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

Statistical Analysis Plan

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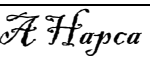
TRIAL STATISTICIAN, SAP AUTHOR	Dr Adrian Hapca		29/09/2020

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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].

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.

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. 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.

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 promote adherence. 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

2.1.1 Primary Outcomes

- To compare using SVR rates the efficacy and compliance of DAAs in 135 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.

2.1.2 Secondary Outcomes

- To compare patient progression through the different trial pathway stages.
- 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.

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 travel expenses, in the form of a local return bus fare 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.

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 RANDOMISATION

5.1.1 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.

5.1.2 Treatment Allocation

Eligible participants infected with genotype 1 HCV will receive Zepatier treatment for 12 weeks. Zepatier contains a combination of Grazoprevir and Elbasvir. 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 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 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.

6 DATA COLLECTION& MANAGEMENT

6.1 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.

6.2 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.

7 STATISTICS AND DATA ANALYSIS

7.1 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

7.2 PROPOSED ANALYSES

Analyses will be conducted according to the principles of intention to treat (ITT) and comply with the ICH E9 ‘Statistical Principles for Clinical Trials’ and carried out by the UKCRC registered Tayside Clinical Trials Unit (TCTU). A 2 sided p value of <0.05 will be taken as significant for all analyses.

As part of descriptive statistics, continuous variables will be summarised by the number of observations, number of missing values, mean, median, standard deviation (SD). Categorical variables will be summarised by the number of observations, number of missing values and number and percentage in each category. Summaries will be provided at baseline and at each subsequent time point and for the change from baseline by intervention group where appropriate.

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). 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. 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 Outcomes

To compare patient progression through the different trial pathway. A study flow chart will be constructed starting with the number of patients tested, the number tested positive, the number consenting, the number initiating treatment in each of the 3 arms and the number completing therapy. Secondary binary outcomes will be analysed using the same procedure, initially as intention to treat with all eligible patients as the denominator. The numerator being sequentially the number initiating treatment in each of the 3 arms and the number completing therapy, 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.

Adherence: to compare the longitudinal evolution of adherence to the prescribed regimen between the fortnightly dispensed groups and the DOT group. 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 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.

The remaining 3 secondary outcomes will be ad hoc analyses performed after the study report as they are dependent on numbers of treatment failures and will be irrelevant if small or dependent on long term follow up.

- 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.

7.3 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.

Table 1: Summary of Objectives, outcomes, proposed statistical analysis.

Objectives/ Research question	Outcome measure	Statistical analysis / variables
Primary		
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	SVR12 rates of participants in the DOT, fortnightly pick-up or fortnightly pick-up with a psychological adherence intervention group	Logistic regression models
Secondary		
To compare patient progression through the different trial pathway.	The number initiating treatment in each of the 3 arms and the number completing therapy in each arm	Logistic regression models
Compare adherence to therapy rates of subjects randomised to either DOT, fortnightly therapy or fortnightly therapy with psychological adherence intervention -	Adherence of daily directly observed therapy group from daily logs Adherence measured by counting tablets returned after each 2 week treatment period (fortnightly pickup groups). Adherence of participants infected with genotype 3 and treated with Sovaldi measured using MEMS® cap.	Logistic regression models
To assess reinfection rates in active PWIDs treated with oral DAA regimes	Hepatitis C viral load from PCR	ad hoc analyses performed after the study report as dependent on long term follow up.
To assess resistance profiles in those who do not achieve SVR.	Profiles of the HCV viral resistance proteins, NS5a and NS3	ad hoc analyses performed after the study report as they are dependent on numbers of treatment failures and will be irrelevant if small numbers.
To assess the types of illicit drugs taken by trial participants and identify any interaction with the DAAs.	Drug misuse history Urine toxicology	ad hoc analyses performed after the study report as they are dependent on numbers of treatment failures and will be irrelevant if small numbers.

Table 2: Summary of Outcome measure and Variable source.

Objectives	Outcome	Variable description / collection pointy	Variable name	Variable location
Primary	P1 - SVR rates at 12 months	12 weeks post treatment completion	SVR12	pCRF/OC – SVR Visit 'PCR for HCV detectable, yes/no?'
Secondary	S1 patient progression through the different trial pathway	The number initiating treatment in each of the 3 arms and the number completing therapy in each arm	Treatment initiation Did participant complete treatment?	pCRF/OC – Visit 2 attended, yes/no? pCRF/OC – End of study form 'yes/no?'
	S2 Adherence of daily directly observed therapy group from daily logs.	Daily log completed daily, adherence calculated at end of treatment	Adherence – total number of tablets remaining from total of 4 (G3) or 6 (G1) periods for zepatier and sovaldi (G3 only)	pCRF/OC – Daily Log
	S2 Adherence measured by counting tablets returned after each 2 week treatment period (fortnightly pickup groups).	Calculated at end of treatment	Adherence – total number of tablets returned at study visit or week. Study visit 3 and week 2&6 for G3 – Zepatier and Sovaldi Study visits 3&4 and week 2,6&10 for G1 – Zepatier only	pCRF/OC – Fortnightly Visit Log
	S2 Adherence of participants infected with genotype 3 and treated with Sovaldi measured using MEMS® cap	Calculated at end of treatment	Adherence	Excel spreadsheet downloaded from MEMS® software
	S3 Hepatitis C viral load from PCR	Annually at clinic visits	HCV PCR viral load	ICE – online clinical results system

	S4 Profiles of the HCV viral resistance proteins, NS5a and NS3	Blood collected at baseline, end of treatment and SVR_{12}	HCV Viral Resistance (if required)	ICE – online clinical results system
	S5 Drug misuse history	Baseline, end of treatment (genotype 1 infection = week12, genotype 3 infection= week8)	When did you last inject?	pCRF/OC – baseline and end of treatment – Illicit drugs
	S5 Urine toxicology	Once during treatment	Drug-drug interaction with medication (if required)	ICE – online clinical results system
Explanatory variables	Therapy, genotype, age, gender, deprivation, employment, comorbidity, and the psycho-social variables assessed	Baseline	Demographics, social history, medical history Therapy = genotype Genotype 1 = 12 weeks Zepatier Genotype 3 = 8 weeks Zepatier/Sovaldi	pCRF/OC – baseline (screening) pCRF/OC – baseline (blood test results screening)

8 DOCUMENT HISTORY

This is document was developed following the study protocol V5
The final version of Statistical Analysis Plan for all analyses of Advance trial is dated 06 September 2019.

9 REPORTING CONVENTIONS

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

10 TECHNICAL DETAILS

All analysis will be performed using SAS 9.4. All data, analysis programs and output will be kept on the TCTU Server and backed up according to the internal IT SOPs.

The analysis programs for outcomes will be reviewed by a second statistician, and any irregularities within the programs will be investigated and fixed and date of finalised analysis programs will be signed and recorded.

11 STATISTICAL REPORT

A statistical report will be created with all analyses according to the SAP. This will form the basis of any future paper or report and will be assessed for consistency.