arm) pathway.

Patient and public involvement

Patient or public involvement groups were not involved in the design of this study. Study design was developed from prior experience of the investigators of working with the stakeholders involved.

Participants

Eligibility criteria:

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 mandatory field

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 hepatitis B virus (HBV) infection. Serological: patients with a positive hepatitis B surface antigen (HBsAg) or isolated positive hepatitis B core antigen (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 (www.hep-druginteractions.org) and product SmPC.
- 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, haematologic, 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, for example, ascites noted on physical examination, 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.

Study setting

HCV testing, administration of DAA treatment, and data collection visits occur in community pharmacies in the pharmacy-intervention pathway. In the education-only pathway, these occur in alignment with standard care. All participant enrolment occurs in community pharmacies.

Enrolment

Participants will be recruited from OST client cohorts in community pharmacies in Scotland, Wales and Australia. Up to 140 HCV-positive participants will be treated, requiring up to 345 to be enrolled. Informed consent will be obtained by a study or clinic nurse and community pharmacists. Participant information documents will be made available in Welsh for any individuals who request this. Participants will have at least 24 hours to consider participation.

INTERVENTIONS

PoC HCV test

The PoC device being used for the trial is supplied by Genedrive Diagnostics . It is a compact CE-IVD (In Vitro Diagnostics) marked device, which incorporates ultra-fast PCR cycling. The device is suitable for use by operators after minimal training and provides a simple positive/

negative reading in under 90 min from the sample collection. The device requires 30 µL of sample.[28] This test is administered at baseline for participants in the pharmacist intervention arm.

HCV medication

The study will use glecaprevir/pibrentasvir 100 mg/40 mg film-coated tablets provided by AbbVie, the funder. Dosage is three tablets taken once daily.

Participants will be prescribed this based on the following criteria:

All genotypes will receive 8 weeks of treatment, if they are HCV treatment-naïve and have an AST to Platelet Ratio Index (APRI) score of ≤1.

Patients with APRI >1 will be evaluated with a further test (eg, Fibroscan). This will take place following commencement of therapy. There will be no change to therapy if results are consistent with portal fibrosis (F) F0–F3; if results are consistent with F4, participants will have their treatment regimen extended by 4 weeks, to a total of 12 weeks.

Enrolled patients who have previously failed therapy with PEGylated-Interferon + ribavirin ± sofosbuvir or sofosbuvir + ribavirin will be prescribed:

- Genotypes 1, 2, 4, 5 and 6 will receive 8 weeks if their APRI is ≤1. Patients with APRI >1 will be evaluated with a further test as previously outlined. Treatment changes will be as previously outlined.
- Genotype 3: 16 weeks (regardless of APRI score).

In Australia, in the education-only arm, any DAA can be prescribed in line with national prescribing guidelines.[29]

Study pathways

Pharmacy-intervention pathway

In this pathway, staff training and educational materials on HCV will be delivered by the trial team to pharmacists. In the immediate period prior to opening to patient consent, the pharmacist will discuss HCV with OST clients to raise awareness of HCV and provide study literature.

The outreach nurse will attend the pharmacy to take informed consent from interested OST clients. From those agreeing to be tested, the nurse will perform conventional venepuncture, taking blood for PoC testing and additional tubes for full blood count, urea and electrolytes, liver function testing, including markers of liver fibrosis (Fibrosis-4 Index, APRI, aspartate transaminas to alanine transaminase ratio (AST:ALT ratio)), and viral parameters (HCV, HIV and HBV). A baseline blood sample per participant will be stored in a −80°C freezer for viral resistance assessment in the event of non-response to DAA treatment despite adherence.

At a subsequent visit, HCV-positive participants will be assessed for DAA treatment by the nurse and complete questionnaires collecting demographic and injecting behaviour information, and the EQ-5D-5L.[30–36] DAA treatment will be arranged—with support from tertiary multidisciplinary teams if required—by the nurse using a patient group direction in the UK, and by the principal investigator in Australia.[37] Treatment will be dispensed by the community pharmacist in line with the participant's OST schedule. Adherence to treatment will be recorded by the community pharmacist.

Participants who test negative following the PoC test will be informed their result is expected to be accurate, but must be confirmed by the central laboratory using the sample taken for viral parameters. Those who are confirmed HCV PCR negative will be revisited or telephoned by the nurse to confirm their status; any eligible patients who are PCR positive, but were below the limit of detection of the PoC device,[28] will then be commenced on treatment.

The next study visit will be at least 12 weeks post-treatment when the nurse will conduct a PoC HCV test, and participants will complete further study questionnaires.

Education-only pathway

In this pathway, staff training and educational materials on HCV will be delivered as in the pharmacy intervention pathway. The community pharmacist will, as in recommended standard practice,[20 38 39] opportunistically discuss HCV with OST patients. Information will be relayed verbally and via standard health service HCV literature. Study information will also be distributed. Patients will be advised to attend the nearest nurse-led clinic (in UK) or referred to their GP (in Australia) for HCV testing and assessment via standard care protocols. OST clients will be provided with a study reply slip to identify their pharmacy when presenting for enrolment. Should they attend without this, their pharmacy can be confirmed directly with their pharmacist.

Eligible patients will be consented to the trial by the clinic nurse (UK), or pharmacist (Australia). Questionnaires and follow-up, as previously described, will be completed in alignment with standard care.

For eligible participants: DAA treatment will be arranged, treatment will be dispensed and follow-up conducted, in line with standard care in all settings. Adherence will be recorded as outlined previously. The SVR^{12} blood test will occur in the local clinic or GP offering this.

Participant journey

In the pharmacist-intervention pathway, all participants receive three or four data collection visits with the outreach nurse in their community pharmacy, depending on the result of their baseline PoC test. In the education-only pathway, all participants receive three data collection visits aligned with standard care schedules.

Participant visit schedules are fully outlined in tabular form in online supplementary file 'Study schedule matrices delineated by pathway', an overview is presented in figure 1.

OUTCOMES AND ANALYSIS

Primary outcome

As outlined in table 1, the primary outcome (SVR^{12}) will be assessed as a binary outcome for subjects and so will use logistic regression modelling while accounting for clustering through generalised linear mixed models. This will be analysed on an intention-to-treat (ITT) basis. The

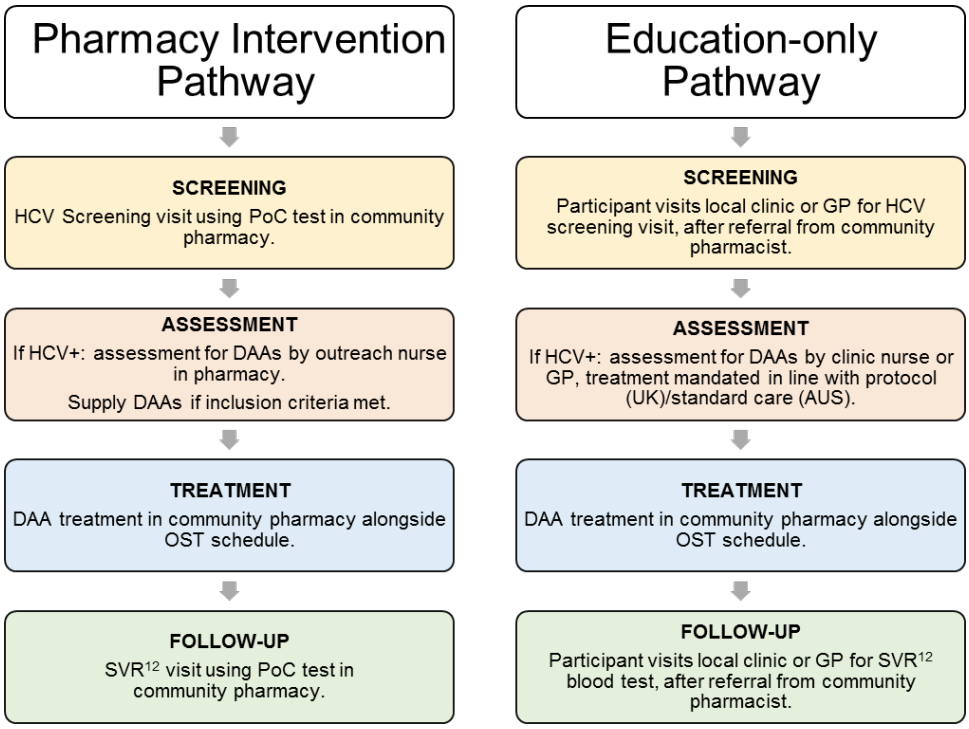

Figure 1 Participant journey overview. The participant journey through the study is displayed per pathway. In the pharmacy-intervention pathway, participants are screened for hepatitis C in their community pharmacy by the study nurse using the Genedrive point-of-care test. If positive and eligible for the study, they are assessed for treatment with direct-acting antivirals by the nurse and commence treatment in their pharmacy. They are then followed-up in their pharmacy at least 12 weeks after finishing treatment to check for a sustained viral response. In the education-only pathway, participants are referred to their local clinic or GP for hepatitis C screening. If positive, they are prescribed in line with standard care. Treatment is dispensed by their pharmacist and they are referred to their local clinic or GP for a sustained viral response test. AUS, Australia, DAA, direct acting antiviral; GP, general practitioner; HCV, hepatitis C virus; OST, opiate substitution therapy; PoC, point of care; SVR^{12}, sustained viral response at 12 weeks.

numerator will be the number of participants who achieve SVR^{12}, and the denominator will be the total number of patients on OST. Additionally, results will be expressed as a proportion of known HCV-infected subjects.

Secondary outcomes

As outlined in table 2, secondary outcomes will be assessed in the same manner, initially as ITT with all eligible patients as the denominator and by modified ITT (mITT) to explore the steps in the pathways. The mITT population will contain all enrolled subjects who tested positive for HCV.

The mITT analyses will include:

- Percentage of patients achieving SVR^{12} in each arm.
- Proportion who start HCV treatment within the duration of the study in each arm.
- Proportion of those initiating treatment that complete the treatment course (≥85% adherence).

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

Sample size calculation

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

Variability has been demonstrated in the proportion of individuals on OST who are HCV positive, with figures

Table 1 Primary objective and outcome measure

Primary objective	Outcome measure	Time point of outcome measured
To evaluate the difference in rates of diagnosis and cure of HCV in patients receiving OST between the pharmacy-intervention and education-only pathways.	Proportion of patients in a population of stable OST clients achieving SVR^{12} in the pharmacy-intervention pathway versus education-only pathway (Intention to Treat).	At least 12 weeks after participants finish their HCV treatment.

HCV, hepatitis C virus; OST, opiate substitution therapy; SVR^{12}, sustained viral response at 12 weeks.

Table 2 Secondary objectives and outcome measures

Secondary objective	Outcome measure	Time point of outcome measured
Determine which pathway leads to more people on OST who are confirmed HCV RNA positive being treated and cured.	Percentage of patients achieving SVR[12] from the patient population that tested positive for HCV in each arm (modified intention to treat).	At least 12 weeks after participants finish their HCV treatment.
Evaluate if the pharmacist-intervention pathway is more cost-effective than the education-only pathway, from the perspective of the NHS (UK) and Medicare (Australia).	Incremental cost-effectiveness ratio to consider the epidemiological impact of scaling up the intervention to all pharmacies in a specific setting in Australia, Scotland and Wales; and cost-benefit calculations. Lifetime horizon between 10–20 years.	End of Study.
Determine which pathway leads to more people on OST being tested for HCV.	Proportion of patients being tested for HCV in each arm.	End of study.
Compare adherence and persistence to HCV therapy in each pathway.	Proportion of patients adhering to therapy in each arm (taking ≥85% of prescribed tablets) as reported in the observed therapy adherence log.	End of study.
Assess the impact of baseline blood tests on treatment decisions.	Proportion of patients in whom changes in therapy are advised due to blood test results, as recorded at start of HCV therapy.	Prior to treatment.

HCV, hepatitis C virus; NHS, national health service; OST, opiate substitution therapy; SVR[12], sustained viral response at 12 weeks.

reported at approximately 40%.[40 41] The power calculation for the study is based on the assumption that each pharmacy will have approximately 4 HCV positive OST clients (assuming around 10 OST clients per pharmacy) who could be identified and assessed for treatment.

The study is powered on SVR[12], that is, the difference in proportions of those HCV positive on OST who achieve SVR[12]. Currently, this is estimated to be 2.5%, and it is anticipated the study will achieve 25%. For a parallel-group design, the number required per arm would be n=48, so 96 in total with 90% power and a two-sided alpha of 0.05. Allowing for clustering, by assuming four patients per pharmacy and an intracluster 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, the aim is to recruit up to 50 pharmacies, which will help reduce intracluster correlation. Estimation was based on software nQuery Advisor V.7 and confirmed by an independent statistician using GPower.

Randomisation

The unit of randomisation is the pharmacy. Up to 50 pharmacies will be randomised to either the pharmacist intervention or the education-only pathway on a 1:1 per-hub basis (Scotland, Wales and Australia). Randomisation will be conducted at the UK Clinical Research Collaboration registered TCTU, University of Dundee, UK.

Statistical methods

To account for the clustered nature of the trial, a mixed-effects logistic regression model will be performed with the parameter indicator of a trial arm in the model, and a random parameter to account for within-cluster correlation.

As all patients will have either achieved SVR[12] 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 the 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 the length of therapy.

Multiple logistic regression modelling will explore the patient and pharmacy characteristics associated with the primary/secondary outcomes. Analyses will be carried out in accordance with the pre-specified statistical analysis plan (SAP).

Health economic analysis

In this analysis, an existing dynamic, deterministic model of HCV transmission, progression and HCV treatment among PWID to evaluate the impact of the pharmacy intervention pathway compared with standard care testing and treatment will be adapted.[42] A Bayesian parameter sampling and model calibration process will be used to take account of uncertainty in key factors (eg, injecting duration, HCV disease progression rates, health utilities, death rates and HCV prevalence) to generate HCV epidemic profiles consistent with each study hub. The model will then be run with and without the intervention to project the degree to which the intervention results in additional benefits.

The economic analysis will be performed from a UK National Health Service and Australian Medicare perspectives with health utilities (in quality-adjusted life years; QALY) attached to each model compartment, and costs attached where relevant.

The effect of the intervention on HCV infections averted and QALY saved will be projected by the model. Results will be presented as mean incremental cost-effectiveness ratio. The probability that the intervention is cost-effective will be estimated for different willingness-to-pay (WTP) thresholds (£20 000 or £30 000 per QALY as used by the National Institute for Health and Care Excellence), and £13 000 in line with a recent estimate[43] of where the UK WTP should lie. Cost-effectiveness acceptability curves will be constructed and univariate sensitivity analyses undertaken, with analysis of covariance methods being used to summarise the proportion of the variability in the incremental costs and QALY explained by the uncertainty in input parameters. Univariate sensitivity analyses will consider such things as changes in the: time horizon; discount rates; PWID HCV chronic prevalence; 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.

Data collection and management

Individual participant data collected at each visit will be recorded in a paper case report form (CRF). Anonymised data will be stored, with participants only distinguishable by study identification number. No personal information is shared outside the participants' local clinical care networks. Data on participant adherence to therapy are collected in a dispensing and adherence log. Screening data will be collected from screening logs completed by pharmacists. Data will be transferred to an electronic data management system provided by the University of Dundee. Once data entry is complete, management and quality control will be conducted in line with Tayside Medical Science Centre SOP DM053: Data management in clinical research.

Data integrity will be monitored on an ongoing basis by the TMG.

Safety reporting

All adverse events (AEs) or serious adverse events (SAEs) will be recorded on the AE log in each participant's CRF and will be assessed by the chief investigator or appropriately qualified delegate. AEs and SAEs will be recorded from the time a participant joins the study until their last study visit. Participants with outstanding AEs or SAEs at the end of the study will be referred by the study team to appropriate onward medical care.

Owing to the significant level of comorbid disease and illness that are expected to present in this population, the investigators will record as AEs/SAEs, but not report as SAEs, in the following categories:

- Hospitalisation for assault or accidental injury.
- Hospitalisation for preplanned surgery.
- Worsening of pre-existing comorbidity.
- 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.

Ethics and dissemination

The research will be conducted in line with the principles of the Declaration of Helsinki and in accordance with the Research Governance Framework Scotland, the UK Policy Framework for Health and Social Care Research, and the Australian Code for the Responsible Conduct of Research. Ethical favourable opinion was gained from East of Scotland Research Ethics committee for UK sites (19/ES/0025) and the Alfred Hospital Ethics Committee (149/19).

Results will be disseminated through peer-reviewed publications, presented at conferences and published on clinicaltrials.gov. Anonymised Individual Participant Data (IPD) will be retained by the study team. Ownership of the data arising from this study resides with the study team and their respective employers. The study team will follow the International Committee of Journal Editors (ICJME) guidelines. Access to IPD will be considered for researchers who supply a methodologically sound proposal. Access will be granted in line with prevailing recommendations[44] via a reputable online controlled access repository. Requests for data access should be sent to the corresponding author (ORCID: 0000-0002-7586-7712). Data which may be shared include all IPD collected during the trial which underlies the final published results, after de-identification; the study protocol; the SAP; the data anagement plan.

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Contributors JFD is the chief investigator for the trial. JFD, JSD, BH, AR and PD made significant contributions to the conceptualisation and design of the trial. CB created the first draft of the manuscript, the data collection tools, monitored data collection, provided study-specific training and coordinated the study. SKI, LJZB, MDP and NP contributed relevant details to the manuscript for each hub. SKI provided trial management oversight for the study. MDP and NP implemented the trial in their local settings. All authors critically revised and approved the manuscript.

Funding AbbVie funded the study and had input in the protocol development.

Competing interests AR has received personal honoraria from AbbVie and Gilead and institutional research grants from MSD, AbbVie, Gilead and Roche. BH has received unrestricted educational grants, payments for advisory boards and payments for presentations from Jannen, Gilead, BMS, Abbvie and Merck in relation to HCV products. He has also received funding from Gilead, Merck, Abbvie and BMS for running meetings in relation to HCV in Wales. He has secured unrestricted funding from Abbvie, Merck and Gilead for project work related to management of HCV. JSD has received investigator initiated research support from AbbVie, Gilead Sciences, Merck and Bristol Myers Squibb; and has received honoraria from AbbVie, Gilead Sciences, and Merck. JFD has received personal honoraria for lectures and institutional research grants from MSD, AbbVie, Gilead, Roche and Janssen. PD has received grants from Gilead, Shire pharmaceuticals. PD is a member of the New Drugs Committee of the Scottish Medicines Consortium. AbbVie were involved in a collaborative, iterative process to develop the study protocol alongside the study Investigators as part of the AbbVie Investigator Initiated Scheme. AbbVie provided input to the protocol with regards to safety measures and reporting; the participant journey; and HCV medication guidance.

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