Trial Protocol

A Direct obserVed therApy vs fortNightly CollEction Study for HCV Treatment – ADVANCE HCV Study

Trial Acronym	**ADVANCE HCV**
Sponsor	**NHS Tayside/University of Dundee**
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Funder	Merck
Chief Investigator	Professor John Dillon
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PROTOCOL APPROVAL
ADVANCE HCV

EudraCT number 2017-001039-38

Signatures

By signing this document I am confirming that I have read, understood and approve the protocol for the above trial.

Prof John Dillon		
Chief Investigator	Signature	Date

LIST OF ABBREVIATIONS

BBV	Blood Borne Virus
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Scheme
CRF	Case Report Form
DAA	Direct Acting Antivirals
DBS	Dried Blood Spot
DMC	Data Monitoring Committee
DOT	Directly Observed therapy
FBC	Full Blood Count
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GP	General Practitioner
HCV	Hepatitis C Virus
IMB	Information-Motivation-Behavioural
ISF	Investigator Site File
LFT	Liver Function Test
MEMS®	medication event monitoring system
NESI	Needle Exchange Service Initiative
PCR	Polymerase Chain Reaction
Peg IFN	Pegylated Interferon
PHQ-9	The Patient Health Questionnaire
PWID	Person Who Injects Drugs
PT	Prothrombin Time
QC	Quality Control
RSI	Reference Safety Information
RBV	Ribavirin
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SVR	Sustained Viral Response
SVR12	Sustained Viral Response at 12 weeks
TCTU	Tayside Clinical Trials Unit
TMF	Trial Master File
TMG	Trial Management Group
U&Es	Urea & Electrolytes

SUMMARY

Hepatitis C is a blood borne virus that can seriously damage the liver. An estimated 50,000 Scots have been infected with Hepatitis C virus (HCV). The main driver for spread of HCV infection is intravenous drug use. As HCV is highly infectious by the blood borne route through needle sharing, it can infect the person who injects drugs (PWID) early in their habit.

The outcome of HCV infection varies considerably between individuals. Some (up to 25%) are able to clear the infection spontaneously, whilst the remaining 75% become chronically infected. Within the subpopulation of chronically infected patients, some will develop serious liver disease, including cirrhosis and hepatocellular carcinoma, within a few years[1].

Around two thirds of people who are infected are unaware of it [2], and often show no symptoms over a long period of time. While there is presently no vaccination for Hepatitis C, improved treatments with shorter duration are now available. This raises the possibility of using therapy as prevention, turning the epidemic off at source, by targeting active PWID who are the main source of new infections. The modelling work of Martin et al[3], illustrates the startling possibility and impact of treating drug users to reduce the prevalence of HCV.

The focus of this trial will be to ascertain whether oral treatment regimens are effective in the treatment as prevention scenario in an active PWID population where illicit drug taking and poor adherence may reduce treatment efficacy. We will trial 3 different methods of delivering treatment and determine which is most successful in this population. Additionally we will trial an unlicensed combined treatment against HCV genotype 3 infection of shortened duration since current regimens for this genotype are limited.

We will recruit 135 participants and randomise them to one of three arms: daily, directly observed therapy; fortnightly dispensing of drugs; fortnightly dispensing of drugs with a psychological adherence intervention. Randomisation will be stratified according to HCV genotype. Participants will be treated for 12 weeks and followed up 12 weeks post treatment for the measurement of sustained viral response (SVR). The primary outcome measure will be SVR at 12 weeks post treatment (SVR_{12}), as this measure of cure is the determinant of sufficient compliance and efficacy within the 3 treatment arms. Analysis will be by modified intention to treat of all participants who receive one dose of therapy, to show non-inferiority fortnightly dispensing is easier to deliver than daily dispensing.

1 INTRODUCTION

1.1 BACKGROUND

Hepatitis C is a blood borne virus that can seriously damage the liver. An estimated 50,000 Scots have been infected with Hepatitis C virus (HCV). The main driver for spread of HCV infection is intravenous drug use. As HCV is highly infectious by the blood borne route through needle sharing, it can infect the PWID early in their habit. With the advent of more effective therapies of shortening duration, it raises the possibility of using therapy as prevention, turning the epidemic off at source, by targeting active infected drug users who are the main source of new infections.

Current treatment pathways focus on populations drawn from those known to drug problem services and former drug users. Some older periodic drug users are tested for HCV and are offered accelerated access into opiate substitution programs and early antiviral therapy. This treatment activity will reduce the health consequences of HCV infection but will have little impact on the group with active acquisition of HCV and hence the prevalence of HCV will remain the same, as any participants cured with anti-virals are more than replaced with new infections.

The modelling work of Martin et al[3], raises the startling possibility of the profound impact of treating small numbers of drug users on the prevalence of HCV, the work shows that treating as few as 10-20 per 1000 drug users per year can reduce HCV prevalence by 50-90% over 10 years. This has generated in the HCV field, the concept of treatment as prevention. The scale of the benefit is exponentially related to prevalence of HCV in the population, the lower the prevalence the bigger the impact. The model has some limitations, it groups all drug users together and assumes a similar risk of infection for those on methadone and those actively injecting and assumes a high rate of turn over from methadone back to active injecting and further assumes treatment is only possible during the opiate substitution phase.

To test the feasibility of the model of Martin et al[3] we ran the “Eradicate C” trial. This trial focuses on treating those drug users outside services where the impact on prevalence could be even more impressive, for such a relatively small investment. This group had never been previously targeted for therapy as it was believed to be too difficult to achieve the required adherence to therapy. The aim was to treat 20-40 highly active injecting drug users per year, recruited from Needle Exchange services. This trial showed that it was possible to treat this participant group with interferon based regimens +/- telaprevir, with SVRs that matched the conventional treatment trial outcomes. Adherence is crucial to therapy success and supervised interferon injections make therapy robust and may cover for lesser adherence to the ribavirin and protease inhibitor. The Eradicate C trial demonstrated that it is possible to deliver interferon based therapies to very active drug users and achieve cure rates that will power treatment as prevention.

1.2 RATIONALE FOR TRIAL

Oral anti-HCV regimens that are interferon free and have virtually no side-effects are now the standard of care in conventional treatment populations. The medication should be taken daily to optimise therapeutic success, and if adherence is poor in the actively injecting population it is possible that the effectiveness of the new oral drugs will be reduced. It is key to know if all oral directly acting antivirals (DAA) regimens are robust and maintain SVR rates in this population. The real world SVR rate combined with drug cost, re-infection rate and emergence of viral resistance will determine if this treatment as prevention model is cost-effective with DAAs. Directly observed therapy (DOT) is the ultimate adherence aid, but it is more costly and draconian so that it may discourage participants, especially this group, from taking up therapy. Therefore we need to demonstrate that treatment uptake and adherence is sufficient to maintain the SVR rate at a level which makes treatment as prevention cost effective. We will compare three means of delivery: daily DOT vs fortnightly pick up of therapy vs. fortnightly pick-up of therapy with a psychological intervention for adherence. The DOT method of treatment has not been explored in this difficult to find and engage population previously. Contingency management in the form of protein drinks for successful completion of each fortnight of treatment will be provided in all three arms of the trial. A comparison of the three pathways mentioned above will show which pathway shows best acceptability to participants and greatest compliance

The advent of DAAs with their reduced side effect profiles, shorter treatment duration and high SVR rates have the potential to reduce the burden of treatment providing high levels of adherence can be maintained. However, the use of DAAs alone are unlikely to be sufficient to achieve the required levels of adherence. In addition, the use of DAAs will not address the psychosocial factors known to influence adherence. To maximise participant outcomes, it will therefore be necessary to design interventions to promote adherence. One factor consistently cited as essential to treatment adherence is the provision of educational interventions regarding HCV, treatment of the condition and prognosis. However, these interventions (e.g.4,5,6) have not been shown to be effective in improving treatment adherence[7]. Several possible reasons exist for this discrepancy. First, the studies were generally of low quality with evidence of systematic bias (e.g. non-randomisation) and varied considerably in the structure and content of the intervention delivered. Second, none of the studies described a clear theoretical model of adherence behaviour upon which the interventions were based. Third, all interventions utilised generic education information about HCV. Evidence suggests that individualised and personalised information is essential in the promotion of adherence (e.g.8,9,10). All the factors likely limited the ability of the education to influence adherence in these studies. Finally, none of the studies investigated adherence in PWID or with DAA treatments only and therefore the effectiveness of such interventions in this population with newer treatment approaches is unknown. This trial will therefore investigate the effectiveness of a nurse-led educational intervention for adherence to DAAs in a PWID population.

Whilst the combination of Grazoprevir and Elbasvir is licensed for treatment of HCV genotype 1, treatment of HCV genotype 3 is more problematic. The C-SWIFT trial has recently shown that the combination of Grazoprevir, Elbasvir and Sofosbuvir is an effective and safe 8 week treatment for HCV genotype 3, resulting in high SVR rates[11]. Whilst all 3 drugs are licensed for treatment of HCV, the combination is not yet licensed. We will use this combination to treat HCV genotype 3 infections in this trial.

Hepatitis C virus is prone to develop resistance to DAAs since it has a high replication rate and therefore forms large numbers of genetically-distinct viral variants. We will investigate whether participants who do not achieve SVR are infected with a drug resistant strain of HCV by sequencing the NS3 and NS5A regions of virus present within their blood. The proteins of these genes are targeted by the DAA medications and if their structure is altered the DAA may no longer be effective.

The trial will also explore whether the taking of illicit drugs affects the efficacy of treatment. While the main effect is likely to be via adherence, it is also possible that some of the illicit drugs may interact with the DAAs. A log of illicit drugs used by the participants will be kept and used to identify any candidate interactions for further investigation.

2 TRIAL OBJECTIVES AND OUTCOMES

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	**Outcome Measure:**	**Time point of outcome measured**
To compare the efficacy of DAAs in HCV positive, active PWIDs, administered via DOT, fortnightly pick-up or fortnightly pick-up with a psychological adherence intervention.	SVR_{12} rates of participants in the DOT, fortnightly pick-up or fortnightly pick-up with a psychological adherence intervention group	12 weeks post treatment completion

Table 2: Secondary Objectives and Outcome Measures

Secondary Objective:	Outcome Measure:	Timepoint of outcome measured
To demonstrate that the achieved SVR rates in HCV PWID participants with DAA treatment are similar to RCT results and therefore a cost-effective treatment	Adherence of daily directly observed therapy group from daily logs	Daily log completed daily, adherence calculated at end of treatment
	Adherence measured by counting tablets returned after each 2 week treatment period (fortnightly pickup groups)	Calculated at end of treatment
	Adherence of participants infected with genotype 3 and treated with Sovaldi measured using MEMS® cap.	Calculated at end of treatment
To assess reinfection rates in active PWIDs treated with oral DAA regimes	Hepatitis C viral load from PCR	Annually at clinic visits
To assess resistance profiles in those who do not achieve SVR.	Profiles of the HCV viral resistance proteins, NS5a and NS3	Blood collected at baseline, end of treatment and SVR_{12}
To assess the types of illicit drugs taken by trial participants and identify any interaction with the DAAs.	Drug misuse history	Baseline, end of treatment (genotype 1 infection = week12, genotype 3 infection= week8)
	Urine toxicology	Once during treatment

3 TRIAL DESIGN

3.1 TRIAL DESCRIPTION

This is a randomised, un-blinded trial which will be conducted in the needle exchange services and pharmacies across Tayside, designed to evaluate the efficacy and feasibility of DAA therapy, in HCV positive, genotype 1 and 3, active PWIDs, administered via three different routes:

1. DOT,
2. Fortnightly pick-up
3. Fortnightly pick-up with psychological intervention.

Participants included in the trial will have a reactive Dry Blood Spot (DBS) test to confirm HCV infection, PCR to confirm active infection and will currently be using illicit drugs, as confirmed by the participant. Drug screening (by urine sample) will not be tested at that time.

Participants will be stratified by the genotype of their HCV infection; genotype 1 vs genotype 3 and randomised to one of three groups; DOT, fortnightly pick-up, or fortnightly pick-up with psychological adherence intervention.

All PWID are encouraged to have a DBS test annually as part of clinical practice in Tayside. Upon receipt of a reactive DBS test, potential participants will be briefed about the trial by the specialist nurse or other trained member of staff and given a participant information sheet (PIS) informing them of what is involved. Willing individuals will provide written informed consent and will then have safety bloods drawn to determine eligibility to proceed. A full list of inclusion/exclusion criteria is detailed in section 4.

Participants in all three arms of the trial will attend a baseline visit, a randomisation visit either one (genotype 3) or two (genotype 1) visits during treatment, an end of treatment visit and an SVR visit, as detailed in Appendix 2.
All participants will be given incentives to continue with their treatment in the trial. These will consist of protein drinks and will be given at each study visit.

Psychological intervention
Participants randomised to fortnightly pick-up with psychological intervention will have an interview with the study nurse, prior to beginning their treatment, which will cover the educational intervention designed to aid their compliance with the drug regimen. The intervention will be based on the Information-Motivation-Behavioural (IMB) Skills Model of Adherence[12] which was originally developed to explain adherence behaviour in HIV. Recent research suggests this model may have applicability in understanding the facilitator and barriers to adherence in HCV patients[8]. The model suggests that provision of medication information, enhancing personal and social motivation and developing behavioural skills that are key determinants of adherence and may improve adherence in this group. The intervention will involve a structured interview in which the trial nurse and participant will develop an action plan that includes personalised information, sources of motivation for adherence and a treatment routine configured to be compatible with the participant's lifestyle. Anticipating barriers to adherence and problem-solving will be included in the treatment routine. The intervention will take place at the randomisation visit and last approximately one hour. During the intervention, participants will be guided by their trial nurse in the completion of a personalised booklet, "Hepatitis C and Me". The booklet contains general and personalised information on Hepatitis C, exercises designed to explore and enhance personal and social motivation for treatment adherence and a behavioural action plan (the skills element of the IMB model). The booklet

uses the principles of node-link mapping to structure the intervention. Node link mapping use a set of visual tools to structure and guide therapeutic conversation and has been shown to enhance memory and compliance with treatment in substance misusers (e.g 13,14). Participants in the other two arms of the trial, who are not receiving the psychological intervention, will be given the current NHS Tayside hepatitis information booklet ("Living with Hepatitis C") which provides generalised information about HCV without personalised information or specific strategies to enhance motivation and behavioural skills.

Reinfection follow up.

Trial participants will be invited to also consent for access to information from their annual clinic visits and HCV testing at any other contact with clinical services for up to 5 years, to detect re-infection.

Illicit drug monitoring

Illicit drug use will be recorded at baseline and at end of treatment (week 8 for genotype 3, week 12 for genotype 1). One sample of urine for toxicology will be taken during treatment. Those participants who fail to achieve SVR will be compared to successful participants for any correlation with particular substance use. For any candidate substance associated with failure to achieve SVR not explained by lack of adherence, biological samples will be analysed for biological mechanisms.

Adherence monitoring

Adherence of those participants randomised to DOT will be documented on a daily log. Those randomised to fortnightly collection of medication will receive Zepatier tablets in blister packaging. They will return their packets of medication every two weeks and any remaining tablets will be counted. Participants infected with HCV genotype 3 will additionally receive bottles containing Sovaldi tablets. These bottles will be fitted with adherence aid caps that record time and date of each cap opening.

3.2 TRIAL FLOWCHART

Please refer to Appendix 1 (section 17.1)

3.3 TRIAL MATRIX

Please refer to Appendix 2 (section 17.2).

4 TRIAL POPULATION

4.1 NUMBER OF PARTICIPANTS

This trial aims to treat 135 active PWID with active HCV infection in Tayside over a two year period. Due to the nature of this trial, trial dropouts are a trial endpoint and will not be replaced.

4.2 INCLUSION CRITERIA

- Male or Female. (Age limit 18-70)
- HCV PCR confirmed active infection, genotype 1 or 3.
- If female, must have negative urine test results for pregnancy during initial screening period (for trial inclusion) and be advised of limited safety data in pregnancy.
- Current illicit drug use established through participant history.
- Able to provide informed consent, agreeing to trial and clinical monitoring criteria

4.3 EXCLUSION CRITERIA

- Aggressive or violent behaviour.
- Unwilling to consent to GP being informed of their participation in the trial
- Platelet count < 75 x 10^{9} /l
- Alanine transaminase > 350U/l
- Inability to provide informed consent.
- Clinical history or abnormal valves for albumin< 30 g/l, Bilirubin >35 umol/l or PT >1.5 consistent with decompensated liver failure Childs-Pugh B or C
- Clinical history of primary hepatocellular carcinoma
- Pregnancy or breast feeding.
- Participation in a drug trial within the previous 30 days
- Hepatitis B surface antigen positive
- HIV infection.
- Hypersensitivity to elbasvir and grazoprevir
- Hypersensitivity to sofosbuvir (genotype 3 infected-participants ony)
- Currently being treated with an inhibitor of organic anion transporting polypeptide 1B, e.g. rifampicin, atazanavir, daruavir, lopinavir, saquinavir, tipranavir, cobicistat or ciclosporin.
- Currently being treated with inducers of cytochrome P450 3A or P-glycoprotein, such as efavirenz, phenytoin, carbamazepine, bosentan, etravirine, modafinil or St John's Wort (*Hypericum perforatum)*
- Currently being treated with amiodarone (Participants infected with genotype 3 HCV only)

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

- Individuals will be identified via the current DBS testing pathway in Needle Exchange centres sited in health care hubs by specialist nurse or other trained member of staff.
- In addition, known HCV positive participants with reactive dry blood spot test attending needle exchange with status having previously been established elsewhere will be approached in Needle Exchange centres or other suitable venues by specialist nurse or other trained member of staff.
- Potential participants (above) will be given a participant information sheet (PIS) and any questions they have about the trial will be answered by the trial team.

5.2 CONSENTING PARTICIPANTS

Potential participants will be approached by research nurses but they may delegate to other individuals who are trained in dried blood spot testing and are part of the managed care network and have right of referral to treatment services. Any such delegation will be recorded on the trial Delegation Log and be authorised by the CI. Potential participants will be provided with information on the trial verbally and via the PIS and be given at least 24 hours to consider participation in line with prevailing TASC SOP. At their return visit for screening they will be interviewed by the trial research nurse and asked to sign an informed consent form once they are satisfied that they have had adequate explanation from the member of staff explaining the trial to them.

Where a participant requests to speak with a physician from the trial team the consent process will not be completed until the participant had spoken to the physician and had all their questions answered to their satisfaction.
Once a participant has consented to take part a GP letter will be sent to their GP to inform them that their patient is in a clinical trial. If the individual is not registered with a GP they will be encouraged to do so. In the meantime, any acute medical problems will be handled by the hepatitis C clinical team.

5.3 SCREENING FOR ELIGIBILITY

Following informed consent, blood will be taken from the participants to assess their liver function and to confirm that they have active infection with HCV genotype 1 or 3 and not with HIV or hepatitis B. Active illicit drug use will be confirmed by participant. Urine sample will be taken from female potential participants and a pregnancy test carried out to confirm that they are not pregnant. Any prescribed medication will be checked for drug-drug interactions with trial medication.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Ineligible or non-recruited participants will be thanked for their interest in the trial and be given a clear explanation as to why they are ineligible. If a clinically significant abnormality is detected relevant clinical management will be instigated and the participants GP informed if the patient consents.

5.5 RANDOMISATION

5.5.1 Randomisation

After successful screening for eligibility and safety, participants will be randomised to either DOT, fortnightly pick up or fortnightly pick up with psychological intervention.
PWID who are eligible for this trial have unpredictable and chaotic lives. It is therefore possible that an individual will consent to take part, provide baseline information and have blood taken for safety and eligibility checking. If eligible they may be randomised. They may then not be seen at the needle exchange for a number of weeks or even months. It is standard clinical practice that pretreatment bloods are valid for a period of 6 months and therefore we will consider baseline bloods taken for the study to be valid for 6 months unless there is a clinical indication to repeat within that period. Any clinical decision on whether bloods need to be repeated within 6 months will be made by the CI. If a consented participant reappears after a period longer than 6 months has elapsed, a documented verbal check will be made to confirm that the individual continues to consent to taking part in the study. The bloods will be re-taken and eligibility will be based on the results of these new blood tests. The blood tests taken closest to the date of treatment initiation will be considered as the baseline data.The viral genotype will not be retested as NHS lab policy is to redo this test only after 5 years have elapsed. After 6 months the baseline CRF will also be repeated to provide up-to-date pretreatment information. In this case, the information originally collected in the baseline CRF will be filed but will not be entered into the electronic data management system (Openclinica) and will not form part of the analysed dataset. To ensure that the correct, most up-to-date baseline data is entered into Openclinica, baseline data will be entered once each participant has started their treatment.

As this is an un-blinded trial, the nurse, or delegated member of staff, and participant will be aware of which arm they are allocated to. Randomisation to each of the three trial groups will be stratified by genotype so that the proportion of genotype 1 vs genotype 3 infected participants will be the same in each group. The Tayside Clinical Trials Unit (TCTU) GCP-compliant online randomisation system, TRuST, will be used by the specialist nurse or delegated, trained member of staff to perform the randomisation.

5.5.2 Treatment Allocation

Eligible participants infected with genotype 1 HCV will receive Zepatier treatment for 12 weeks. Zepatier contains a combination of Grazoprevir and Elbasvir. Whilst it is a licensed medication, Merck will supply GMP ready investigational medical product (IMP) for use in the trial. Those infected with genotype 3 HCV will receive commercial stock sofosbuvir off the shelf in addition to Zepatier for 8 weeks. Treatment regimens for treatment naïve and treatment experienced participants enrolled in the trial will be the same. Zepatier tablets are film-coated and each contains 50 mg Elbasvir and 100 mg Grazoprevir. Sovaldi is provided as a single 400mg tablet.

For participants in group 1, medication will be dispensed daily by the participant's community pharmacist or at the needle exchange. The pharmacist or trial nurse will observe the participant taking the medication and this will be noted in a daily log. Participants will be provided with sufficient tablets for the weekend and other days that the pharmacy/needle exchange is closed. Participants in groups 2 and 3 will fortnightly receive two week's supply of medication from the trial staff. Participants infected with Genotype 1 HCV will be instructed to take one tablet daily from the blister pack. Those infected with Genotype 3 HCV will be instructed to take one tablet daily from the blister pack and one tablet daily from the bottle. The bottle will be fitted with an electronic adherence measuring aid.

5.5.3 Withdrawal procedures

Participants will be informed that they have the right to withdraw from the trial at any time without giving reasons and without prejudicing further treatment. The right to refuse to participate without reasons will be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels that it is in the participant's best interest but, reasons for doing so will be recorded. In these cases the participants remain within the trial for the purposes of follow-up and data analysis.

Although a participant is not obliged to give reason(s) for withdrawing prematurely, if the participant appears lost to follow up, the CI will make a **reasonable** effort to ascertain the reason(s), while fully respecting the individual's rights, and will demonstrate that everything possible was done in an attempt to find any participant lost to follow-up. Those lost to follow-up or withdrawn will be identified and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

6 INVESTIGATIONAL MEDICINAL PRODUCT

6.1 TRIAL DRUG

6.1.1 Trial Drug Identification

Genotype 1 infection will be treated with Zepatier (100mg Grazoprevir and 50mg of Elbasvir) supplied as one film-coated tablet to be taken once per day with or without food for 12 weeks. This is a licensed medication but the drug supplied by the manufacturer will be IMP.

Genotype 3 infection will be treated with Zepatier as above plus Sovaldi (Sofosbuvir 400mg, licensed product), taken as one film-coated tablet once daily with food for 8 weeks. The combination of Zepatier plus Sovaldi has been successfully trialled for treatment of genotype 3 hepatitis C infection (C-SWIFT[11] and C-ISLE[15] trials) but this combination of drugs is not licensed for treatment of HCV genotype 3 infection.

6.1.2 Trial Drug Manufacturer

Merck (Zepatier)
Gilead (Sovaldi)

6.1.3 Marketing Authorisation Holder

Zepatier is manufactured by:
Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon EN11 9BU
United Kingdom
MA number: EU/1/16/1119/001. As stated above, the manufacturer will supply us with IMP product.

Sovaldi is manufactured by:
Gilead Sciences International Ltd
Flowers Building
Granta Park Abington
Cambridge
CB21 6GT
United Kingdom
MA number: EU/1/13/894/001 (for 1 bottle of 28 tablets) and EU/1/13/894/002 (for 3 bottles of 28 tablets).

6.1.4 Labelling and Packaging

Zepatier tablets are packaged in a carton containing two cardboard cards, each containing 2 strips of 7 sealed blisters. Participants randomised to the DOT arm will receive one tablet per day. Those randomised to the fortnightly collection of medication will receive one cardboard card, containing 2 strips of 7 blisters, making 14 blisters in total.

Participants randomised to the DOT arm will receive one Sovaldi tablet per day. Those randomised to the fortnightly collection of medication will receive one bottle containing 14 tablets every 14 days. Commercially available medication event monitoring system (MEMS®) caps will be used on the bottles of Sovaldi to enable measurement of adherence in the participants with genotype 3 infection.

6.1.5 Storage

Drugs will be stored in the Clinical Trial Pharmacy (Ninewells Hospital, Dundee). Following receipt of a prescription, a participant's drug will be dispensed from there to the community pharmacy or needle exchange centre. A drug accountability log will be held in the Clinical Trial Pharmacy. There are no special storage conditions required for either Zepatier or Sovaldi as per their Summary of Product Characteristics (SmPC).

6.1.6 Reference Safety Information (RSI)

Zepatier SmPC and Sovaldi SmPC will be held in the Trial Master File - specifically in Pharmacy Site File (PSF) and Investigator Site File (ISF). The SmPCs will be reviewed at least annually and where there have been any changes to the RSI from the SmPC version approved by MHRA, an amendment will be submitted for regulatory approval. Other changes to the SmPC will not require an amendment.

6.1.7 Accountability procedures

This will be overseen by the Clinical Trials Pharmacist in the Clinical Trials Pharmacy Department (Ninewells). This will be documented as such in the TMF and Accountability Logs will be held in the PSF.

6.2 DOSING REGIME

Following randomisation, participants in the DOT group will be issued with their first dose of medication. Those with genotype 1 infection will be given one Zepatier tablet whilst those with genotype 3 will get one Zepatier tablet and one Sovaldi tablet. Participants in each of the fortnightly dosing regimens will be given two week's supply of medication. No per body weight dose adjustment is required and participants with genotype 1 will be treated for 12 weeks, those with genotype 3 for 8 weeks.12 weeks following the end of treatment blood will be taken from

participants in order to establish whether they have achieved SVR12. Participants will be asked to consent to being followed up annually for five years to enable us to establish reinfection rates. Participants will be asked to use adequate contraception (see section 11.1).

6.3 DOSE CHANGES

No dose change is planned in this trial protocol. If the participant is taken off the trial, their GP and consultant will be informed of the reason for stopping trial medication. The participant will remain in the trial for the entire duration even if the trial medications are stopped, subject to their agreement.

6.4 PARTICIPANT COMPLIANCE

Adherence to the dosing regime is a secondary outcome of this trial. It will be checked and documented in each of the 3 arms of the trial. Those in the DOT arm will have adherence documented by the pharmacist or staff member, while those in the other two arms will be asked about adherence at each trial visit and, for participants being treated for genotype 3 HCV infection, the MEMS® caps records will be analysed. Should compliance be poor, the participant will be advised by the trial nurse or delegated individual on the importance of correct compliance. If any subject misses more than 7 consecutive doses they will be withdrawn from treatment but still followed up to the SVR 12 visit.

6.5 OVERDOSE

Experience of human overdose with these drugs is limited. When tested in healthy volunteers, adverse reactions were similar in frequency and severity to those reported in the placebo groups.

In the event of an overdose, it is recommended that the participant be monitored for any signs/symptoms of adverse reactions and appropriate symptomatic treatment instituted.

6.6 OTHER MEDICATIONS

6.6.1 Permitted Medications

Medications will be permitted as long as they do not interact with the trial drugs. The SmPC and Liverpool HEP interactions website (http://www.hep-druginteractions.org) will be used to identify drugs with potential interactions.

6.6.2 Prohibited Medications

Prohibited medications are those identified by the SmPC and Liverpool HEP interactions website (http://www.hep-druginteractions.org) as having potential interactions with the trial

drugs. GPs will be informed that their patient is participating in the study and will check compatibility prior to prescribing new drugs.

6.6.3 Concomitant Medications

Details of all concurrent medications will be recorded in the CRF.

7 TRIAL ASSESSMENTS

7.1 TRIAL ASSESSMENTS

See participant trial matrix: Appendix 2

Participants who are randomised to the DOT arm of the trial will undergo daily review by their dispensing pharmacist or delegated member of staff.

Participants who are randomised to the fortnightly pick-up with psychological intervention will receive a less than one-hour individual session with a research nurse exploring their motivation and skills to adhere to their treatment regime. The intervention is described in section 3.1 and will involve a structured interview in which the trial nurse and participant will develop an action plan that includes personalised information, sources of motivation for adherence and a treatment routine configured to be compatible with the participant's lifestyle. During the intervention, participants will be guided by their trial nurse in the completion of a personalised booklet, "Hepatitis C and Me".

7.2 SAFETY ASSESSMENTS

For adverse event reporting see section 10 below.
Safety bloods to assess liver and kidney function including liver function tests (LFTs), urea and electrolytes (U&Es) Full blood count (FBC), and prothrombin time (PT) will be assessed prior to the onset of treatment to ensure that the participant can tolerate DAA therapy and at the end of treatment (week 8 for genotype 3 infection, week 12 for genotype 1 infection). LFTs will be measured at week 8 of treatment in all participants due to rare flare in alanine aminotransferase levels.
Female participants will have a urine pregnancy test prior to beginning treatment to ensure that they are not pregnant.

8 DATA COLLECTION& MANAGEMENT

8.1 DATA COLLECTION

Data management will be conducted in compliance with TASC SOPs on Data Management. The data will be principally collected by the nurses appointed to the trial and supported by other trial appointed staff. The data sources will include the CRF, medical notes, laboratory reports and trial specific questionnaires.

Trial-specific data will be collected at baseline, randomisation week 4, week 8 (HCV genotype 1), end of treatment and 12 weeks post treatment.

Most of this data will be entered directly into the CRFs without being routinely recorded in clinical data sources. Participants will be asked to consent to information being collected at routine annual clinic visits for up to 5 years to check for reinfection.

8.2 DATA MANAGEMENT SYSTEM

The data management system provided by TCTU will be OpenClinica. Development and validation of the trial database with QC and extraction of data will be done according to TCTU procedures. The DMS will be based on the protocol and case report form (CRF) for the trial and individual requirements of the investigators. The CRF will collect only information that is required to meet the aims of the trial and to ensure the eligibility and safety of the participant. The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the trial team. The trial database will be compliant with TASC SOPs on Creating and Managing Databases. Extracts for analysis will be based on the dummy data tables provided by the trial team.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

Statistical analysis will be conducted in compliance with TASC SOPS.

We propose to conduct this project as a randomised trial to show that DAA therapy in very active PWIDs administered fortnightly with or without adherence intervention is non-inferior to DOT. We will compare pathways sequentially comparing DOT vs fortnightly delivery and then DOT verses fortnightly pickup with adherence intervention. Fortnightly pick up will be more cost effective than the other two options so long as adherence and efficacy matches that of the DOT and fortnightly plus adherence intervention. If we assume a 95% SVR rate (based on published studies) in the DOT arm of the trial in this population and a non-inferiority limit of 14% (which would be likely to maintain cost-effectiveness) then at a 5% significance level and 90% power

we would need a sample size of 42 in each group 126 in total. To allow for drop-outs we will aim to recruit 135 individuals, 45 per group.

A Statistical Analysis Plan (SAP) will be prepared for analysis of primary and secondary outcomes and will include a plan for handling missing data

9.2 PROPOSED ANALYSES

9.2.1 Primary Outcomes

- To compare using SVR rates the efficacy and compliance of DAAs in135 new HCV positive individuals randomised to one of three groups; DOT, fortnightly therapy and fortnightly therapy with psychological adherence intervention.

The data for these outcomes will be generated directly from the CRFs from the clinical and laboratory data recorded therein.

9.2.2 Secondary Outcomes

- Compare adherence to therapy rates of subjects randomised to either DOT, fortnightly therapy or fortnightly therapy with psychological adherence intervention - treatment of HCV. Adherence rates will be obtained from the daily log data in the DOT group, and from pill counting and MEMs caps data in the two fortnightly therapy groups.
- Assess reinfection rates in the PWID population and treated using all oral DAA regimes. The data for reinfection rates will be will generated from the annual follow up and retesting for chronic HCV infection of all participants treated. This will be from routine clinical follow data and consent will be sought to access this. The analysis is simple, requiring only simple descriptive statistics.
- Assess viral resistance patterns in participants who do not achieve SVR. These data will be obtained by analysing samples for resistance associated variants (RAVs) using standard clinical laboratory assays.
- Assess the types of illicit drugs taken by trial participants and identify any interaction with the DAAs and possible effect on adherence. This data will be generated by the adverse event reporting mechanism within the trial. The particular interest will be around interactions of the trial medication with drugs of misuse. Concomitant drug use during the trial will be recorded in the CRF at baseline and end of treatment and supported by urine toxicology from a urine sample that will be collected during treatment. Data will be recorded in the CRF.

9.2.3 Statistical analysis

Outcomes Data Analysis plan: 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 and the denominator will be total number of patients randomised to each arm. Additionally results will be expressed as a proportion of the estimated HCV infected subjects in needle exchange. 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). A test of interaction between contingency and pathway will be carried out and if not significant contingency will be assessed independently. If significant then the effect of contingency will be assessed by each pathway separately. 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:

a) Proportion of HCV tested.

b) Proportion who start HCV treatment within the duration of the study of those identified with HCV.

c) Adherence: to compare the longitudinal evolution of adherence to the prescribed regimen between the conventional pathway and the pharmacy led pathway. For each patient, daily adherence will be defined using a binary variable Z it indicating whether yes (=1) or no (=0) the subject has taken their medication on day t. This longitudinal binary variable will be directly generated from the patient electronically compiled dosing history. Comparison of binary time series is realized using a logistic regression where dependence among observations from a given patient over time is taken into account. The effect of pathway and contingency management on overall adherence will be tested using the above-described model by testing if either the group coefficient or the interaction between the group and time are significantly different from zero.

d) Proportion who complete the course of those initiating treatment.

Multiple logistic regression modelling will explore the patient and pathway characteristics that are associated with the secondary outcomes and primary outcome. Patient outcomes considered will be age, gender, deprivation, employment, comorbidity, and the psycho-social variables assessed.

9.3 MISSING DATA

The nature of this trial is to assess the applicability of this model in the real world, so incomplete data that impacts the primary outcome will be assumed to be to consistent with failure of therapy and drop-outs won't be replaced. However every effort will be made to obtain missing data and as the primary outcomes are not time point critical a wide latitude for admissibility of data will be employed. We will accept measures of SVR up to 12 weeks after the due SVR_{12} date.

9.4 TRANSFER OF DATA

No participant identifiable data will be transferred off site. Data will be stored, identified by trial number, with a separately held key to link trial number to identifiers that could be used for record linkage.

10 ADVERSE EVENTS

10.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. Each initial AE will be considered for severity, causality or expectedness and may be reclassified as a serious event or reaction based on prevailing circumstances.

An **adverse reaction** (AR) is where it is suspected that an AE has been caused by a reaction to a trial drug

A serious adverse event (SAE), serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR) is any AE, AR or UAR that at any dose:

- results in death
- is life threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- Or is otherwise considered serious

10.2 RECORDING AND REPORTING AES AND SAES

All AEs and SAEs will be recorded from the time a participant consents to join the trial until the last trial visit. Participants with unresolved AEs at their last trial visit will be followed up until resolution or 30 days after their last trial visit whichever is sooner. SUSARS will be followed until resolution.

The CI or delegate will ask about the occurrence of AEs and hospitalisations at every trial visit. AEs will be recorded on the AE Log in the CRF. SAEs will be submitted on an SAE form to the Sponsor Pharmacovigilance Section (pharmacovigilance.tayside@nhs.net) within 24 hours of

becoming aware of the SAE except as described below and to MSD Global Safety group within 2 business days of the study team becoming aware of the event. SAEs will be assessed for expectedness and causality by the Investigator. The evaluation of expectedness will be made based on the knowledge of the reaction and the relevant product information (SmPC or IB). Refer to TASC SOP "Identifying, Recording and Reporting Adverse Events for CTIMPs". Causality will be assessed by the Sponsor
Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an SAE. However any adverse events occurring during such hospitalisation will be recorded.

Due to the large amount of comorbid disease and very high levels of illness and AEs that are expected to be present in this population, we will record as AEs/SAEs, but not report as SAEs to Sponsor Pharmacovigilance Section within 24 hours but will provide as line listings only to be included in the annual Development Safety Update Report (DSUR), in following the categories:

- Any death or hospitalisation for assault or accidental injury
- Hospitalisation for abscesses due to drugs use
- Hospitalisation for wound management due to drugs use
- Any death or hospitalisation due to infection
- Hospitalisation for elective or planned investigation or treatment
- Any death or hospitalisation for deteriorating renal function, high or low potassium levels
- Any hospitalisation due to nausea, vomiting, constipation or diarrhea

All other SAEs will be reported to Sponsor Pharmacovigilance Section within 24 hours and to MSD's Drug Surveillance Department within 2 business days of becoming aware of the event.

10.3 REGULATORY REPORTING REQUIREMENTS

The Sponsor, together with the CI, is responsible for reporting SUSARs to the competent authority, the MHRA, the Research Ethics Committee (REC) and any other competent authorities. Fatal or life threatening SUSARs will be reported within 7 days and non-fatal and non-life threatening SUSARs within 15 days.

10.4 ANNUAL REPORTING REQUIREMENTS

The following reports will be submitted each year as a condition of the authorisation to undertake a clinical trial or as a condition of a favourable opinion from a REC.

The DSUR will be prepared jointly by the Sponsor Pharmacovigilance Section and CI and submitted to the MHRA on the anniversary of date of Clinical Trial Authorisation (CTA).

An NRES CTIMP Safety Report Form will be sent to REC along with the DSUR. A NRES Annual Progress Report for CTIMPs will be prepared and submitted by the CI to REC, and copied to Sponsor, on the anniversary date of the REC favourable opinion.

Reports of SUSARs in the UK, urgent safety measures and any other safety reports submitted, for example, reports of a data monitoring committee, will also be accompanied by a Safety Report Form.

10.5 URGENT SAFETY MEASURES

The CI or other clinician may take appropriate immediate urgent safety measures in order to protect the participants of a CTIMP against any immediate hazard to their health or safety. The MHRA, REC and Sponsor will be notified in writing within three days.

11 PREGNANCY

Pregnancy is not considered an AE or SAE, however an abnormal outcome would be. If a pregnancy occurs, the CI or delegate must collect pregnancy information for female trial participants, who will be advised to stop trial medication immediately.

The CI or delegate should complete the TASC Pregnancy Notification Form and submit to the Sponsor Pharmacovigilance section within 14 days of being made aware of the pregnancy. Any pregnancy should be followed to outcome. Pregnancy follow up information must be recorded on the TASC Pregnancy Follow up form and submitted to the Sponsor Pharmacovigilance section.

11.1 CONTRACEPTIVE ADVICE TO PARTICIPANTS

All participants will be given contraceptive advice. With the aim of avoiding pregnancy during treatment. Avoiding getting pregnant by not having sex at all is obviously effective. If participants follow this strictly, no contraception is needed. If not, the following are effective types of contraception:

- Combined Oral Contraceptive Pill
- EVRA-oestrogen and progestogen: ‘Transdermal Patch’
- Progestogen only pill: ‘mini pill’
- Depoprovera injection (medroxyprogesterone acetate)
- Implanon Implant (Etonogestrel)
- Mirena Coil (Intra-Uterine System)
- IUD-copper containing intrauterine device
- Female sterilisation

- ‘Barrier methods’ such as the condom, diaphragm or cap, with or without spermicide, may also be used.

Male vasectomy is also a good form of contraception but only if the procedure has been confirmed afterwards by a physician to make sure it has worked. No contraception method is 100% reliable by itself. Even surgical sterilisation in men and women has been known to fail very occasionally therefore participants will be advised to use additional contraception from the start of the trial if they or their partner is of child bearing potential.

12 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be co-ordinated by a Trial Management Group, who will meet regularly and co-opt co-investigators and the research nurses to the meeting as required.

12.2 TRIAL MANAGEMENT

A Trial Manager will support the chief investigator (CI) in managing the trial, they will have the support of a trial Coordinator who will work closely with the research nurses. The research Nurses will oversee the trial and will be accountable to the CI.
A trial-specific Delegation of Responsibilities & Signature Log will be prepared for each Site, detailing the responsibilities of each member of staff working on the trial.

12.3 TRIAL STEERING COMMITTEE

The trial management group (TMG) will carry out the duties of the trial steering committee.

12.4 DATA MONITORING COMMITTEE

Since the drugs being used in this trial are licensed an independent Data Monitoring Committee will not be required.

12.5 INSPECTION OF RECORDS

The CI will permit trial related monitoring, audits, REC review, and regulatory inspection(s). In the event of an audit, the CI will allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all trial records and source documentation.

12.6 RISK ASSESSMENT

A trial risk assessment was carried out by the Sponsor Research Governance Manager prior to Sponsorship approval being granted.

12.7 TRIAL MONITORING

The Sponsor will determine the appropriate extent and nature of monitoring for the trial and will appoint appropriately qualified and trained monitors.

12.7.1 Potential Risks

Potential adverse reactions to Zepatier and Sovaldi are as outlined in the SmPC.
Having blood taken may cause some mild bruising.

12.7.2 Minimising Risk

Participants will be monitored closely throughout the trial and adverse event monitoring will be undertaken as required. Every precaution will be taken to minimise discomfort whilst taking bloods, only trained and delegated members of staff will perform this procedure.

13 GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT OF THE TRIAL

The trial will be conducted in accordance with the principles of good clinical practice (GCP).
In addition to Sponsorship approval, a favorable ethical opinion will be obtained from an appropriate REC. Authorisation from the MHRA and appropriate NHS R&D permissions will be obtained prior to commencement of the trial.

13.1.1 Confidentiality

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 trial 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, its designee or Regulatory Authorities. The CI and trial staff involved with this trial will not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

13.1.2 Data Protection

The CI and trial staff involved with this trial 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 trial 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 trial 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.

13.1.3 Insurance and Indemnity

The University of Dundee and Tayside Health Board are Co-Sponsoring the trial.

Insurance. – The University of Dundee will obtain and hold Professional Negligence Clinical Trials Insurance cover for legal liabilities arising from the trial.

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

Where the trial involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

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

14 TRIAL CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

The CI will seek Sponsor approval for any amendments to the Protocol or other trial documents. Amendments to the protocol or other trial docs will not be implemented without approval from the Sponsor and subsequent approval from the appropriate REC and/or MHRA, as appropriate, and NHS R&D Office.

14.2 PROTOCOL DEVIATIONS, BREACHES AND WAIVERS

The CI will not implement any deviation from the protocol without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to trial participants. In the event that the CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented in a TASC Deviation & Breach Log and notified to the Sponsor. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC, Regulatory Authority and local NHS

R&D for review and approvals as appropriate. It is Sponsor policy that waivers to the Protocol will not be approved.

In the event that a serious breach of the protocol or GCP is suspected, this will be reported to the Sponsor immediately using the form “Notification to Sponsor of Potential Serious Breach or Serious Deviation”.

14.3 TRIAL RECORD RETENTION

Archiving of trial documents will be carried out as specified in TASC SOPs (unless otherwise agreed with the Sponsor and by contract). As the data from this trial does not form part of an application for a Marketing Authorisation (MA) all trial documentation will be kept for at least 5 years.

14.4 END OF TRIAL

The end of trial is defined as datalock. The Sponsor and CI have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor, REC, MHRA and NHS R&D Office within 90 days, or 15 days if the trial is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A final report of the trial will be provided to the Sponsor, REC and MHRA within 1 year of the end of the trial.

14.5 CONTINUATION OF DRUG FOLLOWING THE END OF TRIAL

This is not appropriate as the drugs being issued are only to be taken for 12 weeks during the trial.

15 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

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

15.2 PUBLICATION

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

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

The clinical trial report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the trial. The International Committee of Medical Journal Editors recommendation on Authorship and Contributor-ship will be adhered to when presenting papers for publication or acknowledging public responsibility for appropriate portions of the content.

Abstracts will be presented at European Association for the Study of the Liver and American Association for the Study of Liver Diseases annual meetings, 4 papers are anticipated and target journals include Hepatology, J Hepatology and Gut, within 3 years of trial start.

The clinical trial report will be used for publication and presentation at scientific meetings. Trial investigators have the right to publish orally or in writing the results of the trial.
Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

15.3 **PEER REVIEW**

Peer review of the protocol will occur via the Sponsorship Committee and of the resulting publication by the referees of the journal to which the paper (and its protocol) will be submitted.

This trial has been funded by MERCK/MSD who have peer reviewed the grant application.

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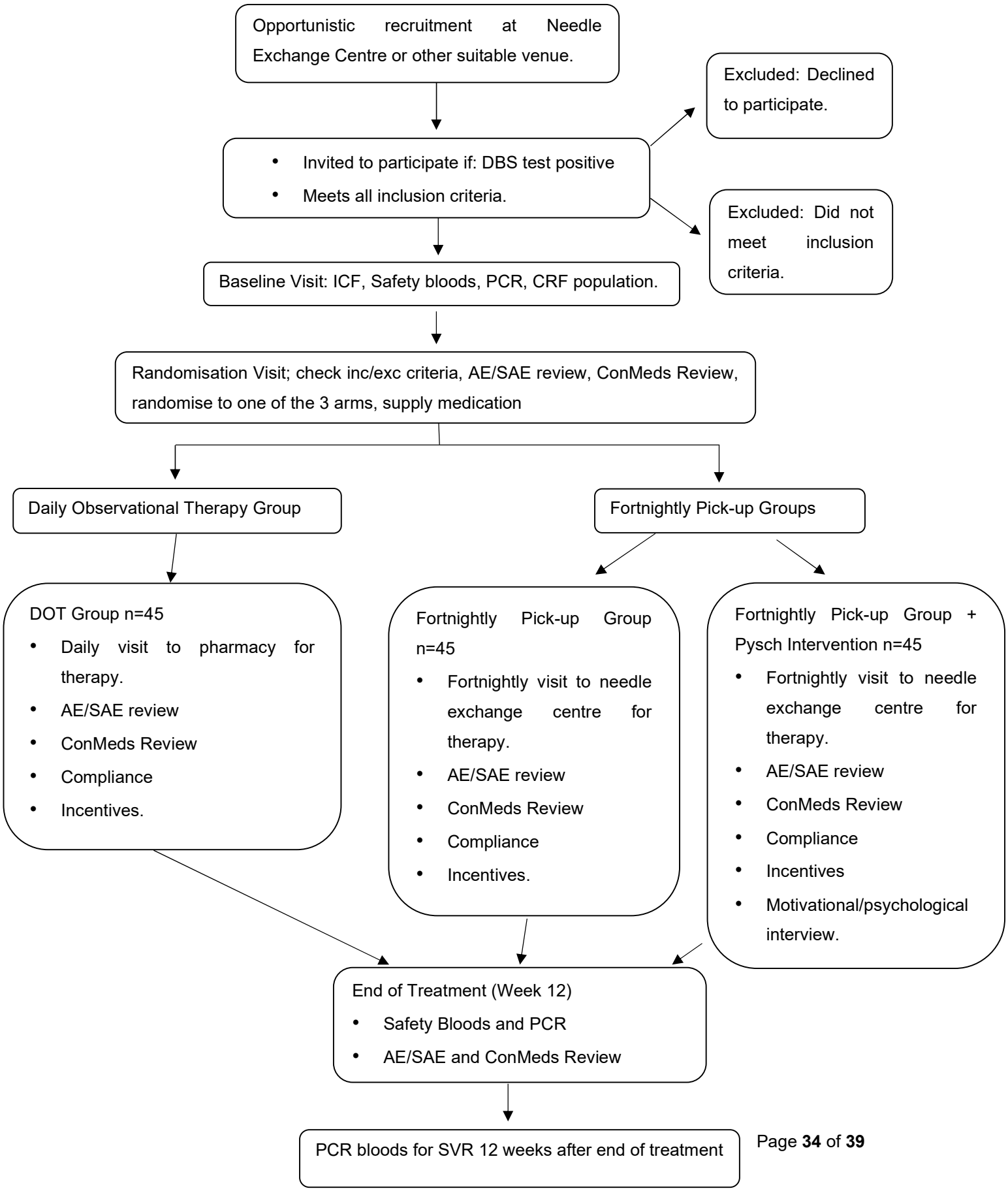
17 APPENDIX

17.1 APPENDIX 1: TRIAL FLOW CHART



17.2 APPENDIX 2: TRIAL MATRIX

Participants infected with genotype 1 HCV

Activity	Visit 1 Baseline	Visit 2 Randomisation		Visit 3		Visit 4		Visit 5 End of treatment	SVR12	DV / USV
		Day 0	Week 2	Week 4 (-7 to+14 days)	Week 6	Week 8 (-7 to +14days)	Week 10	Week 12 (-7 to +14days)	Week 24 (+12weeks)	
Informed Consent	X									
Check Inc/Exc Criteria	X	X								
Medical History	X									
Drug Misuse History	X							X		X
Urine test for illicit drugs			*	*	*	*	*	*		
Demographics	X									
Blood tests; U&Es, FBC, PT	X							X		X
Blood tests; LFTs	X					X		X		
Blood test; PCR	X							X	X	
Research Blood	X							X	X	X
Urine pregnancy test	X									
Adverse Event Assessment		X		X		X		X	X	X
Record or Review Con Meds	X	X		X		X		X	X	X

Check Drug Compliance				X		X		X		
Antiviral Drug Administration		X	X	X	X	X	X			
Psychological interview for those randomised to this intervention		X								

1. Discontinued Visits (DV) and Unscheduled Visits (USV). Additional Standard of Care sampling including LFT's, U&E's, FBC, and PT, (as a minimum), should be performed where the USV is in relation to an AE/SAE which may be attributable.
2. Unscheduled Visits / DOT daily visits - Adverse Event and check for concomitant medications should be performed at any unscheduled visit.

* One urine sample will be taken during treatment for analysis of illicit drug taking.

Participants infected with genotype 3 HCV

Activity	Baseline	Randomisation		Visit 3		Visit 4 End of treatment	SVR_{12}	DV / USV
		Day 0	Week 2	Week 4 (-7 to +14 days)	Week 6	Week 8 (-7 to+14 days)	Week 20 (+12weeks)	
Informed Consent	X							
Check Inc/Exc Criteria	X	X						
Medical History	X							
Drug Misuse History	X					X		X
Urine test for illicit drugs			*	*	*	*		
Demographics	X							
Blood tests; U&Es, FBC, PT	X					X		X
Blood tests; LFTs	X					X		
Blood test; PCR	X					X	X	
Research Blood	X					X	X	X
Urine pregnancy test	X							
Adverse Event Assessment		X		X		X	X	X
Record or Review Con Meds	X	X		X		X	X	X
Check Drug Compliance				X		X		
Antiviral Drug Administration		X	X	X	X			
Psychological interview for those randomised to this intervention		X						

1. Discontinued Visits (DV) and Unscheduled Visits (USV). Additional Standard of Care sampling including LFT's, U&E's, FBC, and PT, (as a minimum), should be performed where the USV is in relation to an AE/SAE which may be attributable.
2. Unscheduled Visits / DOT daily visits - Adverse Event and check for concomitant medications should be performed at any unscheduled visit.

* One urine sample will be taken during treatment for analysis of illicit drug taking.