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TITLE

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 (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 health care 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 0.4-1.0% of the regions’ populations, accordingly it affects between 0.4-0.7% of the populations of countries in this study (Scotland, Wales, and Australia). REACH HCV will evaluate community pharmacy-based diagnostic outreach and HCV treatment against conventional HCV testing and treatment pathways for clients receiving opioid substitution (OST) therapy 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 (PoC) HCV PCR test in their pharmacy by a study outreach nurse. If positive, direct acting antivirals (DAA) 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 (SVR\textsuperscript{12}). 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 (SAP) will be finalised prior to datalock. Analysis will be by intention to treat (ITT) to show superiority. Modified ITT (mITT) 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.

Registration details
The trial is registered on clinicaltrials.gov (NCT: 03935906).

Protocol Version
2.0 – 21/06/2019
STRENGTHS AND LIMITATIONS

Strengths

Pragmatic test-and-treat trial based in community pharmacies which decentralises HCV care to services frequently used by individuals at risk of infection.

Complements prevailing health policy encouraging primary care providers to engage, guide and manage persons at risk of HCV through care.

All aspects of the HCV care cascade are located on site in the intervention arm.

Limitations

The trial is recruiting from a cohort of stable OST clients, limiting the results’ applicability to those at-risk cohorts who lead a less predictable lifestyle.

Use of community pharmacy facilities are subject to fees paid by the study, or additional third-party funding. Adoption of intervention pathway to standard care may be subject to negotiation by the relevant health authorities for use of pharmacy facilities. This will depend on the service model in different countries.
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 (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 0.4-1.0% of the regions’ populations [2]. In line with that, chronic HCV affects between 0.4-0.7% of the populations of countries (Scotland, Wales, and Australia) in this study [3, 4, 5, 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 World Health Organisation (WHO) HCV elimination targets [1]. Recent data estimates HCV antibody prevalence of between 49-57% among PWID in Scotland, Wales and Australia [8,9,10].

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 twelve 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 15-18% of individuals testing positive for HCV then commence treatment [8,15], with further population-level observations noting a 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 amongst 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 [17,18,19,20] 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 health care 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, whilst 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 SVR\textsuperscript{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 United Kingdom (UK) is provided via a joint agreement between Tayside Health Board and University of Dundee; for Australian sites, this is provided by the Alfred Hospital. Overall administration of the trial is provided by Tayside Clinical Trails Unit, a UK Clinical Research Collaboration-registered clinical trials unit [27].

**Trial Design**

This trial is an international, multicentre, cluster randomised two-arm 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.

**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.

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 (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:
  o 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.

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

Point-of-care HCV Test
The PoC device being used for the trial is supplied by Genedrive Diagnostics PLC. It is a compact CE-IVD marked device, which incorporates ultra-fast polymerase chase reaction (PCR) cycling. The device is suitable for use by operators after minimal training and provides a simple positive/negative reading in under 90 minutes from sample collection. The device requires 30µl of sample [28]. This test is administered at baseline for participants in the pharmacist intervention arm.

**HCV Medication**

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

Participants will be prescribed this based on the following criteria:

All genotypes will receive eight 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 (e.g. 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 four weeks, to a total of twelve 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 eight 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 (Fib4, APRI, AST:ALT ratio), and viral parameters (HCV, HIV and HBV). A baseline blood sample per participant will be stored in a -80 degrees Celsius 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 (PGD) [37] in the UK, and by the Principal Investigator in Australia. 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 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 general practitioner (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\textsuperscript{12} blood test will occur in the local clinic or GP offering this.

**Participant Journey**

In the pharmacist-intervention pathway all participants receive 3 or 4 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 3 data collection visits aligned with standard care schedules.

Participant visit schedules are fully outlined in tabular form in tables 1 and 2 in the appendices, an overview is presented here in Figure 1.


### OUTCOMES & ANALYSIS

#### Primary Outcome

As outlined in Table 3, the primary outcome (SVR$^{12}$) will be assessed as a binary outcome for subjects and so will utilise logistic regression modelling while accounting for clustering through non-linear mixed models. This will be analysed on an intention-to-treat (ITT) basis. The numerator will be the number of participants who achieve SVR$^{12}$, the denominator will be total number of patients on OST. Additionally results will be expressed as a proportion of known HCV-infected subjects.

| 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. |

Table 3: Primary Objective and Outcome Measure

#### Secondary Outcomes

As outlined in Table 4, 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\textsuperscript{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 (\geq 85\% adherence).

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

| 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\textsuperscript{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 which 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 \geq 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. |

Table 4: Secondary Objectives and Outcome Measures

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 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$^{12}$, i.e. 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 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, the aim is to recruit 40 pharmacies. Estimation was based on software nQuery Advisor v7 and confirmed by an independent statistician using GPower.

**Randomisation**

The unit of randomisation is the pharmacy. 40 pharmacies will be randomised, prior to study start, 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 UKCRC registered Tayside Clinical Trials Unit, University of Dundee, UK. It is anticipated that 40 pharmacies will be randomised.

**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 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 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. Analyses will be carried out in accordance with the pre-specified SAP.

**Health Economic Analysis**

In this analysis, an existing dynamic, deterministic model of HCV transmission, progression and HCV treatment amongst PWID to evaluate the impact of the pharmacy intervention pathway compared to 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 (e.g. 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 (ICER). 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 [43] of where the UK Willingness to Pay (WTP) should lie. 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 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

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 participants' local clinical care networks. Data on participant adherence to therapy are collected in a dispensing and adherence log. Data will be transferred to an electronic data management system provided by University of Dundee.

Data integrity will be monitored on an ongoing basis by the trial management group.

Safety Reporting

All adverse events (AE) or Serious Adverse Events (SAE) 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.

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 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.

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. Access to IPD will be granted to 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 underlie the final published results, after de-identification; the study protocol; the SAP; the Data Management Plan (DMP).

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.

COMPETING INTERESTS

CB declares no competing interests.

AR has received personal honoraria from AbbVie and Gilead and institutional research grants from MSD, AbbVie, Gilead and Roche.

SI declares no competing interests.

LB declares no competing interests.

NP declares no competing interests.

MDP declares no competing interests.

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.
PTD has received grants from Gilead, Shire pharmaceuticals. PTD is a member of the New Drugs Committee of the Scottish Medicines Consortium.

AbbVie Inc. 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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**FUNDING STATEMENT**

AbbVie funded the study and had input in the protocol development.
### APPENDICES

| Action                                                        | Potential participant visiting pharmacy for OAT | Initial HCV Screen | Treatment Start and/or Consultation | SVR<sup>12</sup> |
|---------------------------------------------------------------|-------------------------------------------------|---------------------|------------------------------------|-------------------|
| Study information/HCV counselling                            | X                                               |                     |                                    |                   |
| Informed consent                                             | X                                               |                     |                                    |                   |
| HCV testing inclusion criteria                                | X                                               |                     |                                    |                   |
| Basic demographics                                           | X                                               |                     |                                    |                   |
| HCV RNA by PoC                                                | X                                               |                     | X                                  |                   |
| Safety & staging bloods                                       | X                                               |                     |                                    |                   |
| Research sample                                              | X                                               |                     |                                    |                   |
| HCV results confirmation                                      | X                                               | X                   |                                    |                   |
| Treatment/ full study inclusion criteria                      | X                                               |                     |                                    |                   |
| Pharmacist receives HCV medication                            | X                                               |                     |                                    |                   |
| Adverse event assessment                                      | X                                               | X                   |                                    |                   |
| Questionnaires (EQ-5D-5L; enhanced demographics; injecting information) | X                                               | X                   |                                    |                   |

Table 1: Study Schedule Matrix for pharmacy intervention pathway, all sites.

| Action                                                        | Potential participant visiting pharmacy for OAT | Initial HCV screen | Treatment Start | SVR<sup>12</sup> |
|---------------------------------------------------------------|-------------------------------------------------|---------------------|------------------|-------------------|
| Study information/HCV counselling                            | X                                               | X                   |                  |                   |
| Informed Consent                                             | X                                               | X                   |                  |                   |
| HCV testing inclusion criteria                                | X                                               | X                   |                  |                   |
| Basic demographics                                           | X                                               | X                   |                  |                   |
| HCV RNA by standard testing protocols                        | X                                               | X                   | X                |                  |
| Safety & staging bloods                                       | X                                               | X                   |                  |                   |
| Research sample                                              | X                                               |                     |                  |                   |
| HCV results confirmation                                      | X                                               | X                   |                  |                   |
| Treatment/full study inclusion criteria                       | X                                               |                     |                  |                   |
| Pharmacist receives HCV medication                            | X                                               |                     |                  |                   |
| Adverse event assessment                                      | X                                               | X                   | X                | X                 |
| Questionnaires (EQ-5D-5L; enhanced demographics; injecting information) | X                                               | X                   | X                | X                 |

Table 2: Study Schedule Matrix for education-only Pathway UK and Australia Delineated
# CONSORT 2010 checklist of information to include when reporting a randomised trial*

| Section/Topic       | Item No | Checklist item                                                                 | Reported on page No |
|---------------------|---------|--------------------------------------------------------------------------------|---------------------|
| **Title and abstract** |         |                                                                                 |                     |
| 1a                  |         | Identification as a randomised trial in the title                              | 1                   |
| 1b                  |         | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | 2                   |
| **Introduction**    |         |                                                                                 |                     |
| 2a                  |         | Scientific background and explanation of rationale                            | 4                   |
| 2b                  |         | Specific objectives or hypotheses                                              | 5                   |
| **Methods**         |         |                                                                                 |                     |
| 3a                  |         | Description of trial design (such as parallel, factorial) including allocation ratio | 5-6                 |
| 3b                  |         | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | 5-6                 |
| **Participants**    |         |                                                                                 |                     |
| 4a                  |         | Eligibility criteria for participants                                          | 5-6                 |
| 4b                  |         | Settings and locations where the data were collected                            | 6                   |
| **Interventions**   |         |                                                                                 |                     |
| 5                   |         | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 6-9                 |
| **Outcomes**        |         |                                                                                 |                     |
| 6a                  |         | Completely defined pre-specified primary and secondary outcome measures, including how and when they were actually assessed | 9-10                |
| 6b                  |         | Any changes to trial outcomes after the trial commenced, with reasons          |                     |
| **Sample size**     |         |                                                                                 | 10-11               |
| 7a                  |         | How sample size was determined                                                  |                     |
| 7b                  |         | When applicable, explanation of any interim analyses and stopping guidelines    |                     |
| **Randomisation:**  |         |                                                                                 |                     |
| 8a                  |         | Method used to generate the random allocation sequence                          | 11                  |
| 8b                  |         | Type of randomisation; details of any restriction (such as blocking and block size) | 11                  |
| 9                   |         | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned |                     |
| **Implementation**  |         |                                                                                 | 11                  |
| 10                  |         | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions |                     |
| **Blinding**        |         |                                                                                 |                     |
| 11a                 |         | If done, who was blinded after assignment to interventions (for example, participants, care providers, those) |                     |
| Item | Description |
|------|-------------|
| 11a  | Statistical methods used to compare groups for primary and secondary outcomes |
| 11b  | If relevant, description of the similarity of interventions |
| 12a  | Statistical methods used to compare groups for primary and secondary outcomes |
| 12b  | Methods for additional analyses, such as subgroup analyses and adjusted analyses |
| 13a  | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome |
| 13b  | For each group, losses and exclusions after randomisation, together with reasons |
| 14a  | Dates defining the periods of recruitment and follow-up |
| 14b  | Why the trial ended or was stopped |
| 15   | A table showing baseline demographic and clinical characteristics for each group |
| 16   | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups |
| 17a  | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) |
| 17b  | For binary outcomes, presentation of both absolute and relative effect sizes is recommended |
| 18   | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory |
| 19   | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) |
| 20   | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses |
| 21   | Generalisability (external validity, applicability) of the trial findings |
| 22   | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence |
| 23   | Registration number and name of trial registry |
| 24   | Where the full trial protocol can be accessed, if available |
| 25   | Sources of funding and other support (such as supply of drugs), role of funders |
| 8-9  | |
| 11-12| |

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).*
Reaching mEthadone users Attending Community pHarmacies with HCV: An international cluster randomised controlled trial protocol (REACH HCV)

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TITLE

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

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SPONSOR

The trial is co-sponsored by University of Dundee/NHS Tayside (1-025-18; TASCgovernance@dundee.ac.uk) in the UK, and sponsored by The Alfred Hospital, Melbourne, in Australia (148/19; research@alfred.org.au).

WORD COUNT

4,270 excluding tables, figures, references, preliminary text, and appendices.
ABSTRACT

Introduction
Hepatitis C (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 health care 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 0.4-1.0% of the regions’ populations, accordingly it affects between 0.4-0.7% of the populations of countries in this study (Scotland, Wales, and Australia). REACH HCV will evaluate community pharmacy-based diagnostic outreach and HCV treatment against conventional HCV testing and treatment pathways for clients receiving opioid substitution (OST) therapy 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 (PoC) HCV PCR test in their pharmacy by a study outreach nurse. If positive, direct acting antivirals (DAA) 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 (SVR12). 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 (SAP) will be finalised prior to datalock. Analysis will be by intention to treat (ITT) to show superiority. Modified ITT (mITT) 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.

Registration details
The trial is registered on clinicaltrials.gov (NCT: 03935906).

Protocol Version
4.0 – 19/03/2020
STRENGTHS AND LIMITATIONS

- Pragmatic test-and-treat trial based in community pharmacies which decentralises 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 OST 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 (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 0.4-1.0% of the regions’ populations[2]. In line with that, chronic HCV affects between 0.4-0.7% 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 World Health Organisation (WHO) HCV elimination targets[1]. Recent data estimates HCV antibody prevalence of between 49-57% among 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 twelve 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 15-18% of individuals testing positive for HCV then commence treatment[8,15], with further population-level observations noting a 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 amongst 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 health care 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, whilst 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 SVR\textsuperscript{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 United Kingdom (UK) is provided via a joint agreement between Tayside Health Board and 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, a UK Clinical Research Collaboration-registered clinical trials unit[27]. Trials conducted by TCTU and subject to independent ad-hoc audit by the study Sponsor and its representatives, as well as relevant regulatory authorities (e.g. 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 NHS 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.

**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 (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, 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.

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

Point-of-care HCV Test

The PoC device being used for the trial is supplied by Genedrive Diagnostics PLC. It is a compact CE-IVD marked device, which incorporates ultra-fast polymerase chase reaction (PCR) cycling. The device is suitable for use by operators after minimal training and provides a simple positive/negative reading in under 90 minutes from sample collection. The device requires 30µl of sample[28]. This test is administered at baseline for participants in the pharmacist intervention arm.

HCV Medication

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

Participants will be prescribed this based on the following criteria:

All genotypes will receive eight 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 (e.g. 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 four weeks, to a total of twelve 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 eight 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 (Fib4, APRI, AST:ALT ratio), and viral parameters (HCV, HIV and HBV). A baseline blood sample per participant will be stored in a -80 degrees Celsius 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 (PGD) 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 general practitioner (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 SVR12 blood test will occur in the local clinic or GP offering this.

Participant Journey
In the pharmacist-intervention pathway all participants receive 3 or 4 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 3 data collection visits aligned with standard care schedules.

Participant visit schedules are fully outlined in tabular form in Supplementary File ‘Study Schedule Matrices Delineated by Pathway’, an overview is presented in Figure 1.

**OUTCOMES & 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 utilise logistic regression modelling while accounting for clustering through generalised linear mixed models. This will be analysed on an intention-to-treat (ITT) basis. The numerator will be the number of participants who achieve SVR\(^{12}\), the denominator will be total number of patients on OST. Additionally results will be expressed as a proportion of known HCV-infected subjects.

| 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. |

Table 1: Primary Objective and Outcome Measure

**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- and pharmacy-level baseline characteristics for the overall population and appropriate subgroups.

| 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\textsuperscript{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 which 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.

Table 2: Secondary Objectives and Outcome Measures

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 reported at approximately 40\%\textsuperscript{[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\textsuperscript{12}, i.e. the difference in proportions of those HCV positive on OST who achieve SVR\textsuperscript{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 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, the aim is to recruit up to 50 pharmacies, which will help reduce intra-
cluster correlation. Estimation was based on software nQuery Advisor v7 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 UKCRC registered Tayside Clinical Trials Unit, 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 trial arm in the model, and a random parameter to account for within-cluster correlation.

As all patients will have either achieved SVR\textsuperscript{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 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. Analyses will be carried out in accordance with the pre-specified SAP.

**Health Economic Analysis**

In this analysis, an existing dynamic, deterministic model of HCV transmission, progression and HCV treatment amongst PWID to evaluate the impact of the pharmacy intervention pathway compared to standard care testing and treatment will be adapted\textsuperscript{42}. 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 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 (ICER). 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\textsuperscript{43} of where the UK Willingness to Pay (WTP) should lie. 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 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 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 University of Dundee. Once data entry is complete, management and quality control will be conducted in line with Tayside Medical Science Centre (TASC) SOP DM053: Data Management in Clinical Research.

Data integrity will be monitored on an ongoing basis by the trial management group.

Safety Reporting

All adverse events (AE) or Serious Adverse Events (SAE) 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 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 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.

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 International Committee of Journal Editors (ICJME) guidelines. Access to IPD will be granted to 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 underlie the final published results, after de-identification; the study protocol; the SAP; the Data Management Plan (DMP).

CONTRIBUTORSHIP STATEMENT

JFD is the Chief Investigator for the trial. JFD, JSD, BH, AR and PTD 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, LB, 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.

COMPETING INTERESTS

CB declares no competing interests.

AR has received personal honoraria from AbbVie and Gilead and institutional research grants from MSD, AbbVie, Gilead and Roche.

SI declares no competing interests.

LB declares no competing interests.

NP declares no competing interests.

MDP declares no competing interests.

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.

PTD has received grants from Gilead, Shire pharmaceuticals. PTD is a member of the New Drugs Committee of the Scottish Medicines Consortium.

AbbVie Inc. 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.

**FIGURE LEGEND**

**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 general practitioner for hepatitis c screening. If positive, they are prescribed in in line with standard care. Treatment is dispensed by their pharmacist and they are referred to their local clinic or general practitioner for a sustained viral response test. Definitions: HCV = Hepatitis C Virus; PoC = Point of Care; DAA = Direct Acting Antivirals; OST = Opiate Substitution Therapy; SVR12 = Sustained Viral Response at 12 weeks; GP = General Practitioner; UK = United Kingdom; Aus = Australia.
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**FUNDING STATEMENT**

AbbVie funded the study and had input in the protocol development.
Figure 1 Participant Journey Overview

**Pharmacy Intervention Pathway**

- **SCREENING**
  - HCV Screening visit using PoC test in community pharmacy.

- **ASSESSMENT**
  - If HCV+: assessment for DAAs by outreach nurse in pharmacy.
  - Supply DAAs if inclusion criteria met.

- **TREATMENT**
  - DAA treatment in community pharmacy alongside OST schedule.

- **FOLLOW-UP**
  - SVR¹² visit using PoC test in community pharmacy.

**Education-only Pathway**

- **SCREENING**
  - Participant visits local clinic or GP for HCV screening visit, after referral from community pharmacist.

- **ASSESSMENT**
  - If HCV+: assessment for DAAs by clinic nurse or GP, treatment mandated in line with protocol (UK)/standard care (AUS).

- **TREATMENT**
  - DAA treatment in community pharmacy alongside OST schedule.

- **FOLLOW-UP**
  - Participant visits local clinic or GP for SVR¹² blood test, after referral from community pharmacist.
## STUDY SCHEDULE MATRICES DELINEATED BY PATHWAY

| Action                                                      | Potential participant visiting pharmacy for OAT | Initial HCV Screen | Treatment Start and/or Consultation | SVR<sup>12</sup> |
|-------------------------------------------------------------|-------------------------------------------------|---------------------|------------------------------------|------------------|
| Study information/HCV counselling                           | X                                               |                     |                                    |                  |
| Informed consent                                            | X                                               |                     |                                    |                  |
| HCV testing inclusion criteria                              | X                                               |                     |                                    |                  |
| Basic demographics                                          | X                                               |                     |                                    |                  |
| HCV RNA by PoC                                              | X                                               | X                   |                                    | X                |
| Safety & staging bloods                                     | X                                               |                     |                                    |                  |
| Research sample                                             | X                                               |                     |                                    |                  |
| HCV results confirmation                                    |                                                 | X                   | X                                  |                  |
| Treatment/ full study inclusion criteria                     |                                                 | X                   | X                                  |                  |
| Pharmacist receives HCV medication                          |                                                 | X                   | X                                  |                  |
| Adverse event assessment                                    | X                                               | X                   | X                                  |                  |
| Questionnaires (EQ-5D-5L; enhanced demographics; injecting information) | X                                               | X                   | X                                  |                  |

Study Schedule Matrix for pharmacy intervention pathway, all sites.

| Action                                                      | Potential participant visiting pharmacy for OAT | Initial HCV Screen | Treatment Start | SVR<sup>12</sup> |
|-------------------------------------------------------------|-------------------------------------------------|---------------------|-----------------|------------------|
| Study information/HCV counselling                           | X                                               | X                   |                 |                  |
| Informed Consent                                            | X                                               | X                   |                 |                  |
| HCV testing inclusion criteria                              | X                                               | X                   |                 |                  |
| Basic demographics                                          | X                                               | X                   |                 |                  |
| HCV RNA by standard testing protocols                       |                                                 | X                   | X X              |                  |
| Safety & staging bloods                                     |                                                 | X                   | X X              |                  |
| Research sample                                             |                                                 | X                   | X                |                  |
| HCV results confirmation                                    |                                                 | X                   | X X              |                  |
| Treatment/full study inclusion criteria                      |                                                 | X                   | X                |                  |
| Pharmacist receives HCV medication                          |                                                 | X                   | X                |                  |
| Adverse event assessment                                    |                                                 | X                   | X X              |                  |
| Questionnaires (EQ-5D-5L; enhanced demographics; injecting information) |                                                 | X                   | X X              |                  |

Study Schedule Matrix for education-only Pathway UK and Australia Delineated
Participation and Consent Form Education Pathway

Title: Reaching mEthadone users Attending Community pHarmacies with HCV

Short title: PharmEC REACH
Project Sponsor: Burnet Institute
HREC Project number: 51704
Principle Investigator: Dr Joseph Doyle
Study nurses: Kate Allardice, Kico Chan, Sally Von Bibra
Location: Melbourne, Australia

Part 1. What does my participation involve?

1. Introduction

You are invited to participate in a research project to look at hepatitis C (HCV) testing and treatment for patients who are taking Opiate Substitution Therapy (OST) through a community pharmacy. You have been asked to take part in this study because you are part of a risk group and take OST. Most people living with hepatitis C don’t know they are infected and therefore don’t get tested. They also might not know that there are very effective and safe HCV treatments available now.

All potentially eligible participants - patients receiving OST - will be given information about the trial from their local community pharmacist. Half of the pharmacies in the study will provide trial information and hepatitis C educational materials to OST patients who consent to take part. These patients will then be given directions to their nearest clinic for testing and follow the current standard of care.

You would be on this pathway if you agree to take part.

The other half of the pharmacies in the trial will be visited by a study nurse who will consent the participants and test them for hepatitis C using blood testing. Results, and a prescription for treatment for those who need it, will be given at following visits. These patients will be followed up at least 12 weeks post treatment completion for a blood test to confirm whether they have been cured.
This Participant Information and Consent document tells you about the project and it explains what would be involved if you decide to take part.

2. **What is the purpose of the research?**

   It is important that the people who require treatment for hepatitis C are given access to it. We want to find out the best way to approach people at risk of hepatitis C and the best way to offer them testing and treatment.

3. **What does participation in this research involve?**

   Participation in this study involves:

   1) **Providing Consent** for the study nurse to access your pharmacy and medical records to see whether you have had testing and treatment; to contact you by phone to see whether you have had testing and treatment and to complete the study questionnaires. You will also be asked to provide consent to allow your data from Medicare and the PBS to be linked. The purpose of data linkage is to assess how participants in the study use health services.

   2) **Completing questionnaires** asking about quality of life, medical, social and drug history, whether you are prescribed any regular medications and about any non-prescribed drugs you may be taking. This will be either just after you start treatment and again 20 weeks later, or 90 days after signing consent if you don’t start treatment.

   3) **Providing a sample of blood** for research purposes if you test positive for Hep C and present with a prescription for treatment at your OST pharmacy. The research nurse will contact you to arrange collection of this sample prior to starting your treatment if possible. The sample will only be labelled with your unique study number and stored at the Burnet Institute. It will be used to check for drug resistance in the case of reinfection or for future research projects that have been approved by a research Ethics Committee.

   4) **Checking for cure in those who are tested and treated** - the study nurse will review your medical and/or pharmacy records approximately 12 weeks after you finish treatment to see whether you have been cured for Hep C.

4. **What will I be asked to do?**

   You will be asked to provide consent for the study nurse to access your medical and pharmacy records. This is so that she can find out whether you have decided to have testing and treatment if you have a positive hepatitis C test result. You will also be asked to provide consent for the study nurse to contact you by phone to complete the study questionnaires.

Participant Information Sheet/ Consent Form EDUCATION V3.0 dated 12Jul 2019 based on Protocol V4.0 dated 05Jul19
If you test positive for Hep C and take a prescription for treatment to the pharmacy where you signed up for the study, you will also be asked to provide a small sample of blood.

5. Other relevant information about the research project

Test results

The study nurse will ask for your consent to access results for blood tests taken as standard care for hepatitis C testing and treatment by your doctor.

Data linkage component

The purpose of data linkage is to assess how participants in the PharmEC REACH study use health services. No information that is collected is used outside the project and therefore will not affect any information held with any health or public services, such as Centrelink.

You will be asked to sign a separate consent form for Medicare (MBS) and Pharmaceutical Benefits Scheme (PBS) information. Medicare collects information on your doctor visits and the associated costs, while the PBS collects information on the prescription medications you have filled at pharmacies. The consent form is sent securely to the Department of Human Services who hold this information confidentially.

Only information used to identify you will be sent to other agencies, and the information will be provided in a secure and confidential way. This information may include: Medicare number, first name, surname and middle initial, date of birth and gender.

Other information you give us, such as in the questionnaires and results from of your blood tests, will only be seen by members of the research team involved in this study.

Will I be reimbursed or receive gifts for being in the study?

Yes, you will be reimbursed $20 or receive a voucher to the value of $20 for the time taken to complete the study questionnaires.

6. Do I have to take part in this research project

Participation is voluntary. If you decide to take part and later change your mind, you are free to withdraw from the study at any time. If you do not want to take part or want to stop the trial, the medical care you get and your relationship with the medical, pharmacy or nursing staff looking after you will not be affected in any way.

7. What are the alternatives to participation?

You do not have to participate in this study and it won’t affect service delivery or the care you receive from your pharmacist or primary health care provider if you don’t. You can ask your local GP about the standard care options for hepatitis C testing and treatment if you wish.

Participant Information Sheet/ Consent Form EDUCATION V3.0 dated 12Jul 2019 based on Protocol V4.0 dated 05Jul19
8. **What are the possible benefits of taking part?**

The study may not immediately benefit you, but if the results of the study are positive this may change the practice of managing patients with hepatitis C and may have an impact on other patients’ health in the future.

9. **What are the possible risks or disadvantages of taking part?**

**What effect could the tests have on me?**

Drawing blood from a vein may cause local pain, bruising, occasional lightheadedness, fainting, and, very rarely, infection at the site of the blood draw.

There are no other anticipated discomforts, risks or side effects from taking part in this study. Any side effects of medication or tests undertaken will be explained to you fully by the doctor or pharmacist involved in your care but these are standard risks that are not associated with this study.

You will not be asked to take an investigational drug on this study as any medication prescribed has been registered in Australia and is available through the PBS.

This research project involves the collection of information about your current injecting drug use. You should not tell us anything specific about illegal behaviours that you have not been charged with or have not been dealt with by a court.

10. **What will happen to my test samples?**

5) Participants who return with a prescription for treatment for Hepatitis C will be asked to provide a small sample of blood to be kept for research purposes. This sample will be coded with your study identifier and stored securely at the Burnet Institute. Any blood tests ordered by your doctor will be analysed by a local pathology provider as is standard of care for hepatitis C treatment.

11. **What if I withdraw from this research project?**

Your participation in this study is voluntary and you may withdraw from the study at any time by informing a member of the research team. At this point, your participation in the study will end and the study staff will stop collecting information from you. However, the information about you collected prior to the date you withdraw will continue to be used and form part of the study. The Burnet Institute must do this to comply with its legal requirements and to maintain scientific integrity of the study. Your decision to withdraw from the study or to revoke your authorisation for the collection and use of information about you will not involve any penalty or loss of access to treatment and care, or other benefits to which you are entitled.

12. **What happens when this research project ends?**
The information collected will be analysed and reported. The results might also be published in scientific journals and / or presented at conferences and seminars. All results will be grouped, de-identified (your name will be removed from the data) information and no-one will be able to identify you.

Part 2. How is the research project being conducted?

13. What will happen to information about me?

The Burnet Institute is the Sponsor for this study in Australia. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. We will keep identifiable information about you securely for seven years after the study has finished. After seven years your identifiable information will be removed and the rest of the information will be kept for research purposes.

Your rights to access, change or move your information are limited, as we need to manage your information in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To protect your rights, we will use the minimum amount of information which is personally identifiable as possible. Identifiable information about you and the information collected about you during the trial will be securely stored by The Burnet Institute in Melbourne. Only specified members of the research team will have access to this information.

Your anonymous coded study information will be stored securely on a password-protected database(s). Specified members of the data management team will also have access to your identifiable information to manage your information and maintain the database.

We will ask you to sign consent to allow us to hold your contact details so that we can let you know about any future research project that might interest you. You can also opt out of this option.

We will also ask your permission to tell your GP that you are taking part in this study.

Information which identifies you will not be published or shared.

Your trial information may be shared with other researchers in the UK/Australia.

Your information will only be disclosed with your permission, or in compliance with the law.

By signing the Consent Form, you authorise the release of, or access to, this confidential information to the relevant study personnel and regulatory authorities such as the Australian Government’s Therapeutic Goods Administration or in compliance with the law.
The data collected about you from other sources, including Department of Human Services and Victorian hospitals, will also be linked to data collected in this study. Data provided by the Department of Human Services, will be de-identified and coded as described above.

Australian and/or Victorian privacy and other relevant laws give you the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like access to your information.

**Will information about this trial be included in a Registry Databank?**

No, data will not be collected and stored as part of a Registry Databank. All data will be stored in a study-specific database in de-identified (coded) form.

**14. Injury**

If you think that personal injury has occurred as a result of your involvement in this study, you must contact a member of the research team immediately.

**15. Who is funding this research?**

This trial is being sponsored by the Burnet Institute in Melbourne and being organised by Dr Joseph Doyle, Deputy Director Disease Elimination Programs. It is being funded by The University of Dundee in Scotland.

**16. Who has reviewed this research project?**

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Alfred Hospital Ethics Committee. The project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

**17. Further information and who to contact**

If you are concerned about your participation in the trial you have the right to discuss your concern with a researcher involved in carrying out the trial or a doctor involved in your care.

If you have a complaint about your participation in the trial first of all you should talk to a researcher involved in the trial. You can also make a formal complaint. You can make a complaint to a senior member of the research team or to the Complaints Officer for the Alfred Hospital.
### Study contact person:

| Name          | Dr Joseph Doyle                  |
|---------------|---------------------------------|
| Position      | Chief Investigator              |
| Telephone     | 03 9282 2111                    |
| Email         | joseph.doyle@burnet.edu.au      |

### Site-Clinical contact person:

| Name          | Kate Allardice                  |
|---------------|---------------------------------|
| Position      | Study nurse                     |
| Telephone     | 03 9282 2167 or 0429 123 054    |
| Email         | Kate.allardice@burnet.edu.au    |

### Complaints:

Please quote Project ID number: 51704

| Name          | Alfred Hospital Ethics Committee |
|---------------|---------------------------------|
| Position      | Complaints Officer              |
| Telephone     | 03 9076 3619                    |
| Email         | research@alfred.org.au          |
Consent Document

Title: Reaching mEthadone users Attending Community Pharmacies with HCV (PharmEC REACH)

Project Number: 51704
Project Sponsor: Burnet Institute
Principal Investigator: Dr Joseph Doyle
Study nurses: Kate Allardice, Kico Chan, Sally Von Bibra

Location: Melbourne, Australia

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of research described in this document.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this clinic to release information to PharmEC REACH study team concerning my disease and treatment for the purpose of the project. I understand that such information will remain confidential.

I agree that the Burnet Institute, study staff, and others may have access to my medical and personal information, as described in this form. I know what happens to my blood samples collected for this study.

I have had the opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed and dated copy of this document to keep.

Name of participant (please print): ____________________________
Signature: ____________________________ Date: ____________________________

Declaration by Study Nurse/Senior Researcher/Pharmacist

I have given a verbal explanation of the project, its procedures and risks and I believe that the participant has understood the explanation.

I understand that I will be given a signed and dated copy of this document to keep.

Name of Study Nurse/ Senior Researcher (please print): ____________________________
Signature: ____________________________ Date: ____________________________

A senior research team member must provide the explanation of, and information concerning, the research project. Note: ALL parties signing the consent section must date their own signature.
PARTICIPANT CONSENT FORM

Consent to release of Medicare and/or Pharmaceutical Benefits Scheme (PBS) claims information for the purposes of PharmEC REACH study

Important Information

Complete this form to request the release of personal Medicare claims information and/or PBS claims information to the PharmEC REACH Study.

Any changes to this form must be initialled by the signatory. Incomplete forms may result in the study not being provided with your information.

By signing this form, I acknowledge that I have been fully informed and have been provided with information about this study. I have been given an opportunity to ask questions and understand the possibilities of disclosures of my personal information.

PARTICIPANT DETAILS

1. Mr □ Mrs □ Miss □ Ms □ Other □
   
   Family name: ________________________________First given name: ________________________________

   Other given name (s): ________________________________

   Date of birth: DD/MM/YYYY

2. Medicare card number: ________________________________

3. Permanent address: _____________________________________________________________

   Postal address (if different to above): _____________________________________________________________

AUTHORISATION

4. I authorise the Department of Human Services to provide my:

   □ Medicare claims history OR
   □ PBS claims history OR
   □ Medicare & PBS claims history

   for the period* 01/06/2019 to: 01/12/2024 to the PharmEC REACH Study.

   *Note: This period cannot exceed 4 ½ years

DECLARATION

I declare that the information on this form is true and correct.

5. Signed: ________________________________ (participant’s signature) Dated: DD/MM/YYYY

Participant Information Sheet/ Consent Form EDUCATION V3.0 dated 12Jul 2019 based on Protocol V4.0 dated 05Jul19

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Participation and Consent Form PharmEC REACH PATHWAY

Title: Reaching mEthadone users Attending Community pHarmacies with HCV

Short title: PharmEC REACH
Project Sponsor: Burnet Institute
Project ID number: 51704
Principle Investigator: Dr Joseph Doyle
Study nurses: Kate Allardice, Sally von Bibra, Kico Chan
Location: Melbourne, Australia

Part 1. What does my participation involve?

1. Introduction

You are invited to participate in research to look at hepatitis C (HCV) testing and treatment in community pharmacies for patients who are taking Opiate Substitution Therapy (OST). You have been asked to take part in this study because you are part of a risk group and taking OST. Most people living with hepatitis C don’t know they are infected and therefore don’t get tested. They also might not know that there are very effective and safe HCV treatments available now.

In this study, we are examining whether providing hepatitis C testing and treatment in the pharmacy where you collect your OST improves rates of diagnosis and treatment in people at risk.

This Participant Information and Consent document tells you about the project and it explains what would be involved if you decide to take part in the project.

2. What is the purpose of the research?

It is important that the people who most require treatment for Hepatitis C are given access to it. We want to find out the best way to approach people at risk of Hepatitis C and the best way to offer them testing and treatment.

3. What does participation in this research involve?

Participant Information Sheet/ Consent Form PharmEC REACH PATHWAY Version 2.0 dated 16Sep2019
Participation in this study involves:

1) Having a **rapid blood test** to check for Hep C along with standard blood testing to confirm the results and to check the health of your liver, kidneys and make sure you are healthy and can take the medication. The study nurse will return in 2 days to give results and a prescription for those who test positive.

2) **If your rapid blood test is negative**, you will see the study nurse again in 14 days to confirm the result with the laboratory test results. If the lab test is positive, you will be given a prescription for treatment at this time. If the lab test is negative there is no need for further involvement.

3) **If your rapid blood test is positive** for HCV infection, the nurse will discuss the results with you and the Pharmacist will be given a prescription for Hep C medication. The Pharmacist will give you this medication whenever you receive your OST. You will receive 8 weeks of therapy with Glecaprevir/Pibrentasvir. This is the generic name for the drug Maviret which is licensed for use with the Therapeutic Goods Administration in Australia for the treatment of HCV. For this study, the pharmaceutical company AbbVie are supporting the study by providing the drug at no cost. If you have liver cirrhosis (indicated by blood test) you will receive 12 weeks. If you have previously failed treatment with Interferon + ribavirin +/- sofosbuvir or sofosbuvir + ribavirin you will receive, 8, 12 or 16 weeks, depending on your blood tests results.

4) **The study nurse will return within 2 weeks** to give all people who have consented to be in the study all of their test results and discuss what they mean.

5) **Completing questionnaires** asking about quality of life, medical, social and drug history, whether you are prescribed any regular medications and about any non-prescribed drugs you may be taking.

6) **Testing for cure:** the study nurse will return approximately 12 weeks after you finish taking Glecaprevir/Pibrentasvir to take blood samples to confirm that you have been cured from Hep C. You will be asked to complete questionnaires again at this time.

7) **Research storage blood sample** A tube of blood will be collected for research purposes; you will not receive any result from this sample. Your blood sample will be stored indefinitely in locked freezers at the Burnet Institute. After the study is completed, the sample may be used for additional exploratory research, for example, on:
   - Pharmacokinetics (how the body processes the medications)
   - The structure, function and subtype of the HCV virus
   - Whether/how the virus develops resistance to the medications
   - How the immune system affects the body’s response to the virus and medications.

Ethics approval will be required for any additional research studies using this sample.
4. What will I be asked to do?

If you take part in the study, you will need to be available to see the study nurse for a maximum of 3 visits at the pharmacy site where you receive your OST.

5. Other relevant information about the research project

Test results

The blood tests performed will include a hepatitis B screening test and HIV screening tests. **This is standard of care in Australia for anyone being tested for HCV infection.** You will receive counselling and information about these tests and what it means if they are positive before having the test. If you are positive for HIV or hepatitis B infection, you will have follow up counselling and medical advice given, along with a referral to see a specialist. All positive HIV, hepatitis C and hepatitis B test results have to be reported to the Victorian Department of Health to help them monitor diseases; we have to do this under Victorian Law.

Data linkage component

The purpose of data linkage is to assess how participants in the PharmEC REACH study use health services. No information that is collected is used outside the project and therefore will not affect any information held with any health or public services, such as Centrelink.

You will be asked to sign a separate consent form for Medicare (MBS) and Pharmaceutical Benefits Scheme (PBS) information. Medicare collects information on your doctor visits and the associated costs, while the PBS collects information on the prescription medications you have filled at pharmacies. The consent form is sent securely to the Department of Human Services who hold this information confidentially.

Only information used to identify you will be sent to other agencies, and the information will be provided in a secure and confidential way. This information may include: Medicare number, first name, surname and middle initial, date of birth and gender.

Other information you give us, such as in the questionnaires and outcome of your blood test will only be seen by members of the research team.

Will I be reimbursed for being in the study?

Yes, you will be reimbursed $20 or receive a Coles/Myers voucher to the value of $20 for the time taken to complete the study questionnaires.

6. Do I have to take part in this research project?

Participation is voluntary. If you decide to take part and later change your mind, you are free to withdraw from the study at any time. If you do not want to take part or want to stop...
your participation in the study, the medical care you get and your relationship with the medical, pharmacy or nursing staff looking after you will not be affected in any way.

7. What are the alternatives to participation?

The study nurse will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss options with your local doctor. This study just looks at offering rapid testing and treatment for HCV in OST pharmacies to see if it improves testing and treatment uptake by at-risk populations - you will still be eligible for HCV tests with a GP that are standard of care within Australia.

8. What are the possible benefits of taking part?

The study may not immediately benefit you, but if the results of the study are positive this may change the practice of managing patients with Hepatitis C and may have an impact on other patients’ health in the future.

You will not benefit financially from your involvement in this research project even if your research blood sample (or knowledge gained from your sample) prove to be of commercial value.

9. What are the possible risks or disadvantages of taking part?

It is important to note, that this is not an investigational drug study. This study is to work out the best way to treat people at risk of Hep C, not to test new drugs.

What effect could the tests have on me?

There are minimal anticipated discomforts, risks or side effects from taking part in this study. Any side effects of the medication or tests undertaken will be explained to you fully by the doctor, nurse or pharmacist involved in your care but these are standard risks that are not associated with this study.

You may feel discomfort during some of the tests or may experience some inconveniences. Blood tests (drawing blood from your arm with a needle) may cause pain, bruising, light-headedness, and rarely infection.

This research project involves the collection of information about your current injecting drug use behaviour. You may feel uncomfortable providing this type of information. This information is collected via a questionnaire using your only study number. You do not have to provide this information to be in the study.

10. What will happen to my test samples?

Your blood tests will be analysed by a local pathology provider as is standard of care for Hep C treatment and you will be provided with the results. As mentioned in section 3 we will be
storing a blood sample for future research; you will not receive any results from this sample. The research sample will be stored indefinitely in locked freezers at the Burnet Institute.

11. What if I withdraw from this research project?

Your participation in this study is voluntary and you may withdraw from the study at any time by informing a member of the research team. At this point, your participation in the study will end and the study staff will stop collecting information from you. However, the information about you collected prior to the date you withdraw will continue to be used and form part of the study. The Burnet Institute must do this to comply with its legal requirements and to maintain scientific integrity of the study. Your decision to withdraw from the study or to revoke your authorisation for the collection and use of information about you will not involve any penalty or loss of access to treatment and care, or other benefits to which you are entitled.

12. What happens when this research project ends?

The information collected will be analysed and reported to the research team. The results might also be published in scientific journals and/or presented at conferences and seminars. All results will be grouped, de-identified information and no-one will be able to identify you.

Part 2. How is the research project being conducted?

13. What will happen to information about me?

The Burnet Institute is the Sponsor for this study in Australia. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. We will keep identifiable information about you for 7 years after the study has finished and been published. After seven years your identifiable information will be removed and the rest of the information will be kept for research purposes. Your rights to access, change or move your information are limited, as we need to manage your information in order for the research to be reliable and accurate. To protect your rights, we will use the minimum amount of information that is personally identifiable as possible. Identifiable information and other information collected about you during the study will be securely stored by The Burnet Institute in Melbourne. Only specified members of the research team will have access to this information.

Your anonymous (coded) study information will be stored securely on a password-protected database(s). Specified members of the data management team will also have access to your identifiable information to manage your information and maintain the database.

If you decide to participate in this study, the study team will inform your healthcare provider/GP.
Information that identifies you will not be published or shared.

Your study information may be shared with other researchers in the UK/Australia.

By signing the Consent Form, you authorise the release of, or access to, this confidential information to the relevant study personnel and regulatory authorities such as the Australian Government’s Therapeutic Goods Administration or as required by law.

The data collected about you from other sources, including the Department of Human Services and Victorian hospitals, will also be linked to data collected in this study. Data provided by the Department of Human Services will be coded as described above.

Australian and/or Victorian privacy and other relevant laws give you the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like access to your information.

14. Injury

If you suffer an injury as a result of your participation in this project, please contact the research staff. Hospital care and treatment will be provided by the public health care system (Medicare) at no cost to you if you are eligible for Medicare benefits and elect to be treated as a public patient.

If you think that personal injury has occurred as a result of your involvement in this study, you must contact a member of the research team immediately.

15. Who is funding this research?

This study is being sponsored by the Burnet Institute in Melbourne and being organised by Dr Joseph Doyle, Deputy Director Disease Elimination Programs. It is being funded by The University of Dundee in Scotland.

16. Who has reviewed this research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Alfred Hospital Ethics Committee. The project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

17. Further information and who to contact
If you are concerned about your participation in the study you have the right to discuss your concern with a researcher involved in carrying out the study or a doctor involved in your care.

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact the Complaints Officer of the Alfred Hospital Ethics Committee.

**Study contact person:**

| Name          | Dr Joseph Doyle                                      |
|---------------|------------------------------------------------------|
| Position      | Chief Investigator                                   |
| Telephone     | 03 9282 2111                                        |
| Email         | joseph.doyle@burnet.edu.au                          |

**Site-Clinical contact person:**

| Name          | Kate Allardice                                       |
|---------------|------------------------------------------------------|
| Position      | Study nurse                                          |
| Telephone     | 03 9282 2167 or 0429 123 054                         |
| Email         | Kate.allardice@burnet.edu.au                        |

**Complaints contact person:**

| Position      | Complaints Officer, Office of Ethics & Research Governance, Alfred Health |
|---------------|------------------------------------------------------------------------|
| Telephone     | 03 9076 3619                                                          |
| Email         | research@alfred.org.au                                                |

Please quote the following Project ID number: 51704
Consent Document

Title: Reaching mEthadone users Attending Community pHarmacies with HCV (PharmEC REACH)

Project ID Number: 51704

Project Sponsor: Burnet Institute

Principal Investigator: Dr Joseph Doyle

Study nurses: Kate Allardice, Sally von Bibra, Kico Chan

Location: Melbourne, Australia

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of research described in this document.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this clinic to release information to the Burnet Institute concerning my disease and treatment for the purpose of the project. I understand that such information will remain confidential.

I agree that the Burnet Institute, study staff, and others may have access to my medical and personal information, as described in the Participant Information Sheet. I know what happens to my blood samples collected for this study.

I have had the opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed and dated copy of this document to keep.

Name of participant (please print): ____________________________

Signature: ____________________________ Date: ____________

Declaration by Study Nurse/Senior Researcher

I have given a verbal explanation of the project, its procedures and risks and I believe that the participant has understood the explanation.

I understand that I will be given a signed and dated copy of this document to keep.

Name of Study Nurse/ Senior Researcher (please print): ____________________________

Signature: ____________________________ Date: ____________

A senior research team member must provide the explanation of, and information concerning, the research project. Note: ALL parties signing the consent section must date their own signature.

Participant Information Sheet/ Consent Form PharmEC REACH PATHWAY Version 2.0 dated 16Sep2019
PARTICIPANT CONSENT FORM

Consent to release of Medicare and/or Pharmaceutical Benefits Scheme (PBS) claims information for the purposes of PharmEC REACH study

Important Information

Complete this form to request the release of personal Medicare claims information and/or PBS claims information to the PharmEC REACH Study.

Any changes to this form must be initialled by the signatory. Incomplete forms may result in the study not being provided with your information.

By signing this form, I acknowledge that I have been fully informed and have been provided with information about this study. I have been given an opportunity to ask questions and understand the possibilities of disclosures of my personal information.

PARTICIPANT DETAILS

1. Mr □ Mrs □ Miss □ Ms □ Other □

Family name: ________________________________ First given name: ____________________________

Other given name (s): __________________________

Date of birth: DD/MM/YYYY

2. Medicare card number: ______________________

3. Permanent address: _____________________________________________________________

Postal address (if different to above): ________________________________________________

AUTHORISATION

4. I authorise the Department of Human Services to provide my:

☐ Medicare claims history OR

☐ PBS claims history OR

☐ Medicare & PBS claims history

for the period* 01/06/2019 to: 01/12/2024 to the PharmEC REACH Study.

*Note: This period cannot exceed 4 ½ years

DECLARATION

I declare that the information on this form is true and correct.

5. Signed: ______________________ (participant’s signature) Dated: DD/MM/YYYY

Participant Information Sheet/ Consent Form PharmEC REACH PATHWAY Version 2.0 dated 16Sep2019
### SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item                  | ItemNo | Description                                                                                                                                                                                                 | Page # |
|-------------------------------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| **Administrative information**|        |                                                                                                                                                                                                              |        |
| Title                         | 1      | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym                                                                                               | 1      |
| Trial registration            | 2a     | Trial identifier and registry name. If not yet registered, name of intended registry                                                                                                                        | 2      |
|                               | 2b     | All items from the World Health Organization Trial Registration Data Set                                                                                                                                   | 1-14   |
| Protocol version              | 3      | Date and version identifier                                                                                                                                                                                   | 2      |
| Funding                       | 4      | Sources and types of financial, material, and other support                                                                                                                                                 | 17     |
| Roles and responsibilities    | 5a     | Names, affiliations, and roles of protocol contributors                                                                                                                                                     | 1; 13  |
|                               | 5b     | Name and contact information for the trial sponsor                                                                                                                                                           | 1      |
|                               | 5c     | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 17     |
|                               | 5d     | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | 5; 13  |
| **Introduction**             |        |                                                                                                                                                                                                              |        |
| Background and rationale      | 6a     | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 4-5    |
|                               | 6b     | Explanation for choice of comparators                                                                                                                                                                       | 4-5    |
| Objectives                    | 7      | Specific objectives or hypotheses                                                                                                                                                                            | 5; 9-10|
| Trial design                  | 8      | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 6-11   |
| **Methods: Participants, interventions, and outcomes** | **Page #** |
|-----------------------------------------------|-----------|
| **Study setting** 9 | Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 7 |
| **Eligibility criteria** 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists) | 6 |
| **Interventions** 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 7-9 |
| **11b** | Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease) | 7 |
| **11c** | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests) | 7-8; 12 |
| **11d** | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 6 |
| **Outcomes** 12 | Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 9-10. |
| **Participant timeline** 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 8/Figure 1 |
| **Sample size** 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 10-11 |
| **Recruitment** 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 7-8; 10-11 |

**Methods: Assignment of interventions (for controlled trials)**

**Allocation:**

| **Sequence generation 16a** | Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 10-11 |
| Category                        | Section | Description                                                                                                                                                                                                 |
|--------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Allocation concealment mechanism | 16b     | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | N/A |
| Implementation                  | 16c     | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions                                                                                | 7; 11 |
| Blinding (masking)              | 17a     | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how                                                                  | 6 |
|                                | 17b     | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial                                      | N/A |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods         | 18a     | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 12 |
|                                | 18b     | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 11 |
| Data management                 | 19      | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 12 |
| Statistical methods             | 20a     | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 11 |
|                                | 20b     | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 11 |
|                                | 20c     | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 11 |
| **Methods: Monitoring**         |         | | |
| Data monitoring                 | 21a     | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 5 |
21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

**Ethics and dissemination**

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Protocol amendments 25 Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

Consent forms uploaded with submission

Consent or assent 26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality 27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy 31a Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions 12-13
| 31b | Authorship eligibility guidelines and any intended use of professional writers |
|-----|--------------------------------------------------------------------------------|
| 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code |

**Appendices**

| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates |
|-----------------------------|----|--------------------------------------------------------------------------------------------------|
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.*