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SuperDOT-C: Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: a pragmatic cluster randomised trial

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SuperDOT-C: Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: a pragmatic cluster randomised trial

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Running Head:

Hepatitis C Testing and Treatment in Community Pharmacies

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Abstract

Introduction: Hepatitis C Virus (HCV) infection affects 0.7% of the general population, and up to 40% of people prescribed Opioid Substitution Therapy (OST). In conventional care, less than 10% of OST users are tested for HCV and less than 25% of these initiate treatment. Community pharmacists see this group frequently to provide OST supervision. This study examines whether a pharmacist-led 'test & treat' pathway increases cure rates for HCV.

Methods and Analysis: This protocol describes a cluster randomised trial where 60 community pharmacies provide either conventional or pharmacy-led care. All pharmacies offer dried blood spot testing (DBST) for HCV. Participants have attended the pharmacy for OST for 3 months; are positive for HCV genotype 1 or 3; not co-infected with HIV and/or hepatitis B; no decompensated liver disease; not pregnant. For conventional care, pharmacists refer HCV positive participants to a local centre for assessment. In the pharmacy-led arm, pharmacists assess participants themselves in the pharmacy. Drug prescribing is by nurse prescribers (conventional arm) or pharmacist prescribers (pharmacy-led arm). Treatment in both arms is delivered as daily modified directly observed therapy (DOT) in a pharmacy. Primary trial outcome is number of sustained viral responses (SVR) at 12 weeks after treatment completion. Secondary trial outcomes are number of tests taken; treatment uptake; completion; adherence; re-infection. An economic evaluation will assess potential cost-effectiveness. Qualitative research interviews with clients and health professionals assess acceptability of a pharmacist-led pathway.

Ethics and Dissemination: This protocol has been ethically approved by the East of Scotland Research Ethics Committee 2 (15/ES/0086) and complies with the Declaration of Helsinki and principles of Good Clinical Practice. Informed consent is obtained before study enrolment and only anonymised data is stored in a secured database, enabling an audit trail. Results will be submitted to international peer-reviewed journals and presented at international conferences.

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Strengths and limitations of this study

- Real world study developed through extensive modelling and feasibility work
- Potential to provide answers to an extremely topical question around approaches to eliminate a disease, in line with a WHO target.

- Utilises a community pharmacy-based pathway in NHS Scotland, but not wider primary care systems
- Relies on close and integrated working between a specialist hepatitis service and community pharmacy services

Introduction

Hepatitis C (HCV) is a blood-borne viral infection causing liver disease. Around 0.7% of the Scottish population are chronically infected with HCV [1]. Patient outcomes from HCV infection vary, with 25% clearing the infection spontaneously and the remainder becoming chronically infected, risking development of cirrhosis and hepatocellular carcinoma [2]. A recent Public Health England report highlighted that less than half of those infected with HCV have been identified, and of those identified less than 3% of those known to be infected with HCV are being treated [3]. The greatest risk of acquiring the virus in the UK is through injecting drug use [4] and evidence suggests around 40% of people receiving Opioid Substitution Therapy (OST) have HCV infection [5]. Only a small proportion of this high-risk and vulnerable population are receiving adequate treatment, despite having daily healthcare interaction with a pharmacist and the availability of a curative intervention with widely available Direct Acting Antiviral (DAA) medication [6].

The conventional care pathway in the United Kingdom recommends that patients with a history of intravenous drug use, or those currently prescribed OST, should be offered HCV testing annually [3]. Testing may be available from their GPs, drug workers, drug agencies, social workers, community pharmacies and needle exchanges [7]. Once diagnosed, patients can be referred to established treatment pathways, usually based around hepatology teams in secondary care. In these established treatment pathways, less than 10% of the OST population are tested for HCV annually. Of those tested, at most 25% start treatment in one of the dedicated centres and 70-80% successfully complete treatment, with treatment failure primarily caused by non-adherence and non-persistence to treatment [8]. Similar patterns are observed in other countries [9]. The inefficiency of established treatment pathways leads to increased preventable deaths from HCV and viral transmission within the injecting population [10].

A variety of reasons may explain the low rates of HCV testing, treatment uptake, and treatment completion. People who inject drugs (PWID) may encounter a number of barriers that prevent them from accessing care, including perceptions and experience of stigma and discrimination, issues with the organisation of care and the treatment policies of providers or payers [11]. There are identified deficiencies in the extent of screening and diagnosis of at-risk populations, as well as the need to simplify pathways to enable treatment initiation and clinical monitoring [12]. People who inject drugs may find it difficult to consistently attend medical clinics [13].

The WHO has set an ambitious goal to eliminate HCV as a public health threat by 2030 [14].

Creating the complex interventions necessary to eradicate HCV requires that well-designed cross-disciplinary programmes are put in place using different strategies to increase screening, testing and diagnosis [15]. Strategies that demonstrate increase testing and treatment uptake include the provision of integrated HCV care pathways; with drug use and psychiatric services delivered by a multidisciplinary team, and with case management services [16]. The delivery of HCV testing and treatment through community-based care pathways has also been shown to be feasible and DBST has been demonstrated to increase the uptake of testing from high-risk populations [17]. Hence, a more central role in the treatment of HCV for community-based pharmacists who are seeing these clients on a daily basis, could – in theory – lead to increased HCV treatment success rates through higher HCV testing, treatment uptake, adherence, and treatment completion rates.

In preparation for the current trial investigating the clinical benefits of pharmacy-delivered HCV treatment, pilot work was undertaken guided by the MRC theoretical framework for developing and evaluating complex interventions [18]. Initial work involved using a co-production approach in partnership with OST patients. This work identified the current experiences of patients in accessing HCV testing and treatment and in accessing OST in pharmacies [19]. The attributes of an ideal service were identified and an estimate of potential uptake made [20]. The implementation of DBST in pharmacies was undertaken and the experiences of patients and providers recorded [21]. A pilot trial has been undertaken to test each stage of the pharmacy-led care pathway and to look for confirmation that an appropriately powered definitive multicenter randomised controlled trial would be feasible [22]. The PRECIS-2 tool was used to assess that the design decisions were concordant with the purpose of the trial (Supplementary material) (23).

The aim of this research is to examine the impact of pharmacy-delivered HCV treatment on HCV treatment success rates amongst OST users. Our research questions are:

Trial

(1) Does a community pharmacist-led HCV treatment pathway increase treatment success rates (sustained virological response, or SVR) compared to the conventional pathway?

(2) Does a community pharmacist-led HCV treatment pathway lead to a higher uptake of HCV testing?

(3) Does a community pharmacist-led HCV treatment pathway lead to a higher uptake and completion of HCV treatment?

(4) Is adherence and persistence to HCV therapy in the pharmacy setting similar to that in the Conventional pathway?

(5) What is the re-infection rate at 12 months after end of treatment in all patients with SVR, and for the pharmacist-led pathway compared to the conventional pathway?

Health Economics Study

(6) Is the pharmacist-led pathway potentially a cost-effective method of testing and treating HCV in people prescribed OST?

Qualitative Study

(7) Is the pharmacist-led pathway an acceptable way to offer testing and treatment for people prescribed OST infected with HCV and are there any unexpected consequences?

Methods:

Design

Super DOT-C is a cluster randomised trial of pharmacy-led anti HCV therapy versus conventional care in HCV infected patients attending community pharmacies. Sixty pharmacies will be enrolled to this study across 5 hubs in Health Boards in NHS Scotland. Pharmacies (and thus their patients) participating in the trial will be randomly allocated to conventional care pathway or the pharmacy-led pathway.

Pharmacies at each site are randomised into two groups: conventional care and pharmacist-led care. Randomisation will be carried out using http://www.randomization.com. The subjects are randomized into one block along with the number of subjects per block/number of blocks and (case-sensitive) treatment labels. The pharmacies in each hub provide the level of randomisation, so patient allocation is dependent on the pharmacy attended.

Eligibility Criteria

Eligible pharmacies are community-based, offer dried blood spot testing for HCV by trained pharmacy staff in line with approved practice in their particular NHS board and have at least 30 patients on OST to ensure adequate recruitment. Patient inclusion criteria are having HCV PCR positive to genotype 1 or 3, are OST users and willing to have their pharmacists supervise their antiviral drug use. Patient exclusion criteria are having another genotype than 1 or 3, evidence of current or previous decompensated liver disease, HIV infection, HBsAg positive with detectable HBV DNA, aggressive or violent behaviour towards the pharmacist, being pregnant, and not being able to provide informed consent.

Interventions

Medication provided

The anti HCV treatment provided in both pathways is identical, ie:

- For HCV genotype 1 sofosbuvir/ledipasvir for 8 weeks
- For HCV genotype 3 sofosbuvir/daclatasvir for 12 weeks

Study Site Staff Training

Staff from each study site will receive training on Good Clinical Practice, quality control, use of study documentation, ensuring common practice, and consenting participants. In addition training to establish testing for blood borne viruses is provided and information on hepatitis C and its treatment is provided. Staff in the pharmacy-led arm are trained on how to interpret laboratory bloods and to perform a Fib4 calculation [24].

The similarities and differences between the two study arms are summarised in Table1 below

Table 1: Treatment pathways: similarities and differences

	Conventional care	**Pharmacy pathway**	**Contrast**
HCV testing	Opportunistic HCV testing on presentation for OST therapy	Opportunistic HCV testing on presentation for OST therapy	The same procedure is provided in each of the study arms
HCV test confirmation	Test result is communicated and - if positive – referred for assessment in local treatment centre	Test result is communicated and – if positive - assessment directly undertaken in the pharmacy	Assessment for treatment is carried out at the pharmacy when the participant visits to obtain OST, not at a different site with a different provider
Treatment initiation	Suitable patients are prescribed treatment by a nurse prescriber at the	Suitable patients are prescribed treatment by a pharmacist prescriber	Treatment initiation is carried out at the pharmacy and not at a

	local treatment centre and access treatment through DOT at their pharmacy	and access treatment through DOT at their pharmacy	different site with a different provider
Treatment monitoring	Treatment monitoring is carried out by the specialist team in their clinic	Treatment monitoring is carried out at the pharmacy	Treatment monitoring is carried out at the pharmacy not at a different site. Monitoring in the conventional pathway requires additional clinic visits
Treatment completion	SVR testing is carried out by DBST at the pharmacy	SVR testing is carried out by DBST at the pharmacy	The same procedure is provided in each of the study arms

Conventional Care Pathway

At the start of the pathway pharmacists will opportunistically discuss HCV infection with their OST patients. The pharmacist will record on a screening log which of the OST patients attending the pharmacy they have approached. Those with unknown HCV status will be offered testing using a DBST in the pharmacy [25]. Patients identified as having HCV antibodies will have a post-test discussion with the pharmacist. During this discussion the pharmacists will obtain informed consent and explain about HCV treatment using a standard infographic (supplementary materials). Next, the pharmacist will offer them referral to the conventional care pathway for assessment and treatment at a local treatment centre. Information will be provided verbally and by offering standard leaflets about HCV. If the patient attends an appointment at one of the local treatment centres, a member of the specialist hepatitis team will invite the patient to undertake assessment for treatment for HCV. Assessment comprises of a pre-treatment checklist of medical co-morbidities, medical history, and concomitant medication to look for drug-drug interactions. The patient will undergo phlebotomy in the local treatment centre to check full blood count, urea and electrolytes, liver function testing, including markers of liver fibrosis [24] (Fib4, APRI, AST:ALT ratio) and viral parameters (genotype and load), as assessment for treatment. Patients who are referred for assessment and treatment will be managed according to the standard local treatment pathway, which includes DAA treatment delivery jointly with OST in

their normal pharmacy; which would qualify as DOT during weekdays, although at weekends patients self-administer. Prescriptions will be provided by a nurse prescriber and dispensed at the participant's normal pharmacy. For doses that patients have to self-administer and the weekend doses when there is no OST distribution, the pharmacist and patient will make a brief if-then action plan (an implementation intention) and coping plan (to overcome anticipated barriers) [26]. The study related data collection will be undertaken by the specialist hepatitis team.

Pharmacist-Led Pathway

Potential participants are offered testing, recruited and consented as in the conventional pathway. In the pharmacy-led pathway however, the pharmacist will offer them anti-HCV therapy delivered solely within the pharmacy. The patients who decline study participation will be entered in the screening log. For the patients who do consent, the pharmacist will complete a pre-treatment checklist of medical co-morbidities, medical history, and concomitant medication to look for drug-drug interactions. The patient will undergo phlebotomy in the pharmacy for safety blood tests, as in the conventional pathway and the pharmacist will assess this information to determine suitability for treatment.

If there are no contra-indications to therapy, the patient will commence the treatment. In patients where there are contraindications or queries about suitability, the pharmacist will contact the central clinical co-ordinator for advice. Unsuitable patients will be referred to the conventional pathway for assessment outside the study as standard clinical care. Prescriptions for treatment will be provided by pharmacist prescriber. Suitable patients entering treatment will have DAA treatment delivered jointly with OST; mostly daily DOT, except at weekends daily dispensing of therapy drugs, as in the conventional pathway. Patients who do not attend the pharmacy for seven consecutive days will be discontinued from the study since they will be deemed to have discontinued their course of DAA treatment and will have had their OST discontinued. The primary study outcome (SVR 12 weeks after treatment completion) is assessed by DBST in the pharmacy for both study arms.

Outcomes and measures

The denominator for the outcomes on treatment uptake is the number of people using OST at the pharmacies participating in the respective arms. For the primary outcome, the numerator will be the number of patients with Sustained Viral Response at 12 weeks post treatment completion (SVR12) after allocation to treatment arm, measured through a test for the presence of HCV RNA (polymerase chain reaction).

For the secondary outcomes on treatment uptake, the numerators are the number of patients who (a) undergo HCV testing, (b) initiate HCV treatment, (c) complete the 12-week HCV course, (d) number of patients with SVR at 12 months (to assess the impact of potential reinfection).

Study schedule

For both arms, screening for HCV by DBST is undertaken prior to recruitment (t_0); participant consent (t_1) is followed by 8 or 12 weeks of treatment according to HCV genotype (t_{12}), 12 weeks post-treatment a final SVR test is taken to determine the study outcome ($t_{endpoint}$)

Sample Size:

Approximately 22,000 patients are prescribed OST across Scotland [26]. Around 85% of these patients receive daily or regular supervision of their OST consumption through one of the 1200 community pharmacies. It is expected that at least 40% of these patients will be infected with HCV, and that around 46% and 48% of infections will be with Genotype 1 and Genotype 3 respectively [26]. The pharmacies acting as cluster sites for this trial have around 1,800 patients attending for supervised OST administration. Sixty community pharmacies based around 5 study sites within Scottish NHS Boards, will be coordinated through the Tayside Clinical Trials Unit (TCTU) of the Tayside Medical Science Centre, University of Dundee.

As the pharmacy-led pathway is a specific population-based intervention, the number of patients on OST treatment at each pharmacy will be the denominator for calculating DBST uptake. The HCV infection status of all the OST patients in the denominator population is not known. National data repeatedly shows approximately 40% of Patients on OST are HCV positive, as this is a randomised trial it can be assumed that the rate of HCV positivity in the OST patients/pharmacies randomised to the pathways should be the same. The study will be powered through rates of HCV therapy offered. Approximately 3% of HCV positive OST patients enter HCV therapy per year via conventional pathways, with 2.5% of the total eligible population achieving SVR per annum. If it is estimated that the new pathway increased this to 15%, a sample in each arm of 141 (2N = 282) will give 90% power at the significance level. The clustered design requires inflation, so if the average infected subjects per pharmacy is 20, the Inflation Factor for sizes of cluster assuming an intra-cluster correlation of 0.05, is 1.95. This leads to a need for 2N = 550.

The sample of 60 pharmacies with an average of 30 OST patients per pharmacy gives 1800 OST patients, assuming 40% HCV positive, gives over 800 potential patients for study. This gives significant protection against any changes in baseline SVR success rates, but also

against pharmacy drop-outs or local issues that prevent an enrolled pharmacy from participation. This is trial of a pathway so all eligible patients are the denominator for the power calculation, not the patients who actually enter the pathway and are treated.

The randomisation of the pharmacies will be stratified by associated hub centre. The endpoint of the study is the effectiveness of the pathway so any drop-outs are part of the study outcomes, so there is no need to increase the sample size to allow for a dropout rate.

Data collection, management and analysis

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

The primary outcome of SVR will be assessed as a binary outcome for subjects and so will utilise logistic regression modelling. The numerator will be the number of subjects achieving SVR at 12 weeks and the denominator will be total number of patients using OST at the participating pharmacies. Additionally results will be expressed as a proportion of the estimated HCV infected subjects on OST. The estimated number of infected patients will be based on national survey data and the empirical rate discovered in the trial (allowing for patients who refuse testing). In order to account for the clustered nature of the trial, a mixed-effects logistic regression model will be performed with the parameter indicator of trial arm in the model and a random parameter to account for within cluster correlation as well as stratified by hub. As all patients will have either achieved SVR 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 will be examined in the logistic model and if present alternative modelling such as negative binomial models will be considered. This will also be adjusted by therapy and genotype; the two factors are interdependent determining length of therapy.

Secondary binary outcomes - will be analysed in the same procedure, initially as intention to treat with all eligible patients as the denominator and then to explore the steps in the pathway by per protocol analysis in particular to analyse on treatment success:

- Proportion of HCV tested: within the duration of the study of those attending pharmacy sites for OST, for the conventional and for the pharmacist-led arm
- Proportion that initiate HCV treatment within the duration of the study of those identified with HCV, for the conventional and for the pharmacist-led arm.

Proportion that complete the course of those initiating treatment: Multiple logistic regression modelling will explore the patient and pharmacy characteristics that are associated with the secondary outcomes and primary outcome. Patient outcomes considered will be:

- age
- gender
- deprivation,
- employment,
- co-morbidity,
- psycho-social variables assessed.

Pharmacy characteristics considered will be:

- geographic location
- type of pharmacy service
- size of OST population.

Determination of re-infection: As the determination of possible re-infection is an important and stated secondary outcome in this study, all patients will be invited to consent for a further DBS HCV PCR one year after end of therapy or at end of the study, whichever is first. Those patients who achieve SVR will be invited to participate at their pharmacy.

Data management

An EXCEL database will be used to hold the study related data. This will be managed and controlled by the coordinating pharmacist in NHS Tayside with site specific data being transcribed from a paper CRF formulated in line with the EXCEL database, with the study protocol and in line with the requirements of the investigators. Development and validation of the study database, QC and extraction of data will be done according to study sponsor procedures. Extracts for analysis will be based on the data tables provided by the study team.

Health Economic Assessment

Economic analysis will be undertaken alongside the trial, utilizing the costs, resource use and effectiveness data generated within the trial. The number of SVRs achieved at the end of the trial will be combined with the cost data to calculate the incremental cost per cure. A longer term analysis incorporating the cost and benefits of potential lifetime gains through citizenship will be undertaken.

Qualitative Assessment

The qualitative research will take the form of a process evaluation building on previous exploratory and preparatory work (22). It will contribute to the assessment of the feasibility and acceptability to service users and providers of a pharmacy-led testing and treatment pathway (including identification of barriers and facilitators and unintended consequences of participation).

Interviews will be conducted with small samples of (i) consenting study participants and (ii) professionals providing the pharmacist led pathway by researchers at University of Dundee.

Qualitative interviews will be conducted with consenting participants and professionals using semi-structured topic guides developed in line with the research aims. Topics will not be explored in a prescriptive manner but as part of an open discussion. This flexible format will enable additional salient topics and insights to emerge. In broad terms, the focus for the different respondent groups will be as follows:

One-to-one interviews with consenting participants (all of whom have engaged with the service) will explore views on issues around the delivery and promotion of the pharmacist-led pathway, their response to the offer and delivery of treatment, and any unintended consequences.

Interviews with professionals will explore issues around implementation of the intervention and the trial elements, identify challenges and ways they have been overcome, and perceived response among participants.

With the interviewee's consent, all interviews and focus group discussions will be recorded as digital audio files, which will then be transcribed in full for thematic analysis. Transcripts will be organized using a thematic framework based on topics specified in the topic guide and emerging themes identified through a process of familiarization with transcript texts.

Discussion

Liver disease has become a major cause of premature death in the developed world and HCV is a major contributor to this burden [28]. The care of people infected with HCV therapy has undergone a paradigm shift due to the efficacy of direct acting antiviral drugs and the consequent simplification of therapy, with highly effective treatment choices marketed across the world [29]. However, new and more effective pathways of care are urgently required in order to enhance testing and linkage to care and treatment [16]. These novel pathways of

care need to be carefully evaluated both for efficacy and cost-effectiveness compared to traditional pathways, as well as for unintended consequences. This pragmatic, cluster-randomised trial can provide strong evidence of the effectiveness of a pharmacist delivered care pathway for HCV eradication therapy in patients receiving OST. A comparison will be undertaken with the current clinical care pathway where patients are referred to a conventional clinic to receive their HCV treatment. Trial design has aimed for high applicability in design decisions [24] and this trial is expected to directly inform the future organisation of care.

Ethics and Dissemination

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

In addition to Sponsorship approval, approval was received for this study (15/ES/0086) from East of Scotland Research Ethics Committee 2 on 27 May 2016. Caldicott guardian approval was given on 16 December 2016 to allow NHS Tayside to pass information to the cluster community pharmacies about the HCV test status of patients that they are seeing to provide OST supervision. NHS R&D approvals have been obtained from each health board taking part in the study.

Harms

Regular follow up of the participants will occur daily in the DOT arm during the study treatment period by a pharmacist familiar in the trial methodology. For those participants allocated to the conventional therapy, regular clinical follow up will occur in line with prevailing conventional NHS standard of care. At each visit participants will be monitored for expected Adverse Events (AEs) as per the Summary of Product (SmPC) characteristics for the drug treatments used in this study. This is in line with the current standard of care for the NHS and only AEs outside these criteria will formally be recorded as Adverse Events

Bloods for viral load would be performed as outlined in the Study Schedule, at the pre treatment visit and at 12 weeks post completion of therapy, as per the attached study schedule. Data on testing, referral, initiation of (and adherence to), therapy are routinely collected for the HCV clinical data base and these data will also be utilised.

In addition baseline and end of treatment checking of prescribed and non-prescribed medications and drug use, as documented in the study concomitant medications log, will be carried out to investigate the relationship between any adverse events and drug interactions.

Consenting Participants

Potential participants will be approached by pharmacy staff familiar with the trial methodology and trained in Good Clinical Practice. They will be provided with information on the study verbally and via the Patient Information Sheet (PIS) and be given at least 24 hours to consider participation.

At their return visit for screening they will be interviewed by the study pharmacist and asked to sign an informed consent form, once they are satisfied that they have had adequate explanation from the pharmacist explaining the trial to them.

Confidentiality

The data will be collected by the researcher (treatment delivering pharmacist or nurse) on a paper CRF with subsequent transcription to electronic CRF. Electronic storage will be in an encrypted form on a password protected device. The medical notes will act as source data for past medical history & blood results

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to study staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

Data Protection

The CI and study staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff. Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

Trial Organisation

Trial management

Overall management of the trial is being provided by the Tayside Clinical Trials Unit (TCTU), a UK Clinical Research Collaboration (UKCRC)-registered clinical trials unit. A study Clinical Trial Manager supported by a Study Coordinator will oversee the study and will be accountable to the Chief Investigator (CI). They will be responsible for checking the Case Report Forms for completeness, plausibility and consistency. However, this remains the overall responsibility of the CI. Any queries will be resolved by the CI or delegated member of the study team.

A study-specific Delegation Log will be prepared for the study at each site, detailing the responsibilities of each member of staff working on the study.

A Trial Steering Committee will be established to oversee the conduct and progress of the study. The Steering Committee will include the investigators above, as well as the NHS Tayside Director of Pharmacy and a representative from the Chief Pharmaceutical Officers Team at the Scottish Government. The Steering Committee will take all executive decisions. The responsibility of the Steering Committee is to ensure the scientific integrity and quality of the project. To achieve this, the specific responsibilities of the Steering Committee include: maintaining adherence to the study protocol; approving changes to study protocol if required; reviewing quality assurance indicators; monitoring study recruitment and the overall study timetable; advising, as required, on specific scientific items that may arise; compliance with legislation; adherence to research governance; reporting to funders; approving publication and dissemination strategies. The Steering Committee will meet every 6 months.

Trial Status

Recruitments commenced in December 2016. On 9 October 2017, 234 were consented to the trial.

Declarations

Trial Funding

This study was funded in partnership by the Scottish Government, Gilead Inc and Bristol-Myers Squib. Funders have no responsibilities for or authority over study design; collection, management, analysis or interpretation of data; writing of the report; and the decision to submit the report for publication

Reporting guideline: SPIRIT 2013 statement: defining standard protocol items for clinical trials

http://annals.org/aim/article/1556168/spirit-2013-statement-defining-standard-protocol-items-clinical-trials

Contributor Statement:

Andrew Radley: study conception, planning and design, protocol preparation, manuscript preparation.
Marijn de Bruin: study conception, planning and design, protocol preparation manuscript preparation
Sarah Ingles: protocol preparation, randomisation, study management, manuscript preparation
Peter T Donnan: study conception and design, statistical analysis plan, protocol preparation, manuscript preparation
John F Dillon: study conception and design, protocol preparation, manuscript preparation

Competing Interests:

Mr Radley: Honorariums from Gilead and Abbvie; Research Grants from Gilead and Roche
Professor Dillon: Research Grants, and Honorariums from Abbvie, Bristol Myers Squibb, Gilead, Janssen, Merck Roche Sharp & Dohme and Roche.
Dr Inglis: None
Prof Donnan: Research grants from Novo Nordisk, GSK, Shire pharmaceuticals, Gilead and Bristol Myers Squibb. Member of the New Drugs Committee of the Scottish Medicines Consortium.
Prof de Bruin: None

Data Sharing Statement:

The original protocol and substantive amendments are available. Data generated by the study will be made available post publication as per standard operating procedures for the University of Dundee Clinical Trials Centre

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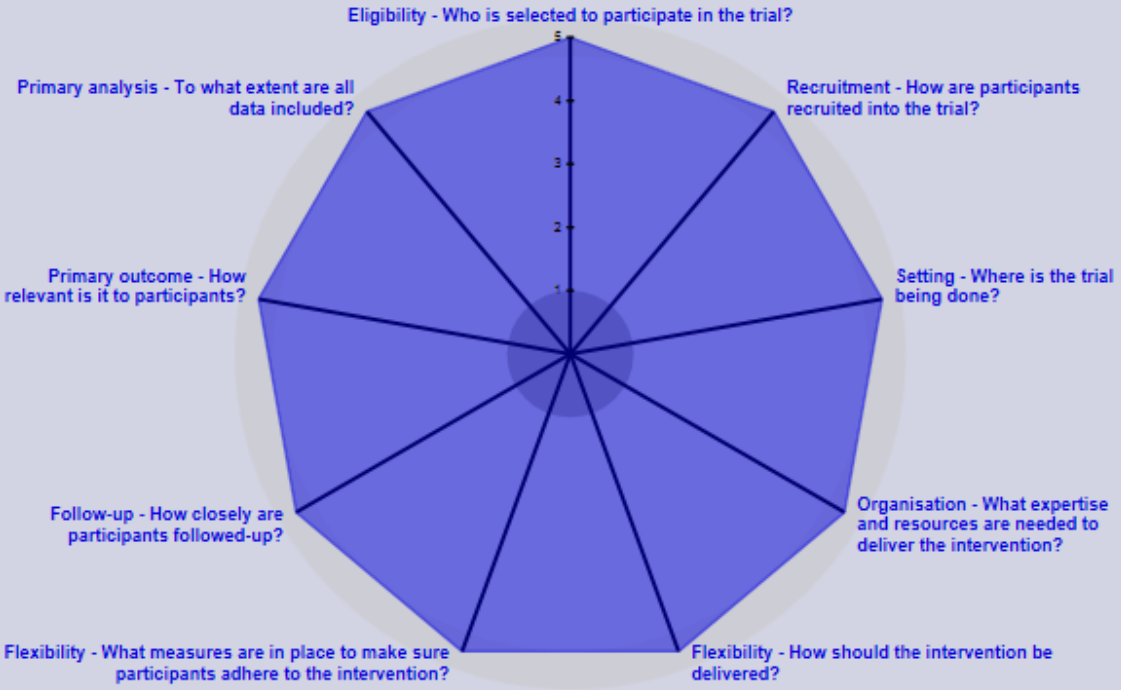
Super.DOTc

Intervention	**Health services delivery and reconfiguration - Phase 3 Cluster RCT**
Number of sites	**6**
Countries involved	**1**
Sample size	**300**
Type of statistical analyses	
Participant characteristics	**Age: 25-55** **Condition: hep c infection** **Baseline severity: 40% and prevelant**
Duration of trial	**18 months**
Primary outcome	**Sustained viral response rate**



Show Score Ranges

Scores:

(shows median if more than one score was entered)

Elig.	Recr.	Setting	Org. Int.	Flex. Del.	Flex. Adherence	Follow-Up	Prim. Out.	Prim. An.
5	5	5	5	5	5	5	5	5

Hepatitis C Testing And Treatment Pathway

- Dry Blood Spot Testing is simple & easy to do
- DBST finds out whether you have been exposed to HCV
- Most people catch HCV by injecting
- Some people rid themselves of the virus (1 in 3)
- Most people need tablets to cure themselves

- A reactive DBST means you may still be infected
- We can tell if you are still infected and need treatment by taking a blood test. The test results arrive quickly
- The results will remain confidential
- Getting a blood test means you can get the treatment you need

- Curing HCV means 1 or 2 tablets a day
- The treatment might last 8 or 12 weeks
- You get the tablets at the chemist each day
- Almost all people are cured by the tablets
- They have very few side effects. These are minor
- The tablets must be taken every day

I feel so much better

- Curing HCV is a great achievement
- It will improve the way you feel
- Getting cured is straightforward nowadays
- You can get cured just by following this pathway and attending the pharmacy each day

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
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	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	16
	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	16
	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)	17

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	3
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, 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 (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
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)	10

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
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	n/a
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	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	11
	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	13
	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	13
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	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
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)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
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	15
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	16
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	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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	n/a

*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.

BMJ Open

Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: A study protocol for a pragmatic cluster randomised trial

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Addiction, Patient-centred medicine, Public health
Keywords:	Hepatitis C, Clinical Pathways, Community Pharmacy, Randomised controlled trial, Direct-Acting antivirals

Clinical effectiveness of pharmacy-led versus conventionally delivered antiviral treatment for Hepatitis C in patients receiving opioid substitution therapy: A study protocol for a pragmatic cluster randomised trial

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Running Head:

Hepatitis C Testing and Treatment in Community Pharmacies

Corresponding Author:

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Key Words: Hepatitis C; clinical pathways; community pharmacy; Randomised controlled trial; direct-acting antivirals

Abstract

Introduction: Hepatitis C Virus (HCV) infection affects 0.7% of the general population, and up to 40% of people prescribed Opioid Substitution Therapy (OST) in Scotland. In conventional care, less than 10% of OST users are tested for HCV and less than 25% of these initiate treatment. Community pharmacists see this group frequently to provide OST supervision. This study examines whether a pharmacist-led 'test & treat' pathway increases cure rates for HCV.

Methods and Analysis: This protocol describes a cluster randomised trial where 60 community pharmacies provide either conventional or pharmacy-led care. All pharmacies offer dried blood spot testing (DBST) for HCV. Participants have attended the pharmacy for OST for 3 months; are positive for HCV genotype 1 or 3; not co-infected with HIV and/or hepatitis B; no decompensated liver disease; not pregnant. For conventional care, pharmacists refer HCV positive participants to a local centre for assessment. In the pharmacy-led arm, pharmacists assess participants themselves in the pharmacy. Drug prescribing is by nurse prescribers (conventional arm) or pharmacist prescribers (pharmacy-led arm). Treatment in both arms is delivered as daily modified directly observed therapy (DOT) in a pharmacy. Primary trial outcome is number of sustained viral responses (SVR) at 12 weeks after treatment completion. Secondary trial outcomes are number of tests taken; treatment uptake; completion; adherence; re-infection. An economic evaluation will assess potential cost-effectiveness. Qualitative research interviews with clients and health professionals assess acceptability of a pharmacist-led pathway.

Ethics and Dissemination: This protocol has been ethically approved by the East of Scotland Research Ethics Committee 2 (15/ES/0086) and complies with the Declaration of Helsinki and principles of Good Clinical Practice. Informed consent is obtained before study enrolment and only anonymised data is stored in a secured database, enabling an audit trail. Results will be submitted to international peer-reviewed journals and presented at international conferences.

ClinicalTrials.gov Identifier**:** NCT02706223

Protocol version 3.0

Date 27 May 2016

Strengths and limitations of this study

- Real world study developed using the Medical Research Council (MRC) Guideline on complex interventions
- Potential to provide answers to an extremely topical question around approaches to eliminate a disease, in line with a World Health Organisation (WHO) target.
- Utilises a community pharmacy-based pathway in NHS Scotland, but not wider primary care systems
- Relies on close and integrated working between a specialist hepatitis service and community pharmacy services

Background

Hepatitis C (HCV) is a blood-borne viral infection causing liver disease. Around 0.7% of the Scottish population are chronically infected with HCV [1]. Patient outcomes from HCV infection vary, with 25% clearing the infection spontaneously and the remainder becoming chronically infected, risking development of cirrhosis and hepatocellular carcinoma [2]. A recent Public Health England report highlighted that less than half of those infected with HCV have been identified, and of those identified less than 3% of those known to be infected with HCV are being treated [3]. The greatest risk of acquiring the virus in the UK is through injecting drug use [4] and evidence suggests around 40% of people in Scotland receiving Opioid Substitution Therapy (OST) have HCV infection [5]. Only a small proportion of this high-risk and vulnerable population are receiving adequate treatment, despite having daily healthcare interaction with a pharmacist and the availability of a curative intervention with widely available Direct Acting Antiviral (DAA) medication [6].

The conventional care pathway in the United Kingdom recommends that patients with a history of intravenous drug use, or those currently prescribed OST, should be offered HCV testing annually [3]. Testing may be available from their GPs, drug workers, drug agencies, social workers, community pharmacies and needle exchanges [7]. Once diagnosed, patients can be referred to established treatment pathways, usually based around hepatology teams in secondary care. In these established treatment pathways, less than 10% of the OST population are tested for HCV annually. Of those tested, at most 25% start treatment in one of the dedicated centres and 70-80% successfully complete treatment, with treatment failure primarily caused by non-adherence and non-persistence to treatment [8]. Similar patterns are observed in other countries [9]. The inefficiency of established treatment pathways leads to increased preventable deaths from HCV and viral transmission within the injecting population [10].

A variety of reasons may explain the low rates of HCV testing, treatment uptake, and treatment completion. People who inject drugs (PWID) may encounter a number of barriers that prevent them from accessing care, including perceptions and experience of stigma and discrimination, issues with the organisation of care and the treatment policies of providers or payers [11]. There are identified deficiencies in the extent of screening and diagnosis of at-risk populations, as well as the need to simplify pathways to enable treatment initiation and clinical monitoring [12]. People who inject drugs may find it difficult to consistently attend medical clinics [13].

The WHO has set an ambitious goal to eliminate HCV as a public health threat by 2030 [14].

Creating the complex interventions necessary to eradicate HCV requires that well-designed cross-disciplinary programmes are put in place using different strategies to increase screening, testing and diagnosis [15]. Strategies that demonstrate increase testing and treatment uptake include the provision of integrated HCV care pathways; with drug use and psychiatric services delivered by a multidisciplinary team, and with case management services [16]. The delivery of HCV testing and treatment through community-based care pathways has also been shown to be feasible and DBST has been demonstrated to increase the uptake of testing from high-risk populations [17]. Hence, a more central role in the treatment of HCV for community-based pharmacists who are seeing these clients on a daily basis, could – in theory – lead to increased HCV treatment success rates through higher HCV testing, treatment uptake, adherence, and treatment completion rates.

In preparation for the current trial investigating the clinical benefits of pharmacy-delivered HCV treatment, pilot work was undertaken guided by the MRC theoretical framework for developing and evaluating complex interventions [18]. Initial work involved using a co-production approach in partnership with OST patients. This work identified the current experiences of patients in accessing HCV testing and treatment and in accessing OST in pharmacies [19]. The attributes of an ideal service were identified and an estimate of potential uptake made [20]. The implementation of DBST in pharmacies was undertaken and the experiences of patients and providers recorded [21]. A pilot trial has been undertaken to test each stage of the pharmacy-led care pathway and to look for confirmation that an appropriately powered definitive multicenter randomised controlled trial would be feasible [22]. The PRECIS-2 tool was used to assess that the design decisions were concordant with the purpose of the trial (Supplementary file 1) [23].

The aim of this research is to examine the impact of pharmacy-delivered HCV treatment on HCV treatment success rates amongst OST users. Our research questions are:

Trial

(1) Does a community pharmacist-led HCV treatment pathway increase treatment success rates (sustained virological response, or SVR) compared to the conventional pathway?

(2) Does a community pharmacist-led HCV treatment pathway lead to a higher uptake of HCV testing?

(3) Does a community pharmacist-led HCV treatment pathway lead to a higher uptake and completion of HCV treatment?

(4) Is adherence and persistence to HCV therapy in the pharmacy setting similar to that in the Conventional pathway?

(5) What is the re-infection rate at 12 months after end of treatment in all patients with SVR, and for the pharmacist-led pathway compared to the conventional pathway?

Health Economics Study

(6) Is the pharmacist-led pathway potentially a cost-effective method of testing and treating HCV in people prescribed OST?

Qualitative Study

(7) Is the pharmacist-led pathway an acceptable way to offer testing and treatment for people prescribed OST infected with HCV and are there any unexpected consequences?

Methods:

Design

Super DOT-C is a cluster randomised trial of pharmacy-led anti HCV therapy versus conventional care in HCV infected patients attending community pharmacies (Table 1). Sixty pharmacies will be enrolled to this study across 5 hubs in Health Boards in NHS Scotland. Pharmacies (and thus their patients) participating in the trial will be randomly allocated to conventional care pathway or the pharmacy-led pathway.

Pharmacies at each site are randomised into two groups: conventional care and pharmacist-led care. Randomisation will be carried out using http://www.randomization.com. The subjects are randomized into one block along with the number of subjects per block/number of blocks and (case-sensitive) treatment labels. The pharmacies in each hub provide the level of randomisation, so patient allocation is dependent on the pharmacy attended.

Eligibility Criteria

Eligible pharmacies are community-based, offer DBST for HCV by trained pharmacy staff in line with approved practice in their particular NHS board and have at least 30 patients on OST to ensure adequate recruitment. Patient inclusion criteria are having HCV Polymerase Chain Reaction (PCR) positive to genotype 1 or 3, are OST users and willing to have their pharmacists supervise their antiviral drug use. Patient exclusion criteria are having another genotype than 1 or 3, evidence of current or previous decompensated liver disease, Human Immunodeficiency Virus (HIV) infection, surface antigen of Hepatitis B Virus (HBV) HBsAg positive with detectable HBV DNA, aggressive or violent behaviour towards the pharmacist, being pregnant, and not being able to provide informed consent.

Interventions

Medication provided

The anti HCV treatment provided in both pathways is identical, i.e:

- For HCV genotype 1 sofosbuvir/ledipasvir for 8 weeks
- For HCV genotype 3 sofosbuvir/daclatasvir for 12 weeks

Study Site Staff Training

Staff from each study site will receive training on Good Clinical Practice, quality control, use of study documentation, ensuring common practice, and consenting participants. In addition training to establish testing for blood borne viruses is provided and information on hepatitis C and its treatment is provided. Staff in the pharmacy-led arm are trained on how to interpret laboratory bloods and to perform a Fib4 calculation [24].

Table 1: Treatment pathways: similarities and differences

	Conventional care	**Pharmacy pathway**	**Contrast**
HCV testing	Opportunistic HCV testing on presentation for OST therapy	Opportunistic HCV testing on presentation for OST therapy	The same procedure is provided in each of the study arms
HCV test confirmation	Test result is communicated and - if positive – referred for assessment in local treatment centre	Test result is communicated and – if positive - assessment directly undertaken in the pharmacy	Assessment for treatment is carried out at the pharmacy when the participant visits to obtain OST, not at a different site with a different provider
Treatment initiation	Suitable patients are prescribed treatment by a nurse prescriber at the local treatment centre and access treatment	Suitable patients are prescribed treatment by a pharmacist prescriber and access treatment through DOT at their pharmacy	Treatment initiation is carried out at the pharmacy and not at a different site with a different provider

	through DOT at their pharmacy		
Treatment monitoring	Treatment monitoring is carried out by the specialist team in their clinic	Treatment monitoring is carried out at the pharmacy	Treatment monitoring is carried out at the pharmacy not at a different site. Monitoring in the conventional pathway requires additional clinic visits
Treatment completion	SVR testing is carried out by DBST at the pharmacy	SVR testing is carried out by DBST at the pharmacy	The same procedure is provided in each of the study arms

Conventional Care Pathway

At the start of the pathway pharmacists will opportunistically discuss HCV infection with their OST patients. The pharmacist will record on a screening log which of the OST patients attending the pharmacy they have approached. Those with unknown HCV status will be offered testing using a DBST in the pharmacy [25]. Patients identified as having HCV antibodies will have a post-test discussion with the pharmacist. During this discussion the pharmacists will obtain informed consent and explain about HCV treatment using a standard infographic (supplementary file 2). Next, the pharmacist will offer them referral to the conventional care pathway for assessment and treatment at a local treatment centre. Information will be provided verbally and by offering standard leaflets about HCV. If the patient attends an appointment at one of the local treatment centres, a member of the specialist hepatitis team will invite the patient to undertake assessment for treatment for HCV. Assessment comprises of a pre-treatment checklist of medical co-morbidities, medical history, and concomitant medication to look for drug-drug interactions. The patient will undergo phlebotomy in the local treatment centre to check full blood count, urea and electrolytes, liver function testing, including markers of liver fibrosis [24] (Fib4, APRI, AST:ALT ratio) and viral parameters (genotype and load), as assessment for treatment. Patients who are referred for assessment and treatment will be managed according to the standard local treatment pathway. Daily supervised OST treatment is delivered by the pharmacy, in which the doses of methadone or buprenorphine are provided by the pharmacy staff, who observe consumption. In both arms of the study DAA treatment is delivered jointly

with OST in their normal pharmacy; which would qualify as DOT during weekdays, although at weekends patients usually self-administer. Prescriptions will be provided by a nurse prescriber and dispensed at the participant's normal pharmacy. For doses that patients have to self-administer and the weekend doses when there is no OST distribution, the pharmacist and patient will make a brief if-then action plan (an implementation intention) and coping plan (to overcome anticipated barriers) [26]. The study related data collection will be undertaken by the specialist hepatitis team.

Pharmacist-Led Pathway

Potential participants are offered testing, recruited and consented as in the conventional pathway. In the pharmacy-led pathway however, the pharmacist will offer them anti-HCV therapy delivered solely within the pharmacy. The patients who decline study participation will be entered in the screening log. For the patients who do consent, the pharmacist will complete a pre-treatment checklist of medical co-morbidities, medical history, and concomitant medication to look for drug-drug interactions. The patient will undergo phlebotomy in the pharmacy for safety blood tests, as in the conventional pathway and the pharmacist will assess this information to determine suitability for treatment.

If there are no contra-indications to therapy, the patient will commence the treatment. In patients where there are contraindications or queries about suitability, the pharmacist will contact the central clinical co-ordinator for advice. The pharmacist-led pathway requires an assessment which includes identification of concurrent specific medical conditions, screening of safety bloods, calculation of a Fib-4 score, assessment of interacting concurrent medication and assessment of factors likely to impinge on treatment compliance. Potential participants with a FIB-4 score of > 3.25 are referred on to the Conventional Care Pathway for review. The Pharmacist-led Pathway therefore excludes this group from being entered into the trial. Instead, they are assessed for treatment through the Conventional Care Pathway where they are reviewed in hospital by a medical consultant who decides if it is safe to proceed with treatment and if yes, may select different drugs'. Unsuitable patients are therefore referred to the conventional pathway for assessment outside the study and provided with standard clinical care. Prescriptions for treatment will be provided by pharmacist prescriber.

Each time that patients pick up their medication from the pharmacy, a daily log is completed, recording any occurrence of side-effects or adverse events.

Participants who do not attend the pharmacy for seven consecutive days will be discontinued from the study since they will be deemed to have discontinued their course of DAA treatment and will have had their OST prescription suspended.

Participants are likely to be retained within the study through the mechanism of daily attendance for receipt of supervised OST; this is a powerful mechanism making people return to the pharmacy. It is intended that data will still be collected on participants who may not complete their course of treatment, since partial completion may produce an SVR also.

The primary study outcome (SVR 12 weeks after treatment completion) is assessed by DBST in the pharmacies for both study arms.

Outcomes and measures

The denominator for the outcomes on treatment uptake is the number of people using OST at the pharmacies participating in the respective arms. For the primary outcome, the numerator will be the number of patients with Sustained Viral Response at 12 weeks post treatment completion (SVR12) after allocation to treatment arm, measured through a test for the presence of HCV RNA (polymerase chain reaction).

For the secondary outcomes on treatment uptake, the numerators are the number of patients who (a) undergo HCV testing, (b) initiate HCV treatment, (c) complete the 12-week HCV course, (d) number of patients with SVR at 12 months (to assess the impact of potential reinfection).

Study schedule

For both arms, screening for HCV by DBST is undertaken prior to recruitment (t_0); participant consent (t_1) is followed by 8 or 12 weeks of treatment according to HCV genotype (t_{12}), 12 weeks post-treatment a final SVR test is taken to determine the study outcome ($t_{endpoint}$)

Sample Size:

Approximately 22,000 patients are prescribed OST across Scotland [26]. Around 85% of these patients receive daily or regular supervision of their OST consumption through one of the 1200 community pharmacies. It is expected that at least 40% of these patients will be infected with HCV, and that around 46% and 48% of infections will be with Genotype 1 and Genotype 3 respectively [9]. The pharmacies acting as cluster sites for this trial have around 1,800 patients attending for supervised OST administration. Sixty community pharmacies based around 5 study sites within Scottish NHS Boards, will be coordinated through the Tayside Clinical Trials Unit (TCTU) of the Tayside Medical Science Centre, University of Dundee.

As the pharmacy-led pathway is a specific population-based intervention, the number of patients on OST treatment at each pharmacy will be the denominator for calculating DBST uptake. The HCV infection status of all the OST patients in the denominator population is not

known. National data repeatedly shows approximately 40% of Patients on OST are HCV positive, as this is a randomised trial it can be assumed that the rate of HCV positivity in the OST patients/pharmacies randomised to the pathways should be the same. The study will be powered through rates of HCV therapy offered. Approximately 3% of HCV positive OST patients enter HCV therapy per year via conventional pathways, with 2.5% of the total eligible population achieving SVR per annum. If it is estimated that the new pathway increased this to 15%, a sample in each arm of 141 (2N = 282) will give 90% power at the significance level. The clustered design requires inflation to account for intracluster correlation, so if the average infected subjects per pharmacy is 12, the Inflation Factor for sizes of cluster assuming an intra-cluster correlation of 0.05, is 1. 55. This leads to a need for 2N = 437.

The sample of 60 pharmacies with an average of 30 OST patients per pharmacy gives 1800 OST patients, assuming 40% HCV positive, gives 700 to 800 potential patients for study. This gives significant protection against any changes in baseline SVR success rates, but also against pharmacy drop-outs or local issues that prevent an enrolled pharmacy from participation. This is trial of a pathway so all eligible patients are the denominator for the power calculation, not the patients who actually enter the pathway and are treated.

The randomisation of the pharmacies will be stratified by associated hub centre. The endpoint of the study is the effectiveness of the pathway so any drop-outs are part of the study outcomes, so there is no need to increase the sample size to allow for a dropout rate.

Data collection, management and analysis

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

The primary outcome of SVR will be assessed as a binary outcome for subjects and so will utilise logistic regression modelling. The numerator will be the number of subjects achieving SVR at 12 weeks and the denominator will be total number of patients using OST and having an HCV infection diagnosed at the participating pharmacies. Additionally results will be expressed as a proportion of the estimated HCV infected subjects on OST. The estimated number of infected patients will be based on national survey data and the empirical rate discovered in the trial (allowing for patients who refuse testing). In order to account for the clustered nature of the trial, a mixed-effects logistic regression model will be performed with the parameter indicator of trial arm in the model and a random parameter to account for within cluster correlation as well as stratified by hub. As all patients will have either achieved SVR 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 will be examined in the logistic model and if present alternative modelling such as negative binomial models will be considered. This will also be adjusted by therapy and genotype; the two factors are interdependent determining length of therapy.

Secondary binary outcomes - will be analysed in the same procedure, initially as intention to treat with all eligible patients as the denominator and then to explore the steps in the pathway by per protocol analysis in particular to analyse on treatment success:

- Proportion of HCV tested: within the duration of the study of those attending pharmacy sites for OST, for the conventional and for the pharmacist-led arm
- Proportion that initiate HCV treatment within the duration of the study of those identified with HCV, for the conventional and for the pharmacist-led arm.

Proportion that complete the course of those initiating treatment: Multiple logistic regression modelling will explore the patient and pharmacy characteristics that are associated with the secondary outcomes and primary outcome. Patient outcomes considered will be:

- age
- gender
- deprivation,
- employment,
- co-morbidity,
- psycho-social variables assessed.

Pharmacy characteristics considered will be:

- geographic location
- type of pharmacy service
- size of OST population.

Determination of re-infection: As the determination of possible re-infection is an important and stated secondary outcome in this study, all patients will be invited to consent for a further DBS HCV PCR one year after end of therapy or at end of the study, whichever is first. Those patients who achieve SVR will be invited to participate at their pharmacy. People prescribed Opioid Substitution Therapy (OST) are retained in the service for many years, since their progress of recovery and becoming drug-free is slow. In addition, movement out of Dundee, which is relatively geographically isolated, is minimal. We are therefore confident that we can identify all patients still in receipt of a prescription for OST and invite them to be re-tested for

Hepatitis C. Since the network of pharmacies providing OST, are also trained to provide testing, we believe this is feasible

Data management

An EXCEL database will be used to hold the study related data. This will be managed and controlled by the coordinating pharmacist in NHS Tayside with site specific data being transcribed from a paper Case Report Form (CRF) formulated in line with the EXCEL database, with the study protocol and in line with the requirements of the investigators. Development and validation of the study database, quality control and extraction of data will be done according to study sponsor procedures. Extracts for analysis will be based on the data tables provided by the study team.

Health Economic Assessment

Economic analysis will be undertaken alongside the trial, utilizing the costs, resource use and effectiveness data generated within the trial. The number of SVRs achieved at the end of the trial will be combined with the cost data to calculate the incremental cost per cure. A longer term analysis incorporating the cost and benefits of potential lifetime gains through citizenship will be undertaken.

Qualitative Assessment

The qualitative research will take the form of a process evaluation building on previous exploratory and preparatory work (22). It will contribute to the assessment of the feasibility and acceptability to service users and providers of a pharmacy-led testing and treatment pathway (including identification of barriers and facilitators and unintended consequences of participation).

Interviews will be conducted with small samples of (i) consenting study participants and (ii) professionals providing the pharmacist led pathway by researchers at University of Dundee.

Qualitative interviews will be conducted with consenting participants and professionals using semi-structured topic guides developed in line with the research aims. Topics will not be explored in a prescriptive manner but as part of an open discussion. This flexible format will enable additional salient topics and insights to emerge. In broad terms, the focus for the different respondent groups will be as follows:

One-to-one interviews with consenting participants (all of whom have engaged with the service) will explore views on issues around the delivery and promotion of the pharmacist-led pathway, their response to the offer and delivery of treatment, and any unintended consequences.

Interviews with professionals will explore issues around implementation of the intervention and the trial elements, identify challenges and ways they have been overcome, and perceived response among participants.

With the interviewee's consent, all interviews and focus group discussions will be recorded as digital audio files, which will then be transcribed in full for thematic analysis. Transcripts will be organized using a thematic framework based on topics specified in the topic guide and emerging themes identified through a process of familiarization with transcript texts.

Patient and Public Involvement

In developing the research question and outcome measures for study, pilot work was undertaken using focus groups of people prescribed OST and their carers', to explore their experiences of using community pharmacies [19]. The priorities and experiences of people prescribed OST were further evaluated through a discrete choice experiment, which was used to aid the design of the pharmacy-led pathway [20]. A process evaluation was employed as part of the development of the DBST intervention in pharmacies, where recipients were asked about their experiences and preferences for testing for hepatitis C [21]. The process evaluation approach was also repeated as part of a feasibility study in which the assessment and treatment of hepatitis C in this group was piloted, to further understand how the intervention would be accommodated by participants [22]. The information gained from this exercise has been fed back to groups of service users attending the local community support and harm reduction centre. Patients have not been involved in the recruitment to this study

Discussion

Liver disease has become a major cause of premature death in the developed world and HCV is a major contributor to this burden [27]. The care of people infected with HCV therapy has undergone a paradigm shift due to the efficacy of direct acting antiviral drugs and the consequent simplification of therapy, with highly effective treatment choices marketed across

the world [28]. However, new and more effective pathways of care are urgently required in order to enhance testing and linkage to care and treatment [16]. These novel pathways of care need to be carefully evaluated both for efficacy and cost-effectiveness compared to traditional pathways, as well as for unintended consequences. This pragmatic, cluster-randomised trial can provide strong evidence of the effectiveness of a pharmacist delivered care pathway for HCV eradication therapy in patients receiving OST. A comparison will be undertaken with the current clinical care pathway where patients are referred to a conventional clinic to receive their HCV treatment. Trial design has aimed for high applicability in design decisions [24] and this trial is expected to directly inform the future organisation of care.

Ethics and Dissemination

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

In addition to Sponsorship approval, approval was received for this study (15/ES/0086) from East of Scotland Research Ethics Committee 2 on 27 May 2016. Caldicott guardian approval was given on 16 December 2016 to allow NHS Tayside to pass information to the cluster community pharmacies about the HCV test status of patients that they are seeing to provide OST supervision. NHS R&D approvals have been obtained from each health board taking part in the study.

Harms

Regular follow up of the participants will occur daily in the DOT arm during the study treatment period by a pharmacist familiar in the trial methodology. For those participants allocated to the conventional therapy, regular clinical follow up will occur in line with prevailing conventional NHS standard of care. At each visit participants will be monitored for expected Adverse Events (AEs) as per the Summary of Product (SmPC) characteristics for the drug treatments used in this study. This is in line with the current standard of care for the NHS and only AEs outside these criteria will formally be recorded as Adverse Events

Bloods for viral load would be performed as outlined in the Study Schedule, at the pre treatment visit and at 12 weeks post completion of therapy, as per the attached study schedule. Data on testing, referral, initiation of (and adherence to), therapy are routinely collected for the HCV clinical data base and these data will also be utilised.

In addition baseline and end of treatment checking of prescribed and non-prescribed medications and drug use, as documented in the study concomitant medications log, will be carried out to investigate the relationship between any adverse events and drug interactions.

Consenting Participants

Potential participants will be approached by pharmacy staff familiar with the trial methodology and trained in Good Clinical Practice. They will be provided with information on the study verbally and via the Patient Information Sheet (PIS) and be given at least 24 hours to consider participation.

At their return visit for screening they will be interviewed by the study pharmacist and asked to sign an informed consent form, once they are satisfied that they have had adequate explanation from the pharmacist explaining the trial to them.

Confidentiality

The data will be collected by the researcher (treatment delivering pharmacist or nurse) on a paper CRF with subsequent transcription to electronic CRF. Electronic storage will be in an encrypted form on a password protected device. The medical notes will act as source data for past medical history & blood results

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access to study staff only. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and study staff involved with this study will not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

Data Protection

The CI and study staff involved with this study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and study staff will also adhere, if appropriate, to the current version of the NHS Scotland Code of Practice on Protecting Patient Confidentiality. Access to collated participant data will be restricted to the CI and appropriate study staff. Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

Trial Organisation

Trial management

Overall management of the trial is being provided by the Tayside Clinical Trials Unit (TCTU), a UK Clinical Research Collaboration (UKCRC)-registered clinical trials unit. A study Clinical Trial Manager supported by a Study Coordinator will oversee the study and will be accountable to the Chief Investigator (CI). They will be responsible for checking the Case Report Forms for completeness, plausibility and consistency. However, this remains the overall responsibility of the CI. Any queries will be resolved by the CI or delegated member of the study team.

A study-specific Delegation Log will be prepared for the study at each site, detailing the responsibilities of each member of staff working on the study.

A Trial Steering Committee will be established to oversee the conduct and progress of the study. The Steering Committee will include the investigators above, as well as the NHS Tayside Director of Pharmacy and a representative from the Chief Pharmaceutical Officers Team at the Scottish Government. The Steering Committee will take all executive decisions. The responsibility of the Steering Committee is to ensure the scientific integrity and quality of the project. To achieve this, the specific responsibilities of the Steering Committee include: maintaining adherence to the study protocol; approving changes to study protocol if required; reviewing quality assurance indicators; monitoring study recruitment and the overall study timetable; advising, as required, on specific scientific items that may arise; compliance with legislation; adherence to research governance; reporting to funders; approving publication and dissemination strategies. The Steering Committee will meet every 6 months.

Trial Status

Recruitments commenced in December 2016. On 9 October 2017, 234 were consented to the trial.

Declarations

Trial Funding

This study was funded in partnership by the Scottish Government, Gilead Inc and Bristol-Myers Squib. Funders have no responsibilities for or authority over study design; collection, management, analysis or interpretation of data; writing of the report; and the decision to submit the report for publication

Reporting guideline: SPIRIT 2013 statement: defining standard protocol items for clinical trials

http://annals.org/aim/article/1556168/spirit-2013-statement-defining-standard-protocol-items-clinical-trials

Contributorship Statement:

AR: study conception, planning and design, protocol preparation, manuscript preparation.
MdB: study conception, planning and design, protocol preparation manuscript preparation
JFD: study conception and design, protocol preparation, manuscript preparation
SI: protocol preparation, randomisation, study management, manuscript preparation

Competing Interests:

Mr Radley: Honorariums from Gilead and Abbvie; Research Grants from Gilead and Roche
Professor Dillon: Research Grants, and Honorariums from Abbvie, Bristol Myers Squibb, Gilead, Janssen, Merck Roche Sharp & Dohme and Roche.
Dr Inglis: None
Prof Donnan: Research grants from Novo Nordisk, GSK, Shire pharmaceuticals, Gilead and Bristol Myers Squibb. Member of the New Drugs Committee of the Scottish Medicines Consortium.

Prof de Bruin: None

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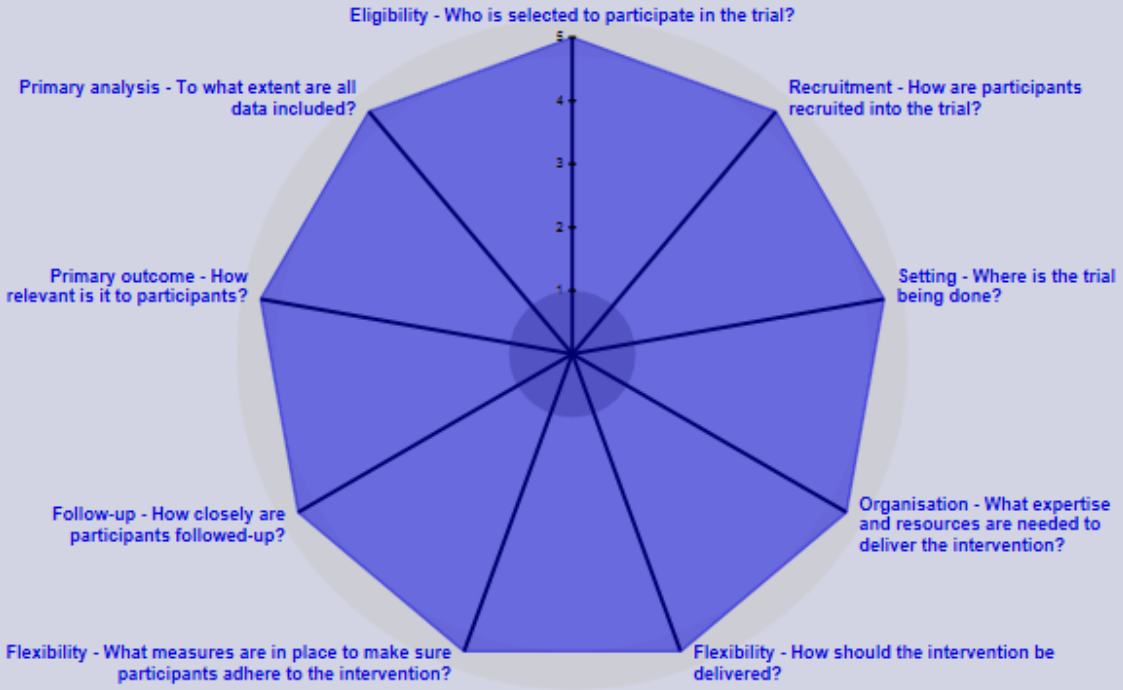
Supplementary File 1

Super.DOTc

Intervention	**Health services delivery and reconfiguration - Phase 3 Cluster RCT**
Number of sites	**6**
Countries involved	**1**
Sample size	**300**
Type of statistical analyses	
Participant characteristics	**Age: 25-55** **Condition: hep c infection** **Baseline severity: 40% and prevelant**
Duration of trial	**18 months**
Primary outcome	**Sustained viral response rate**



Show Score Ranges

Scores:

(shows median if more than one score was entered)

Elig.	Recr.	Setting	Org. Int.	Flex. Del.	Flex. Adherence	Follow-Up	Prim. Out.	Prim. An.
5	5	5	5	5	5	5	5	5

Hepatitis C Testing And Treatment Pathway

- Dry Blood Spot Testing is simple & easy to do
- DBST finds out whether you have been exposed to HCV
- Most people catch HCV by injecting
- Some people rid themselves of the virus (1 in 3)
- Most people need tablets to cure themselves

- A reactive DBST means you may still be infected
- We can tell if you are still infected and need treatment by taking a blood test. The test results arrive quickly
- The results will remain confidential
- Getting a blood test means you can get the treatment you need

- Curing HCV means 1 or 2 tablets a day
- The treatment might last 8 or 12 weeks
- You get the tablets at the chemist each day
- Almost all people are cured by the tablets
- They have very few side effects. These are minor
- The tablets must be taken every day

I feel so much better

- Curing HCV is a great achievement
- It will improve the way you feel
- Getting cured is straightforward nowadays
- You can get cured just by following this pathway and attending the pharmacy each day

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
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	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	16
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	16
	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	16
	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)	17

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	3
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, 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 (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
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)	10

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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
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	n/a
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
	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	11
	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	13
	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	13
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	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
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)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
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	15
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	16
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	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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	n/a

*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.