1.0 Title Page

Full / Long Title

Response guided therapy with sofosbuvir and velpatasvir for 12 or 24 weeks in patients with genotype 3 chronic hepatitis C virus: is longer therapy worthwhile?

Short title and/or Acronym

Extend-3

Sponsor

Queen Mary University of London

Representative of the Sponsor:

Dr Sally Burtles
Director of Research Services & Business Development
Joint Research Management Office
QM Innovation Building
5 Walden Street
London
E1 2EF
Phone: 020 7882 7260
Email: sponsorsrep@bartshealth.nhs.uk

REC Number 16/LO/0879

Sponsor Reference 011094

2.0 Research Reference Numbers

IRAS Number:	200503
EudraCT Number:	2016-000599-87
ISRCTN Number / Clinical trials.gov Number:	Await UKCRN registration

3.0 Signature Pages

Chief Investigator Declaration

I confirm that the following protocol v2.9.3 date 13.11.16, has been written by me and I, as the Chief Investigator, agree to conduct the trial in compliance with this version of the protocol.

I will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and all subsequent amendments of the clinical trial regulations, current Research Governance Framework, the World Medical Association Declaration of Helsinki (1996), GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the study publically available through publication and/or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator: Graham Foster

Chief Investigator Site: Queen Mary University of London

Signature: .. ..

Date: 13.11.16

Name (please print):.....Graham R. Foster.....

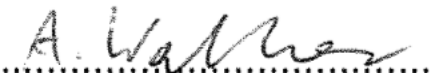
Statistician Declaration

The clinical study as detailed within this research protocol (Version 2.9.3 date 13.11.16), involves the use of an investigational medicinal product and will be conducted in accordance with the current Research Governance Framework for Health & Social Care the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials, ICH E10 - Choice of Control Groups and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Statistician: Alex J Walker

Job title: Medical statistician

Statistician Site/Organisation: University of Nottingham

Signature: ..... 
.....

Date: .13/11/2016

Name (please print): .....Alex Walker.....

Principal Investigator

I, as Principal Investigator confirm that I have read and understood the following protocol. I agree to conduct the trial in compliance with this version of the protocol. I will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and any subsequent amendments of the clinical trial regulations, current Research Governance Framework, GCP guidelines, the World Medical Association Declaration of Helsinki (1996), the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

Principal Investigator Name: Graham R Foster

Principal Investigator Site: Royal London Hospital, Barts Health NHS

Signature:..... .

Date: 13.11.16

Name (please print): .....Graham R. Foster.....

This page must be signed by each PI at every site, and kept in the ISF, a copy of this page must be sent to the lead site/coordinating centre as evidence.

4.0 Key Trial Contacts

Chief Investigator	Professor Graham Foster Liver Unit, Centre for Immunobiology Blizard Institute, Queen Mary University of London 4 Newark Street, London E1 2AT g.r.foster@qmul.ac.uk
Trial Co-ordinator/Manager	David Lieberman Clinical Research Centre Barts Health NHS
Sponsor	Queen Mary University of London
Laboratories	Local NHS laboratories (virology, haematology, biochemistry) Royal London Hospital St George's Hospital St Mary's Hospital King's College Hospital Royal Free Hospital
Funder(s)	National Institute for Health Research
Clinical Trials Unit	NA
Statistician	Alex J Walker University of Nottingham Alex.walker@nottingham.ac.uk
Trials pharmacist	James Rickard james.rickard@bartshealth.nhs.uk Rumbi Hungwe Rumbi.hungwe@bartshealth.nhs.uk Aidan O'Callaghan Aidan.OCallaghan@bartshealth.nhs.uk Victoria Low Victoria.Low@bartshealth.nhs.uk Barts Health NHS Trust Royal London Hospital Outpatients Pharmacy London E1 1BB 0203 594 6679/80
Committees (DMEC, TSC, TMG)	Trial Steering Committee (dual function as DMC) – William Irving, Stephen Ryder, Sulleman Moorea

5.0 Trial Summary

Full title	Response guided therapy with sofosbuvir and velpatasvir for 12 or 24 weeks in patients with genotype 3 chronic hepatitis C virus: is longer therapy worthwhile?
Short title and/or Acronym	Extend-3
Trial Design Methodology	Randomised, open-label
Phase of the Trial	IV
Study Duration	16 months from first recruit to when the last subject has completed all study processes 9 months recruitment maximum 16 weeks treatment period 12 weeks follow up
Study setting	Multisite (<10) within England, NHS
Investigational Medicinal Product(s)	sofosbuvir/velpatasvir for 24 weeks (12 weeks additional drug to standard treatment of 12 weeks)
Medical condition or disease under investigation	Chronic hepatitis C virus infection; liver cirrhosis
Planned Sample Size	60
(Maximum) Treatment duration	16 weeks (recruited to start at treatment week 8 out of 12; if randomised to extended treatment will complete further 12 weeks of treatment)
Follow up duration	3 months
End of Trial definition	3 months after last study visit of last randomised subject

6.0 Protocol Contributors

Key Protocol Contributors	Full contact details including phone, email and fax numbers
Graham R Foster (Chief Investigator)	g.r.foster@qmul.ac.uk 0207 882 7241/ 7242
Michelle CM Cheung (Coordinating centre principle investigator)	Michelle.cheung@qmul.ac.uk
Alex J Walker (Statistician)	Alex.walker@nottingham.ac.uk
David Lieberman (trial coordinator/ manager)	David.lieberman@bartshealth.nhs.uk
Victoria Low (pharmacist) Rumbi Hungwe (pharmacist) James Rickard (Assistant chief pharmacist)	Victoria.Low@bartshealth.nhs.uk Rumbi.hungwe@bartshealth.nhs.uk James.rickard@bartshealth.nhs.uk
Ayesha De Costa (senior lecturer in clinical trials - Pragmatic Clinical Trials Unit)	a.decosta@qmul.ac.uk
William Alazawi (Senior Lecturer and Consultant in Hepatology)	w.alazawi@qmul.ac.uk

7.0 List of Contents

8.0 List of Abbreviations / Glossary of Terms

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EudraVIGILANCE	European Union Drug Regulating Authorities Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISRCTN	International Standard Randomised Controlled Trial Number
JRO	Joint Research and Development Office
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
QMUL	Queen Mary University of London
QP	Qualified Person for release of trial drug

Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee

9.0 Introduction

9.1 Background

There are estimated 160,000 individuals chronically infected with hepatitis C virus (HCV) in England (0.4% of adult population), with a predominance of genotype 1 (45%) and genotype 3 (45%) HCV infections [1]. Chronic HCV infection causes progressive liver inflammation and fibrosis, leading to cirrhosis, when an individual becomes at risk of liver failure, liver cancer and death. In England there are estimated around 10,000 individuals with HCV-related cirrhosis or liver cancer [1].

The primary goal of HCV treatment is to eliminate viral replication, which is defined as a sustained virological response (undetectable HCV RNA 12 weeks after treatment completion (SVR12)). Standard of care treatment is rapidly changing with the approval of direct-acting antivirals (DAAs) that are highly effective at curing HCV and are well tolerated. DAAs achieve successful cure without using interferon, a drug associated with unpleasant side effects, which limit its use in many patients, particularly those with advanced liver disease or cirrhosis. For genotype 1 infected patients a number of DAA regimes are available and all offer high cure (SVR) rates of >90% in patients with cirrhosis [2-4]. For genotype 3 (G3) HCV infected patients with cirrhosis however, current treatment options are suboptimal. Approved interferon-free DAA regimes within the EU include 24 weeks of sofosbuvir + ribavirin, 24 weeks of sofosbuvir/ledipasvir + ribavirin, 24 weeks of sofosbuvir + daclatasvir +/- ribavirin, and most recently 12 weeks of sofosbuvir/velpatasvir +/- ribavirin.

Within the NHS in England, availability of interferon-free DAA therapies are restricted to specific subpopulations of patients with G3 HCV, chiefly determined by the presence of cirrhosis and intolerances to interferon. DAA treatments are very expensive - list price for a 12 week course costs in excess of £40,000, and regimes containing ribavirin can be associated with significant side effects (mainly anaemia, fatigue, pruritis and irritability). Therefore it is important to optimise the duration of treatment to minimise side effects and improve the cost effectiveness of therapy.

Clinical data on efficacy in genotype 3 HCV

For patients with G3 HCV and cirrhosis, 24 weeks of sofosbuvir + ribavirin achieves SVR in 68% [5]. Combinations with sofosbuvir (an inhibitor of the NS5B protein required for HCV replication) and an NS5A inhibitor (also targeting HCV replication) offer better cure rates with higher proportions of patients achieving SVR. NS5A inhibitors differ widely in their *in vitro* activity against genotype 3 HCV, with ledipasvir being significantly less active compared to daclatasvir or velpatasvir [6-8]

In a small clinical trial using sofosbuvir, ledipasvir and ribavirin for 12 weeks, 100% (in 26 patients) treatment-naive patients with cirrhosis achieved SVR, but this was reduced to 74% (16/22) for treatment-experienced patients who previously did not respond to interferon-based regimes [9]. The EU license recommends a conservative 24 weeks of treatment with ribavirin [6] but this combination is not NICE approved.

In a randomised trial of 152 patients with genotype 3 HCV treated with 12 weeks of sofosbuvir and daclatasvir, SVR for those with cirrhosis was markedly lower at 63% compared to those without cirrhosis at 96% [10]. In a smaller follow-on study involving 50 patients with advanced fibrosis or cirrhosis, the addition of ribavirin resulted in SVR of 88% after 12 weeks of treatment, and extending therapy to 16 weeks did not significantly increase the proportion of patients who responded [11]. In another small trial of 18 patients, which included those with advanced fibrosis and cirrhosis,

treatment with 24 weeks of daclatasvir + sofosbuvir +/- ribavirin achieved a SVR of 89% [12]. Again, clinical trial evidence did not allow robust conclusions regarding optimal duration of therapy for this drug combination, and authorities have adopted a conservative approach of licensing the maximal duration of 24 weeks. However 'real-world' data from patients with advanced cirrhosis treated outside of clinical trials showed that 12 weeks of sofosbuvir + daclatasvir + ribavirin is not inferior to 24 weeks [13-14]. Within the NHS in England, the 12 week regime is currently the first line recommended interferon-free treatment for patients with G3 HCV and cirrhosis, which differs from the license recommendation [7]. The 24 week regime is available if clinically indicated but without clear understanding of which patients the longer, more expensive treatment is indicated for.

In July 2016 the latest drug combination of sofosbuvir/velpatasvir +/- ribavirin became licensed in the EU and is in the process of being made available within the NHS, and is likely to replace sofosbuvir + daclatasvir due to more favourable pricing. In a phase 3 clinical trial, 12 weeks of sofosbuvir/velpatasvir in patients with G3 HCV and cirrhosis achieved SVR of 93% (40/43) and 89% (33/37) in treatment-naive and treatment-experienced cohorts, respectively [15]. For patients with decompensated cirrhosis (Child Pugh B cirrhosis), 12 weeks of sofosbuvir / velpatasvir resulted in only 50% SVR, which increased to 85% with addition of ribavirin, but was not improved with extension to 24 weeks of sofosbuvir/velpatasvir which achieved 50% SVR [16]. However the numbers treated were small with 12 to 14 patients per group. Compared to other genotypes where SVRs of nearly 100% were observed in non-decompensated patients, and nearly 90% in decompensated patients [16-17], G3 HCV remains more difficult to treat. The license therefore recommended that the addition of ribavirin to a 12 week regime may be considered for patients with G3 infection, and for patients with decompensated cirrhosis sofosbuvir/velpatasvir should be used with ribavirin for 12 weeks [8].

Ribavirin is associated with many side effects which are particularly difficult to tolerate in patients with advanced liver disease. In a direct comparison of DAA treatment with and without ribavirin within a randomised trial, ribavirin use was associated with higher proportions developing adverse events, in particular anaemia (31% with vs. 4% without ribavirin), which was not seen when extending treatment without ribavirin use [16]. 15% of patients treated with sofosbuvir/velpatasvir + ribavirin for 12 weeks required discontinuation of ribavirin due to adverse events. Therefore, optimising treatment to improve SVR without the need for ribavirin is hugely beneficial, offering the chance to improve cure in patients who are unsuitable or unwilling to take ribavirin. The most recent international treatment guidelines from European Association for Study of the Liver (EASL) recommends that for genotype 3 infected patients who are not suitable to take ribavirin, 24 weeks of sofosbuvir/velpatasvir is an option, but this guidance is at present based on limited data [23].

DAA treatments containing sofosbuvir and an NS5A inhibitor are extremely efficacious for the majority of patients, including those with traditional negative response predictors such as Afrocarribean race and obesity [18]. Genotype 3 HCV and cirrhosis adversely impact SVR but given the high cost of therapy, it is important to further define the subpopulation of patients who are at highest risk of treatment failure, in order that additional or modified treatments are worthwhile and cost-effective to offer.

Predictors of response

Analysis of nearly 500 patients with advanced cirrhosis treated with sofosbuvir + NS5A inhibitor +/- ribavirin within the NHS England Expanded Access Programme found detectable viral load at treatment week 2 to be a significant predictor of treatment failure (OR 2.6, 95% CI 1.1-6.3) [14]. The impact of on-treatment response was strongest for genotype 3 HCV, where there was a 20% difference in failure rate between patients who were viraemic versus non-viraemic by treatment

week 2 (32/10 (30.5%) vs. 7/70 (10.0%) [14]. Amongst 175 genotype 3-infected patients with available HCV result at treatment week 2, 105 (60%) remained viraemic. In this cohort week 2 viral response has a 82% sensitivity and 90% negative predictive value for treatment failure (unpublished data).

Similarly a subanalysis of the clinical trial of genotype 3 HCV infected patients who received sofosbuvir and the NS5A inhibitor daclatasvir showed that for those with cirrhosis, SVR 70% in week 2 viral responders, compared to 50% in patients with detected virus at week 2 [19]. In another study, viral response at week 2 or 4 of treatment with sofosbuvir/velpatasvir did not predict treatment outcome [20] but the analysis used a lower viral threshold than the one used in this protocol. In a further study of genotype 3 infections treated with a number sofosbuvir combination therapies, week 2 viral response again showed predictive value [26].

Proposed study

This trial will investigate if extension of sofosbuvir and velpatasvir treatment from 12 to 24 weeks improves efficacy (SVR rates) in genotype 3 infected patients who are difficult to treat, based on the presence of HCV ($\geq$ 30iu/mL) at treatment week 2.

We hypothesise that in patients who respond slowly to antiviral therapy, extending treatment from 12 to 24 weeks will lead to a significant improvement in SVR; conversely for patients who rapidly clear virus on treatment the standard duration is sufficient (response-guided therapy). We speculate that the magnitude of the improved response will be sufficient to justify marked increase in drug costs and any increase in side effects associated with the extended treatment duration.

Investigational Medicinal Product (IMP)

The study involves 2 drug compounds - sofosbuvir 400mg and velpatasvir 100mg, available as a fixed-dose combination single tablet, marketed under the brand name 'Epclusa'. The IMP is taken orally once per day for 12 weeks, in addition to standard 12 weeks of sofosbuvir/velpatasvir (total 24 weeks treatment).

The recommended treatment for all genotypes of HCV according to EU license is as follows:

- patients without cirrhosis and with compensated cirrhosis - Epclusa (sofosbuvir/velpatasvir 400/100mg) for 12 weeks; addition of ribavirin may be considered for genotype 3 infected patients with compensated cirrhosis
- patients with decompensated cirrhosis - Epclusa + ribavirin for 12 weeks

Patients co-infected with human immunodeficiency virus (HIV) and patients with recurrent HCV post-liver transplant follow the same recommendation.

Mechanism of action: Velpatasvir is an inhibitor of the HCV non-structural (NS) 5A protein, which exerts activity across all genotypes (1-6) of HCV. Sofosbuvir is an inhibitor of the HCV NS5B RNA polymerase. Both proteins are essential for HCV replication.

Safety: The safety profile of Epclusa is based on pooled data in 1035 patients from Phase 3 clinical studies of patients with or without compensated cirrhosis, who received 12 weeks of sofosbuvir/velpatasvir. The most frequently reported adverse reactions were headache (29%), fatigue (25%) and nausea (14%). These and other adverse events were reported at a similar frequency in placebo treated patients. The proportion of patients who discontinued treatment due to adverse events was 0.2% and the proportion of patients who experienced severe adverse events was 3.2%. [8]

The safety profile of sofosbuvir/velpatasvir (with and without ribavirin) in Child Pugh B decompensated cirrhosis has been evaluated in one open-label study of 267 patients, including 90 patients who received 24 weeks of sofosbuvir/velpatasvir (without ribavirin). Observed adverse events were consistent with the expected clinical sequelae of decompensated liver disease, or the known toxicity profile of ribavirin. Anaemia occurred in 3-4% in patients using 12-24 weeks of sofosbuvir/velpatasvir, which increased significantly to 31% with addition of ribavirin [16].

For further information on the clinical pharmacology, virology, safety and efficacy of sofosbuvir + velpatasvir, please refer to the Summary of Product Characteristics.

9.2 Assessment and management of risk

This study will provide information on the relative efficacy of 12 and 24 weeks treatment with sofosbuvir/velpatasvir in patients infected with genotype 3 HCV with cirrhosis who are difficult to cure. Successful treatment of HCV prevents or reduces the risk of decompensation of liver function, cancer development and death. G3 HCV is associated with accelerated progression of disease and higher risk of primary liver cancer compared to other genotypes of infection [21]. It is recommended that treatment should be prioritised for patients with advanced fibrosis or cirrhosis [22].

The real world safety profile of sofosbuvir + NS5A inhibitors are well established through compassionate use studies where large numbers of patients have been treated, and the safety of sofosbuvir/velpatasvir is described in a number of phase 3 clinical trials [13-17]. In general sofosbuvir/velpatasvir is very well tolerated. However ribavirin is associated with a wide range of side effects, chiefly anaemia with a reduction in haemoglobin of 30-40 g/L and irritability. Prolonged therapy increases the impact of the ribavirin associated anaemia and many patients prefer to avoid or minimise the duration of ribavirin exposure. The trial treatment avoids use of any ribavirin and thus offers benefits over the licensed regime which recommends adding ribavirin to a 12 week course of sofosbuvir/velpatasvir. This is in line with the latest international guidance from European Association of Study of the Liver that patients with genotype 3 HCV infection who have contraindications to the use of ribavirin, or poor tolerance to ribavirin on treatment should receive sofosbuvir and velpatasvir for 24 weeks without ribavirin [23].

As outlined above there is no clear evidence that extended duration of therapy with sofosbuvir/velpatasvir increases the response to therapy and therefore it is unclear whether or not the increased side effects associated with extended duration therapy are justified. In a direct comparison between 12 and 24 weeks of therapy in patients with advanced cirrhosis, there was no significant increase in adverse events observed in the extended duration [16]. Large cohort studies in patients with advanced liver disease have highlighted the potential risks of antiviral therapy with reports of rare but significant side effects including drug induced liver damage [24] and lactic acidosis [25]. Clearly prolonged exposure to unnecessary therapy should be avoided.

Response-guided therapy in which the duration of anti-viral therapy is modified depending upon early virological response was widely used in patients receiving interferon based treatments for chronic HCV infection [26]. This approach is therefore feasible and accepted by patients. However this approach has not yet been evaluated for DAA treatments aside from retrospective studies. Response guided therapy allows optimisation of scarce NHS resources providing significant population benefits and reduces drug exposure in individual patients, thereby reducing side effects. This trial therefore has the potential for both societal and individual patient benefits. The value of response-guided therapy for high cost DAA treatments and need for prospective trials to evaluate its utility has been recently widely discussed and called upon [27, 28].

There is no established second line therapy for patients who fail to respond after treatment with current DAA treatments, and retreatment is not offered on the NHS treatment programme. However clinical trials of new 'triple therapy' regimens involving sofosbuvir, novel NS5A inhibitors and novel protease inhibitors are on-going and it is probable that such treatments will be available in the near future.

Patients randomised to the 'shorter' study treatment arm may be disadvantaged if they have a lower chance of cure compared to those on the 'extended', and may develop drug resistance following failed therapy, but 12 weeks being the licensed duration is the standard of care offered within the NHS. If extension proves to offer little benefit, patients will have undergone longer, unnecessary treatment but trial data suggests there are minimal additional side effects. Within the NHS, regimes which differ from the licensed recommendation but with robust evidence supporting their use have been provided to improve the treatment options available. NHS England has agreed to support the additional funding for the extended study treatment, with a view to adopting response-guided treatment extension should it prove beneficial.

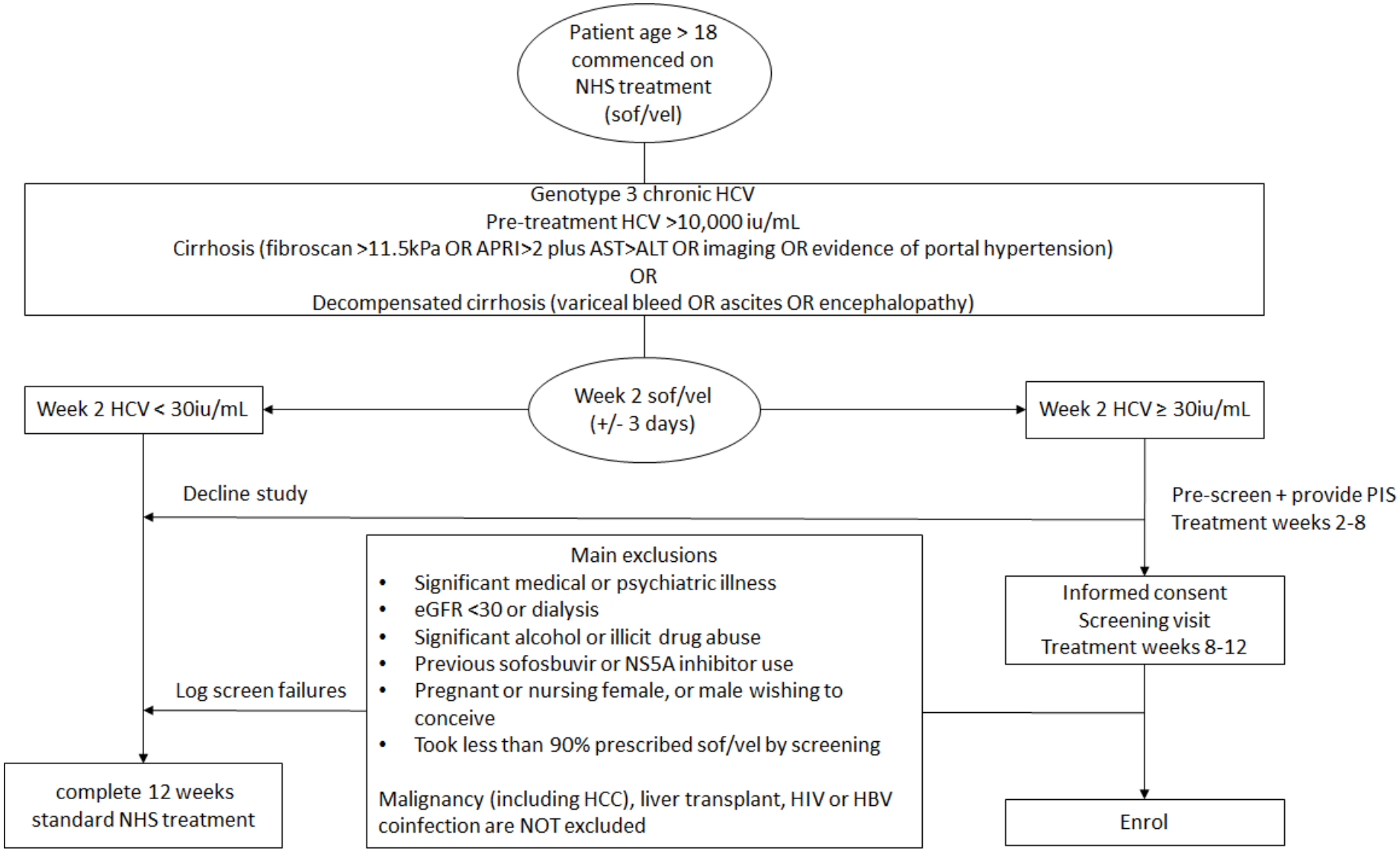
This trial is categorised as: Type B = Somewhat higher than the risk of standard medical care

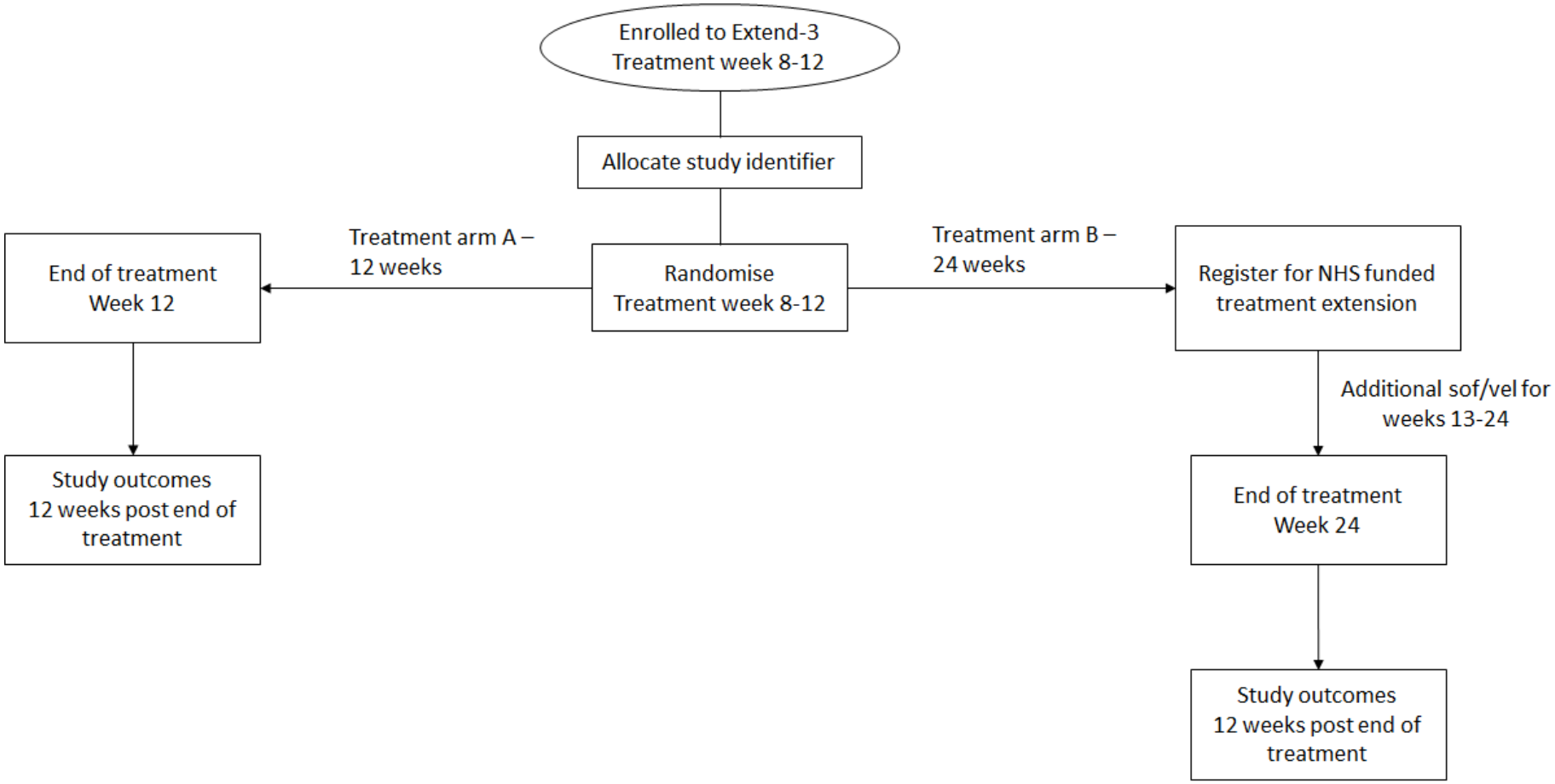
9.3 Rationale for study design

Randomised controlled trials provide the most robust data to show comparative efficacies of different treatments. In Extend-3, patients will be randomised to one of two durations of treatments in a parallel, open-label study. Clinical trial data from a small number of patients failed to show significant improvement with extended treatment, but this trial will select those patients who are 'slow' responders who have the highest risk of treatment failure, and thus have the highest potential to benefit from additional treatment. The trial will test the utility of a treatment response guided approach in selecting an appropriate duration of therapy.

Given there is published data on the safety profiles of 12 and 24 weeks of sofosbuvir/ velpatasvir, with no significant differences in adverse events or discontinuations, blinding will not further inform on their use. The primary end point of the trial is virological response, determined by an independent laboratory who will not be informed of the patient treatment allocation, and therefore the lack of patient blinding will not impair the integrity of the study.

10.0 Trial Flowchart




Enrolled to Extend-3
Treatment week 8-12
Allocate study identifier
Randomise
Treatment week 8-12
Treatment arm A –
12 weeks
Treatment arm B –
24 weeks
End of treatment
Week 12
Study outcomes
12 weeks post end of
treatment
Register for NHS funded
treatment extension
Additional sof/vel for
weeks 13-24
End of treatment
Week 24
Study outcomes
12 weeks post end of
treatment

11.0 Trial Objectives and Design

11.1 Primary Objective/s

To compare the efficacy (the proportion of randomised patients who achieve a sustained virological response – defined as undetectable HCV RNA (below limit of quantification up to 15 iu/mL) at 12 weeks (up to 16 weeks) after end of treatment – SVR12) of 12 OR 24 weeks of sofosbuvir/velpatasvir in patients with genotype 3 chronic HCV and cirrhosis, who have detectable viraemia (≥ 30 iu/mL) at week 2 (+/- 3 days) of treatment with sofosbuvir/velpatasvir.

Patients randomised must have completed at least 90% of sofosbuvir/velpatasvir at screening, and patients randomised to 24 weeks must have taken at least one dose of the extension phase treatment.

11.2 Secondary Objective/s

To assess the safety and tolerability of sofosbuvir/velpatasvir for 12 and 24 weeks.

To assess patient reported outcomes (defined as SF36 scores at the end of therapy) in patients receiving 12 or 24 weeks of sofosbuvir/velpatasvir

11.3 Endpoints

11.3.1 Primary Endpoint

Proportion of patients with undetectable HCV RNA (below limit of quantification up to 15 iu/mL) in serum at 12 weeks (+ 4 weeks) after end of treatment (SVR12)

11.3.2 Secondary Endpoint

- Proportion of patients requiring study treatment discontinuation
- Proportion of patients with serious adverse events (SAEs) during the study period. SAE is defined as a medical event which results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect
- Quality of life assessed by SF36 questionnaires at the end of study treatment and at the end of study follow up (3 months post-treatment)

11.4 Exploratory or Tertiary endpoints/outcomes

None

11.5 Objectives and End Points Summary

Primary Objective	Primary Endpoint	Outcome Measures
Compare efficacy between 12 and 24 weeks treatment (sofosbuvir/velpatasvir) in patients with genotype 3 HCV and cirrhosis who have detectable virus after 2 weeks therapy	SVR12 defined as HCV RNA below limit of quantification up to 15 iu/mL - 12 weeks (up to 16 weeks) after treatment discontinuation	• Proportion of patients in 12 week arm achieving SVR12 • Proportion of patients in 24 week arm achieving SVR24
Secondary Objective	Secondary Endpoints	Outcome Measures
	• Study treatment discontinuation • Serious adverse events • Quality of life questionnaire at treatment end • Quality of life questionnaire at 3 months post-treatment	Proportion of patients in 12 and 24 week arm developing any of listed secondary endpoints Quality of life score at the end of treatment and at 3 months post treatment, and change in scores over 3 months, for patients in 12 and 24 week treatment arm

11.6 Trial Design

This is an open-label, parallel design study of 12 and 24 weeks of sofosbuvir/velpatasvir. Subjects are initially started on NHS standard of care treatment, and are consented to participate between treatment week 8-12 (of the standard 12 week course). This design is chosen for several reasons:

- To maximise the time between fulfilling entry criteria (i.e. week 2 ≥ 30iu/mL) and consent, to allow subjects time to consider participation
- Given sofosbuvir/velpatasvir is generally well tolerated, early discontinuation is usually due to non-adherence. By recruiting patients after at least 8 weeks, the study is more likely to recruit subjects willing to adhere to extended treatment. The study specifies that subjects have taken at least 90% of prescribed drugs by screening
- Sofosbuvir/velpatasvir is an expensive treatment and in order to prevent wastage of prescribed NHS treatment when subjects commence on the trial, they are recruited only after the final prescription (each prescription is for one bottle of sofosbuvir/velpatasvir which contains 4 weeks of drug) has been dispensed at treatment week 8. Therefore, only subjects randomised to extended treatment will be dispensed with study drugs.

Maximum duration of participation is 16 weeks for Arm A (12 weeks treatment) - 4 weeks of observation during standard of care treatment, 12 weeks of follow-up, and 28 weeks for Arm B (24 week treatment arm) – 16 weeks of study treatment (4 weeks of standard of care treatment plus 12 weeks of additional IMP treatment), 12 weeks of follow-up.

Treatment week 0 is defined as commencement of sofosbuvir/velpatasvir on NHS treatment programme, before enrolment into the study. Subjects can be pre-screened for study eligibility once week 2 virological response becomes available. Patient information sheet can be provided to interested subjects, but they cannot be consented to participate until week 8 of treatment. Screening and randomisation can take place until the end of standard treatment at week 12.

Upon enrolment into the study until treatment week 12, subjects will proceed according to protocol but they will complete drugs prescribed as part of NHS treatment prior to enrolment. This is in order to reduce wastage of high cost drugs. Sites must ensure sufficient time between enrolment and end of 12 weeks treatment, to dispense additional IMP for participants randomised to arm B (24 weeks).

Study visits are as follows:
Arm A (12 weeks of sofosbuvir/velpatasvir)
Screening / baseline (treatment week 8 up to week 12)
Randomisation by coordinating centre
Treatment week 12 (end of study treatment)
Treatment week 16 (post treatment week 4)
Treatment week 20 (post treatment week 8)
Treatment week 24 (post treatment week 12 – study endpoints & end of study)

Arm B (24 weeks of sofosbuvir/velpatasvir
Screening / baseline (treatment week 8 up to week 12)
Randomisation by coordinating centre
Treatment week 12
Treatment week 16
Treatment week 20
Treatment week 24 (end of study treatment)
Treatment week 28 (post treatment week 4)
Treatment week 32 (post treatment week 8)

Treatment week 36 (post treatment week 12 – study endpoints & end of study)

11.7 Study Setting

Multi-site study within NHS England, with approximately 5 sites planned:

- Royal London Hospital, London
- Royal Free Hospital, London
- St Mary's Hospital, London
- King's College Hospital, London
- St George's Hospital, London

These sites are selected based on their role as leads or 'hubs' for the regional NHS HCV treatment programme, or 'Operational Delivery Network (ODN)'. They are also experienced clinical trial centres. Hub sites host regular (usually weekly) multidisciplinary team meetings to decide HCV management decisions for patients within the ODN, which may consist of patients from different hospitals within the same NHS Trust, or patients from hospitals within the geographical region but of another NHS Trust.

NHS England mandates that every patient started on direct acting antivirals (including sofosbuvir/velpatasvir) treatment is managed through an MDT, such that treatment decisions which may include participation in clinical trials, can be openly considered, and there is equity of access to expertise regardless of the location of the patient.

Through this NHS infrastructure, patients potentially eligible for the study will be identified through the usual care pathway. The study will recruit from 5 NHS 'hubs', which manages patients referred in from hospitals within the Operational Delivery Network, thus increasing the reach of the study. Enrolled participants will be treated at the study site (i.e. hub site) which leads the ODN they belong to, regardless of their referring hospital.

The Trial Steering Committee will review recruitment during the trial period (e.g. at around month 6) and if recruitment is inadequate, additional sites outside of London which are NHS England treatment hubs will be considered.

12.0 Eligibility Criteria

12.1 Inclusion Criteria

A total of 60 participants will be enrolled. Participants must meet all of the following criteria to be eligible:

- Voluntarily signed informed consent form
- Aged 18 years or older
- Chronic HCV infection, defined by anti-HCV antibody or HCV RNA detection for greater than 6 months
- Infected with genotype 3 HCV (identified by referring hospital)
- Meets NHS England treatment criteria to commence sofosbuvir/velpatasvir
- Pre-treatment HCV RNA >10,000 iu/mL (can be any time before treatment week 0)
- HCV RNA > or equal to 30 iu/mL at treatment week 2 (+/- 3 days)

- Has cirrhosis defined by: evidence of portal hypertension, OR APRI >2 plus AST:ALT ratio >1, OR radiological evidence of cirrhosis, OR fibroscan score >11.5kPa, OR liver biopsy showing cirrhosis
- Patients with decompensated cirrhosis (variceal bleeding, ascites and encephalopathy) can be included
- Patients with malignancy including hepatocellular carcinoma can be included
- Patients with liver transplant can be included
- Patients coinfected with chronic hepatitis B virus or human immunodeficiency virus can be included
- Female subjects of childbearing potential must have documented negative pregnancy test prior to enrolment (negative urinary pregnancy test), and if engaged in heterosexual intercourse must use protocol specified method of contraception (see below) during study drug treatment and for 30 days after last dose
- Male subjects engaged in heterosexual intercourse with a female of childbearing potential should protocol specified method of contraception during study drug treatment and for 30 days after last dose

12.2 Exclusion Criteria

- Any of the above inclusion criteria not met
- Any of the following criteria excludes a subject from enrolling into this study
- Clinically-significant medical or psychiatric illness (other than chronic HCV) in the past, present, or being evaluated, that may interfere with participant treatment, safety, assessment or compliance with the protocol.
- Severe renal impairment with eGFR <30 mL/min/1.73m^2 or requiring dialysis
- Alcohol consumption or illicit drug abuse likely to interfere with participant treatment, safety, assessment or compliance with protocol, as deemed by the investigator
- Previous exposure to sofosbuvir (or other NS5B inhibitor) or NS5A inhibitor
- Severe allergy to study drugs, its metabolites or formulation excipient (see SmPC for details)
- Any investigational medicinal product ≤ 6 weeks prior to treatment start
- Pregnant or nursing female, or males wishing to conceive during the period of study treatment + 30 days after
- Patients who adhered to less than 90% of prescribed sofosbuvir/velpatasvir at screening
- In accordance with the SmPC of sofosbuvir/velpatasvir concomitant use of the following medications are contraindicated:

  Anticonvulsants - carbamazepine, phenytoin, phenobarbital, oxcarbazepine
  Antimycobacterials – rifampicin, rifabutin, rifapentine
  Antiretrovirals - efavirenz
  St John's wort
  Modafinil
  Proton-pump inhibitors should be avoided and if necessary, should be administered 4 hours after at maximum doses equivalent to 20mg omeprazole per day.
  Amiodarone should be avoided and if necessary, close monitoring is required

  Please consult the SmPC and Section 15.16 and 17 for list of medications to be used with caution or monitoring.

Participants taking these medications must have discontinued prior to starting sofosbuvir/velpatasvir (this is expected to be in line with standard care practice). Definition of child-bearing potential and effective contraception:

Subjects are considered not of child-bearing potential if they are surgically sterile (undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal (women aged ≥ 45 years of age with cessation of previously occurring menses for ≥ 12 months) or they have medically-documented ovarian failure.

Effective contraception include:

- True abstinence: when this is in line with the preferred and usual lifestyle of the subject (Periodic abstinence, e.g. calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of the trial, and withdrawal are not acceptable methods of contraception)
- Male partner vasectomy or other medical condition causing azoospermia
- Male partner using condom
- Intrauterine device
- Female barrier method (cervical cap or diaphragm with spermicidal agent)
- Tubal sterilisation
- Levonorgestrel implant
- Injectable progesterone
- Oral contraceptive (combined or progesterone only)
- Contraceptive vaginal ring
- Transdermal contraceptive patch

13.0 Trial Procedures

13.1 Recruitment

13.2 Participant identification

Within the NHS HCV treatment delivery pathway, all treatment centres in England are arranged in networks according to geographical regions, with a centre lead or 'hub' which coordinates treatment decisions via multidisciplinary team (MDT) meetings. All sites within the study are approved centre leads for London, thus facilitating participant identification and recruitment. In accordance with European guidelines, NHS England mandates that all patients receiving NHS funded therapy undergo viral load testing after 2 weeks of treatment. Recruiting centres will monitor all potentially eligible patients who have initiated antiviral therapy and those who are viraemic after 2 weeks will be contacted by their treating centre and asked to consider enrolment in the study. Those who agree to consider the trial will be provided with the patient information sheet and offered an opportunity to discuss the trial with the study team. Those who agree to participate will sign the informed consent form and then undergo screening prior to enrolment in the trial.

13.3 Informed Consent Procedures

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are outside standard routine care at the participating site (including the collection of identifiable participant data).

13.3.1 Responsibility for obtaining consent

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent occurs then details should be provided in the Site Delegation Log.

Consent should be taken by a doctor within the study.

13.3.2 Consent Considerations

The right of a participant to refuse participation without giving reasons will be respected.

The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent, for example if during the trial new Research Safety Information becomes available, or following an amendment that affects the patient, or new information needs to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner.

13.3.3 Population

The study population is of patients chronically infected with genotype 3 HCV and compensated or decompensated cirrhosis. Subjects are selected based on poor predicted response to treatment with sofosbuvir/velpatasvir (on the NHS programme), defined by persistence of HCV (≥30 iu/mL) in patient serum after 2 weeks (+/-3 days) of therapy.

13.3.4 Vulnerable participant's considerations

NA

13.3.5 Written/ reading / translation considerations

Owing to the ethnic diversity of London, significant number of participants who cannot read or write in English, or cannot read or write at all, may be involved in this study. This is particularly as genotype 3 HCV is common amongst South Asians. It would be impractical for this study to make available translated versions of study documents in many languages. Instead, the study requires that oral translation is available to facilitate consent, e.g. via telephone translator service, hospital translator, or an impartial translator who is not part of the study (family members should not be used for consenting). The translator will sign the consent form as well as the participant. Where a telephone service is used, the investigator will sign that translation has taken place to facilitate consent. Where participants cannot sign consent, such as due to lack of written language, an impartial witness (such as the translator) can sign on their behalf.

13.3.6 Participants lacking capacity

This study excludes participants unable to provide informed consent. Conditions such as severe psychiatric illness or hepatic encephalopathy, or participants under influence of alcohol or illicit drugs which impair their capacity to consent, are excluded. This is at the discretion of investigators to judge.

13.3.7 Minors

NA

13.3.8 Consenting process

The investigator is responsible for obtaining written informed consent from each participant after adequate explanation of the study aims, methods, and possible risks. Patient Information Sheet and consent form approved by REC and in compliance with GCP, local regulatory requirements and legal requirements should be provided. The investigator who is taking consent is responsible for assessing the capacity of the participant to sign informed consent.

Patients deemed suitable for the study by their treating physician will be asked to consider participating. Those willing to consider participating in the study will be provided with a Patient Information Sheet. Participants must be allowed opportunities for questions and at least 24 hours to consider their participation. The date that the Patient Information Sheet is given to the participant must be documented within the medical notes to ensure that sufficient time is given. If for any reason, less than 24 hours is given, the justification for this should be documented.

13.3.9 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies

None

13.4 Screening Procedures

Following consent, participants are screened for inclusion/exclusion criteria. All participants who undergo screening should be logged and the investigator who performed this assessment should be documented.

Screening takes place between treatment week 8 up to end of treatment week 12. Sites must ensure that there is sufficient time between screening and end of week 12 treatment for additional IMP dispensing for participants randomised to arm B (24 weeks treatment), such that there is no interruption in study drug supply.

Review of clinical records for eligibility

- Anti-HCV antibody or HCV RNA detection for greater than 6 months before screening
- HCV genotype 3

- Document pre-treatment HCV viral load – must be >10,000 iu/mL (use last result at any time before treatment week 0)
- Commenced NHS treatment with sofosbuvir/velpatasvir
- Document date and result of HCV RNA at treatment week 2 (+/- 3 days) – must be detectable HCV (≥30 iu/mL, Roche TaqMan quantitative test, or other validated methods)
- Document criteria for determining cirrhosis (evidence of portal hypertension, OR APRI >2 plus AST:ALT ratio >1, OR radiological evidence of cirrhosis, OR fibroscan score >11.5kPa, OR liver biopsy showing cirrhosis)
- Document presence (or history of) decompensation (variceal bleeding, ascites and encephalopathy)
- Any liver imaging (e.g. USS/CT/MRI) within 6 months of treatment week 0 – to document presence of hepatocellular carcinoma
- Document previous history of hepatocellular carcinoma or other malignancy
- Document if co-infected with chronic hepatitis B virus (HBsAg) or HIV (antibody)
- Document complete medical, surgical and psychiatric history, and investigator assessment of suitability for trial enrolment
- Baseline eGFR (within 3 months of treatment week 0) must be >30 ml/hr and patient not requiring dialysis
- Current alcohol and illicit drug use - if positive history, document whether investigator deems participant suitable
- Document previous hepatitis C treatment history (pegylated interferon, ribavirin, DAA, trial medication), response to treatment and any adverse events or intolerances
- No previous exposure to sofosbuvir (or other NS5B inhibitor) or NS5A inhibitor
- Document complete drug history – see Exclusions for list of prohibited concomitant medications.
- Document allergies
- Document if any investigational medicinal product ≤ 6 weeks prior to treatment start
- Document participant is not a pregnant or nursing female, or wishing to conceive during the study treatment period + 30 days after
- Document adherence to sofosbuvir/velpatasvir (reported number of missed pills) from treatment week 0 (NHS programme) to screening date – participants must have at least 90% adherence

Document contraception and breast-feeding advice, and currently in use or chosen method of protocol-specified contraception (if applicable)

Examination to assess eligibility (must be performed by study doctor)

- Physical examination – cardiovascular, respiratory, gastrointestinal, others as deemed appropriate by study doctor
- Document if any active decompensation

Tests

- check for negative urine b-HCG for females of child-bearing potential

Record baseline laboratory tests (within 3 months of treatment week 0) and date of tests: haemoglobin, platelets, bilirubin (total), alanine transaminase (ALT) albumin, creatinine, eGFR (Cockcroft-gault or MDRD formula)

A log of participants who are screened but not randomised should be documented. For CONSORT reporting, those not randomised should have demographic data (age, gender, ethnicity), whether enrolled, documented. The reason for not undergoing randomisation should be documented.

13.5 Patient Allocation

13.5.1 Randomisation Method

Participants who fulfill inclusion/ exclusion criteria will be randomised. This takes place anytime after enrolment between treatment week 8 to 12. Sites must ensure sufficient time to randomise participants and dispense additional IMP for those in the arm B (24 weeks) such that there will not be more than 24 hours before commencing week 13 treatment.

Participants will be allocated into treatment arms A and B in a 1:1 ratio, by block randomisation, and stratified by whether they have compensated cirrhosis or decompensated cirrhosis at baseline. Participants with previous history of decompensation will be considered as having decompensated cirrhosis for the purpose of stratification. This is in order to generate equal numbers within each arm, with balanced severity of liver disease distributed. Clinical trial data suggests that severity of liver disease and presence of decompensated cirrhosis are one of the most important factors determining treatment outcome [8].

There may be other patient factors which influence treatment success, but further stratification for a study of 60 participants would not be appropriate. Block randomisation will enable interim analysis to be performed with balanced groups.

13.5.2 Randomisation Procedure

Stratified block randomisation will be performed using a computer or web-based system. This will be performed by the Pragmatic Clinical Trial Unit, QMUL, with a trial-specific randomisation procedure. Anonymised randomisation outcome can be accessed by the trial coordinator and/or study investigator.

Unblinding or emergency access to randomisation codes will not be required for this open-label study.

13.5.3 Cohort allocation/sequential allocation

NA

13.6 Blinding

NA

13.7 Unblinding

NA

13.8 Trial Schedule

13.8.1 Schedule of Treatment for each visit

13.8.2 Schedule of Assessment (in Diagramatic Format)

Study Visits Schedule for Arm A – 12 weeks of sofosbuvir/velpatasvir							
	Treatment week	0-8	8-12	12	16	20	24
	Visit windows			+/- 7 days	+/- 14 days	+/- 14 days	+ 28 days
Assessments		Pre-enrolment	Screening/ baseline	End of treatment	Post treatment	Post treatment	End of study
NHS treatment visits		x					
Informed consent			x				
Review inclusion/exclusions	Supply participant card		x				
Randomisation			x				
Pregnancy test (if applicable)	Urine test		x				
Document contraception/ breastfeeding advice (if applicable)			x	x	x		
Record demographics			x				
History			x				
Physical examination	Cardiovascular Respiratory Gastrointestinal		X X X				
Review concomitant medications			X	x			
Prescription and dispensing of NHS treatment		x					
Prescription and dispensing study drugs							
Drug accountability	Record missed doses		x	x			
Adverse events recording	Events since week 0 Events since last visit		x	 x	 x	 x	 x
Laboratory samples	FBC Urea & electrolytes, creatinine LFTs Albumin HCV RNA			X X X X X X	X X X X x (optional)	X X X X x (optional)	X X X X X x
Quality of life questionnaire				x			x

Study Visits Schedule for Arm B – 24 weeks of sofosbuvir/velpatasvir							
	Treatment week	0-8	8-12	12	16	20	24
	Visit windows			+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days
Assessments		Pre-enrolment	Screening/ baseline	Study treatment	Study treatment	Study treatment	End of treatment
NHS treatment visits		x					
Informed consent			x				
Review inclusion/exclusions	Supply participant card		x				
Randomisation			x				
Pregnancy test (if applicable)	Urine test		x				
Document contraception/ breastfeeding advice (if applicable)			x	x	x	X	X
Record demographics			x				
History			x				
Physical examination	Cardiovascular Respiratory Gastrointestinal		X X X				
Review concomitant medications			X	x	X	X	X
Prescription and dispensing of NHS treatment		x					
Prescription and dispensing study drugs				X	X	X	X
Drug accountability	Record missed doses		x	x	X	X	X
Adverse events recording	Events since week 0 Events since last visit		x	 x	 x	 x	 x
Laboratory samples	FBC Urea & electrolytes, creatinine LFTs Albumin HCV RNA			X X X X x (optional)	X X X X x (optional)	X X X X x (optional)	X X X X X x
Quality of life questionnaire							x

	Treatment week	28	32	36
	Visit windows	+/- 14 days	+/- 14 days	+ 28 days
Assessments		Post treatment	Post treatment	End of study
NHS treatment visits				
Informed consent				
Review inclusion/exclusions				
Randomisation				
Pregnancy test (if applicable)	Urine test			
Document contraception/ breastfeeding advice (if applicable)		x		
Record demographics				
History				
Physical examination	Cardiovascular Respiratory Gastrointestinal			
Review concomitant medications				
Prescription and dispensing of NHS treatment				
Prescription and dispensing study drugs				
Drug accountability	Record missed doses			
Adverse events recording	Events since week 0 Events since last visit	 X	 X	 x
Laboratory samples	FBC Urea & electrolytes, creatinine LFTs Albumin HCV RNA	X X X X x (optional)	X X X X x (optional)	X X X X X x
Quality of life questionnaire				x

13.8.3 Trial assessments

Pre-Screening
All adult patients infected with genotype 3 HCV with cirrhosis (see eligibility for definition), who commenced on NHS treatment with sofosbuvir/velpatasvir, with HCV RNA above or equal to 30 iu/mL at treatment week 2 (+/- 3days) can be considered for study entry. Clinicians will inform patient of their slow response to therapy, risk of treatment failure and potential improvement with extended treatment, and offer enrolment in the study. If patient accepts invitation, clinician will contact the study team to provide the Patient Information Sheet for his or her to review.

Screening/ baseline
Treatment weeks 8 up to 12

After a patient gives informed consent to participate, the following will be performed:

- document date when participant receives PIS (at least 24 hours before consent)
- 3 copies of informed consent signed
- enter participant into screening log (for those not enrolled, document reason e.g. not fulfilling inclusion/exclusion criteria)

Note consent must be taken by a study doctor.

Determine inclusion / exclusion criteria

- document genotype, baseline HCV viral load and date(last result prior to treatment week 0, must be >10,000 iu/mL to be eligible), HCV viral load at treatment week 2 (+/-3 days)
- document criteria used to determine cirrhosis or decompensated cirrhosis from clinical records
- document any imaging (e.g. ultrasound / CT / MRI, with dates) within 6 month before treatment start, if available – to determine presence of hepatocellular carcinoma
- document hepatitis B virus and HIV status
- for females of child-bearing potential only - urinary pregnancy test negative
- document contraception and breast-feeding advice in the medical records
- document complete medical, surgical and psychiatric history – and study doctor assessment of whether subject is eligible
- document baseline (within 3 months of treatment week 0) laboratory tests – eGFR must be >30ml/hr and patient not requiring dialysis
- document alcohol and illicit drug use – and study doctor assessment of whether subject is eligible

Document demographics

- date of birth
- gender
- ethnicity (Caucasian, Asian, Oriental, Afrocarribean, others)

Obtain history

- previous HCV treatment experience (pegylated interferon/ribavirin; clinical trial; DAA) - note participants exposed to SOF (or other NS5B inhibitor) or DCV (or other NS5A inhibitor) are excluded
- document responses and any adverse events or intolerances to previous treatment, if known

Physical examination - full examination of the cardiovascular, respiratory, gastrointestinal systems as minimum. Assessment of whether the subject has active hepatic decompensation. Other systems as deemed appropriate by investigator.

This should be completed by a study doctor.

Record concomitant medications including over the counter and herbal medications

- review drug-drug interactions (see protocol Trial Medication section, sofosbuvir/velpatasvir SmPC and www.hep-druginteractions.org for guidance)
- prohibited concomitant medications must be discontinued at least 21 days before treatment start as per Exclusions section of protocol
- other investigational medicinal products within 6 weeks of treatment start are excluded
- record if known allergy to any of study drugs

Document if participant is pregnant, breastfeeding, or wishing to conceive during the study treatment period + 30 days after

Document contraceptive and breast feeding advice (if applicable) and currently in use or chosen method of protocol specified contraception.

Record baseline laboratory results and dates (within 3 months of treatment start)

- haemoglobin
- platelet count
- urea & electrolytes, creatinine
- eGFR (using Cockcoft-Gault or MDRD formula) NB eGFR <30ml/hr is an exclusion
- total bilirubin
- ALT
- INR or PT (include lab reference PT range), if available
- Albumin

Record the following regarding current treatment

- start date of sofosbuvir/velpatasvir (treatment week 0)

Record the following between treatment start and screening visit

- Any adverse events/ serious adverse events
- Any treatment discontinuation (of Sofosbuvir/velpatasvir)
- Any missed doses of treatment reported – note patient must have at least 90% adherence at screening
- Record batch/lot number and expiry of NHS dispensed bottle of sofosbuvir/velpatasvir

Study doctor must assess whether subject fulfils eligibility.

Note: enrolled participants will complete sofosbuvir/velpatasvir dispensed as part of their NHS treatment and are not dispensed additional study drug, unless they are randomised to the extended treatment arm.

Investigators should review administration instructions with participant and remind them to bring empty bottle for pill check at the next visit.

Study assessments

Once enrolled (treatment weeks 8 up to 12), participants will be randomised. Randomisation must occur before the last dose of treatment at week 12 so that participants in the 24 week arm will be supplied with adequate study drugs. Study sites must ensure there is sufficient time to arrange dispensing of additional study drug so that treatment is not interrupted.

After the participant is enrolled they will carry a patient card to identify them as part of the study.

Visits outside of the study schedule are permitted - relevant data will be captured at the next study visit as per protocol.

Treatment week 12 (study window +/- 7 days) – for arm A (12 weeks) – end of treatment

Record the following between screening visit and end of treatment:

- Concomitant medications review
- Any adverse events/ serious adverse events
- Any treatment discontinuation (of Sofosbuvir/velpatasvir)
- Any missed doses of treatment reported - investigators will perform pill count and review returned empty bottles

If participants have left over medication, at the discretion of the study doctor they can complete the remainder tablets, but the end of treatment visit must take place within 7 days of completing medication.

Perform blood samples - FBC, U&Es, creatinine, LFTs, albumin, HCV viral load

Document contraception advice and currently used method (if applicable).

Obtain quality of life questionnaire (SF36) at end of treatment – this does not have to be at the same time as the other visit procedures as long as it is obtained within the visit window

Other procedures or examination performed, as deemed appropriate by investigator, should be recorded in medical notes.

Treatment week 12, 16, 20 (study window +/- 7 days) – for arm B (24 weeks)

Record the following between previous visit and this visit:

- Concomitant medications review
- Any adverse events/ serious adverse events
- Any treatment discontinuation (of Sofosbuvir/velpatasvir)
- Any missed doses of treatment reported - investigators will perform pill count and review returned empty bottles

Perform blood samples - FBC, U&Es, creatinine, LFTs, albumin. HCV viral load is optional – record if available

Document contraception advice and currently used method (if applicable).

Dispense study medication

- Drugs are prescribed and dispensed every 28 days
- Record batch or lot number, expiry date of dispensed drugs, and date of dispensing
- review administration instructions with participant

Participants who have lost or insufficient medication, at the discretion of their investigator, can have the next due prescription dispensed early. Missing doses should be recorded. (see section 15.19 on assessment of compliance).

Other procedures or examination performed, as deemed appropriate by investigator, should be recorded in medical notes.

Treatment week 24 (study window +/- 7 days) – for arm B (24 weeks) – end of treatment

Record the following between screening visit and end of treatment:

- Concomitant medications review
- Any adverse events/ serious adverse events
- Any treatment discontinuation (of Sofosbuvir/velpatasvir)
- Any missed doses of treatment reported - investigators will perform pill count and review returned empty bottles

If participants have left over medication, at the discretion of the study doctor they can complete the remainder tablets, but the end of treatment visit must take place within 7 days of completing medication.

Perform blood samples - FBC, U&Es, creatinine, LFTs, albumin, HCV viral load

Document contraception advice and currently used method (if applicable).

Obtain quality of life questionnaire (SF36) at end of treatment – this does not have to be at the same time as the other visit procedures as long as it is obtained within the visit window

Other procedures or examination performed, as deemed appropriate by investigator, should be recorded in medical notes.

Post-treatment follow up - treatment week 16 & 20 (+/-14 days) for arm A (12 weeks) or treatment week 28 & 32 (+/-14 days) for arm B (24 weeks)

Record the following since the last study visit

- Any serious adverse events

Perform blood samples - FBC, U&Es, creatinine, LFTs, albumin, optional HCV viral load

Document contraception advice and currently used method (if applicable) – required up to 30 days after last dose of study drug.

Other procedures or examination performed, as deemed appropriate by investigator, should be recorded in medical notes.

End of study - treatment week 24 (+ 28 days) for arm A (12 weeks) or treatment week 36 (+ 28 days) for arm B (24 weeks)

Record the following since the last study visit

- Any serious adverse events

Perform blood samples - FBC, U&Es, creatinine, LFTs, albumin, HCV viral load

Obtain quality of life questionnaire (SF36) at end of treatment – this does not have to be at the same time as the other visit procedures as long as it is obtained within the visit window

Other procedures or examination performed, as deemed appropriate by investigator, should be recorded in medical notes.

Study team notifies participant's usual clinician that participant has reached trial endpoints, and returns them to the usual care pathway.

13.8.4 Follow up Procedures

After the final study visit at 3 month post-treatment, participants will be returned to their routine clinical care pathway. Investigators will inform the patient's usual clinician of the outcome of antiviral treatment - whether the patient has achieved HCV cure or not, which can be determined based on assessments during this study visit.

Participants who withdraw from the study will be returned to their routine care pathway at the point of withdrawal. They may consent to allow the study team to collect treatment virological outcome (at 3 months post-treatment) from their usual clinician. Participants who withdraw from treatment but consent to continue with study follow-up will be returned to their routine care at 3 months post-treatment.

13.8.5 Qualitative assessments – Nested studies

NA

13.8.6 Radiology Assessments

NA

13.9 Withdrawal criteria

Participants have the right to withdraw consent for study participation at any time. Participants will be informed before enrolment that if they wish to withdraw from the study, or if they are withdrawn for any reasons (such as those listed below), study treatments will be discontinued and no further study procedures or visits will be performed. However, participants will be asked at enrolment to consent to having their treatment virological outcome (SVR at 12 weeks after treatment discontinuation) collected, if available. Participants can opt to withdraw this consent, and withdraw

completely from the study; at this point no further data will be collected. Data obtained up to the point of withdrawal will be kept.

When a participant is withdrawn from the study, this is recorded in the medical notes, along with his or her consent (or withdrawal of consent) for collection of treatment virological outcome data.

Participants who withdraw from the study will be notified that they will discontinue treatment with study drugs, and unused study drugs must be returned. They have the option to continue treatment with sofosbuvir/velpatasvir (or other HCV treatment regimes) as routine NHS standard of care at the discretion of their usual clinician. If a participant withdraws during treatment week 8-12, while taking the NHS-supplied sofosbuvir/velpatasvir, the drugs should be returned according to the local NHS pharmacy policy and they may continue to use the drugs on the advice of their usual clinician.

Participants who experience intolerable toxicity or for other clinical reasons according to the investigator can discontinue the study drugs. Dose reduction of sofosbuvir/velpatasvir is not permitted. Participants who discontinue treatment can remain on the study (for follow up) provided they do not withdraw consent.

Any female participant who becomes pregnant during the treatment period will be withdrawn from treatment. Outcome of pregnancy will be followed up (which may occur after the planned study period), including spontaneous or voluntary termination, birth defects, maternal and/or newborn complications, and will be recorded as a significant adverse event. Any female participant who becomes pregnant during treatment and in the first 30 days after treatment end may remain on the study and be followed up as protocol. Any male participant who has conceived with a female partner during treatment or for 30 days after treatment end may remain on the study, but will be consented to follow up the outcome of the conception.

There are no stopping rules for treatment related to treatment response outcome, i.e. participants should continue the entire treatment duration (12 or 24 weeks depending on treatment arm) regardless of their viral response on treatment. Participants who do not achieve negative HCV RNA viral load at the end of treatment do not have the option to further extend their therapy (or switch to the 24 week arm if they are randomised to the 12 week arm), unless if a participant withdraws from the study, and their usual clinician wishes to extend their treatment. Non-response at the end of 12 weeks treatment is rare with direct acting antivirals.

Reasons for withdrawal from study, if known (participants do not have to state reason to justify decision) should be documented.

Participant may not re-enter the study after withdrawal, unless if no treatment doses are missed.

Withdrawn participants will not be replaced, unless if the Trial Steering Committee or Chief Investigator deem the total sample size to be underpowered for the purposes of the study.

13.10 Early withdrawal

The following should be performed if a participant withdrawals before the end of study:

- document timepoint when withdrawal occurs and if allocated study treatment has been completed
- document reason (if known) by participant or investigator
- document if withdrawal is due to safety reasons (e.g. related to any SAE)

- if withdrawal is during study treatment, document if participant consents to continue with study follow up
- unused study drugs must be returned and destroyed
- participants have the option to continue treatment (or with a different treatment) outside of the study, at the discretion of their usual clinician
- document that data and samples collected until the point of withdrawal will be kept and used
- document if participant consents to the collection of their virological outcome (SVR12) if data is collected outside of the study (e.g. by their usual clinician, regardless of whether or not treatment is continued after withdrawal from the study)
- participant are not allowed to re-enter the study unless if no study drug is missed during the withdrawal period

13.11 End of trial (EOT)

The CI is delegated the responsibility of submitting the EOT notification to REC and MHRA once reviewed by sponsor. The EOT notification must be received by REC and MHRA within 90 days of the end of the trial.

If the study is ended prematurely, the Chief Investigator will notify the Sponsor, REC & MHRA including the reasons for the premature termination (within 15 days).

End of trial is defined as 3 months after the last randomised participant completes the study procedures.

14.0 Laboratories and samples

14.1 Central Laboratories

Analyses for the main study which are standard NHS diagnostic tests will be performed at accredited local laboratories at each study site.

Central laboratories will not be required.

14.2 Local Laboratories

All laboratory analyses required for this study are considered 'standard' diagnostic tests and will be performed at the NHS laboratory associated with the study site, using validated assays (i.e. Royal London Hospital, Royal Free Hospital, St George's hospital, St Mary's Hospital, Kings College Hospital). All laboratories are CPA accredited and GCP compliant.

Each laboratory will provide their accreditation documentation, methodology and reference ranges.

The list of laboratory data required pre study enrolment and tests to be performed during the study are as follows:

Haematology - haemoglobin, platelet count
Biochemistry - total bilirubin, AST, albumin, creatinine, eGFR (by Cockcroft Gault or MDRD formula)
Virology - HCV genotyping, HCV viral load quantification

14.3 Sample Collection/Labelling/Logging

Samples will be whole blood collected from participants using trained phlebotomists at each study site. For local laboratories, the local NHS health trust SOP will be followed.

These samples will NOT be anonymised and results will be accessible to authorised healthcare personnel as per standard NHS diagnostic tests.

14.4 Sample Receipt/Chain of Custody/Accountability

Samples processed during the study which are standard NHS diagnostic tests will follow local site SOP and the associated NHS Health Trust is accountable.

14.5 Sample Analysis Procedures

14.5.1 The arrangements for sample analysis

For analyses which are NHS standard diagnostic tests, please refer to lab manuals.

14.5.2 Sample Storage Procedures

Storage of study samples will be according to NHS laboratory SOP and will be identifiable to the participant.

14.6 Sample and Data Recording/Reporting

Sample results will be recorded in participants' medical records, as well as in study CRF (anonymised).

14.7 End of study

Laboratory data will be recorded and reported in the standard way as other non-study NHS samples, and will be available for review by personnel authorised to handle confidential patient records who are outside of the study.

15.0 Trial Medication

15.1 Name and description of investigational medicinal product(s)

This study involves the use of two medications in a fixed dose combination – Epclusa 400mg/100mg film-coated tablet, which contains 400mg sofosbuvir and 100mg velpatasvir.

Dose reduction is not permitted but discontinuation, at the discretion of the participant or investigator, is permitted. This must be documented in the participant medical notes and reported on CRF.

All subjects will initially start treatment with sofosbuvir/velpatasvir outside of the study, on the NHS treatment programme. Subjects must not have taken ribavirin along with sofosbuvir/velpatasvir. Subjects are recruited during NHS treatment period, between treatment weeks 8-12. Therefore, subjects have been dispensed with their 3rd prescription of sofosbuvir/velpatasvir (supplied as 28 tablets per bottle – i.e. one bottle every 4 weeks) by the time of study enrolment. In order to avoid wastage of high cost drugs when patients enter this study, they will continue to take the dispensed supply between weeks 8 to 12. Subjects randomised to the 12 week arm (Arm A) will receive no further drug supply. Subjects randomised to the extended treatment will receive additional study drug for weeks 13-24. (Arm B)

Study drugs (only required for weeks 13-24) will be supplied in their original manufacturer's packaging, which ensures the integrity of the product during transport and storage. Study drugs will be labelled at the site trial pharmacy (or delegate) with approved clinical trial labels in accordance with Annex 13. It should contain:

- participant's study details
- dosing instructions
- contact details for study investigator
- the phrase 'keep out of reach of children'
- the phrase 'for clinical trial use only'
- trial reference code (EudraCT number)

The original manufacturer's Patient Information Leaflet will be provided.

Each dispensing episode will be for a 4 week supply. Patients are to return the IMP container before the next 4 weeks is dispensed.

15.2 Legal status of the drug

Sofosbuvir/velpatasvir is licensed in the EU for use in patients with all genotypes of chronic HCV, including patients with decompensated cirrhosis, co-infection with HIV and those with post-liver transplant HCV recurrence. Thus sofosbuvir/velpatasvir is approved for use in the study target population. The license recommends for most patients sofosbuvir/velpatasvir should be used for 12 weeks. For patients who are harder to treat, namely genotype 3 HCV infected patients with compensated cirrhosis, addition of ribavirin can be considered, and for patients with decompensated cirrhosis, ribavirin should be added.

Ribavirin is associated with significant adverse events, and it is therefore advantageous to offer ribavirin-free treatments for patients who are least able to tolerate it. This trial uses 24 weeks of sofosbuvir/velpatasvir, as the test treatment, to compare with the standard of care for 12 weeks.

The 24 week duration has been evaluated in a Phase III trial showing no increased adverse events compared to the 12 week duration, unlike the combination with ribavirin [16]. The 24 week regime has not been recommended according to the drug license as the longer duration was not associated with significantly improved efficacy; however the study was not powered to detect significant differences in SVR between treatment groups and only 12 patients received the 24 week duration. The use of sofosbuvir/velpatasvir with ribavirin for 24 weeks can, according to license, be considered for patients who previously failed therapy on an NS5A containing regime. International guidance from EASL in 2016 recommends patients with genotype 3 HCV infection who have contraindications to the use of ribavirin, or poor tolerance to ribavirin on treatment should receive sofosbuvir/velpatasvir for 24 weeks without ribavirin [23].

Given the lack of clear evidence guiding the use of treatments in subpopulations of HCV patients, NHS England provides treatments which are off-label but supported by robust data. NHS England has indicated that if this study provides evidence supporting the use of 24 weeks of sofosbuvir/velpatasvir, the regime will become adopted into the treatment portfolio.

Response-guided duration of treatment is not routinely used for DAA therapies therefore the MHRA has deemed the above study treatments as IMPs when used for either durations, since the current practice does not involve the use of on-treatment viral load to determine the duration of treatment required.

This study is being carried out under a Clinical Trial Authorisation (CTA).

The study excludes participants with renal failure (defined as eGFR <30ml/hr or dialysis dependent) as the treatment drugs are not licensed for this population.

15.3 Summary of Product Characteristics (SmPC) or IB

Please see Summary of Product Characteristics for sofosbuvir/velpatasvir (Epclusa).

15.4 Drug storage and supply

All participants in this study are initially treated with sofosbuvir/velpatasvir for at least 8 weeks as standard NHS treatment. Drug supply is registered on Blueteq which allows monitoring of high cost drugs by NHS England. Prescriptions and dispensing will take place every 4 weeks.

Upon enrolment into the study, from week 8 to 12, sofosbuvir/velpatasvir will be considered standard therapy. In order to avoid wastage of high cost drugs, patients will complete the medication which is NHS-dispensed, but the next due prescription will be supplied as IMP. Therefore, subjects in the 12 week arm (Arm A) will not receive further study drug after completing their dispensed NHS prescription for week 8 to 12. Subjects in the extended treatment arm (Arm B) will have further study drug dispensed for week 13 to 24. The extended treatment must be registered on BlueTeq.

The study drugs will be supplied in their original packaging but labelled with trial medication labelling. Storage and supply will be in accordance to the Trial Pharmacy SOP (or that of contracted delegate).

15.5 Supplier

The IMPs will be sourced from commercial stock by the site and will be delivered to the study sites according to their contracts with the NHS Trust. Study drug will be purchased by the NHS Trust of the study site and reimbursed by NHS England.

See IMP Manual for details of local drug supply and IMP management plan for detail of trial-wide supply procedures.

15.6 Manufacturer

Sofosbuvir/velpatasvir (Epclusa 400mg/100mg) is manufactured by Gilead Sciences Ltd.

15.7 How the drug should be stored

The IMPs requires no special storage conditions (below 25 degrees Celsius)., NHS Trust and study site clinical trial pharmacy guidelines. Records of storage will be maintained by the delegated site pharmacy and any excursions from the storage instructions will be documented, and reported to the PI, CI and Sponsor.

Instructions for storage once dispensed from pharmacy is as per Patient Information Leaflet which is included with the study IMP packaging. The manufacturers advise no special storage conditions are required.

15.8 Details of accountability

The study site pharmacy is responsible for dispensing in line with local procedures to ensure the integrity of the drugs. All NHS Trust pharmacies will adhere to their local policy on accountability of drugs.

The batch or lot number and expiry date of dispensed drugs should be recorded.

Investigators will perform pill count and review returned empty bottles during on-treatment study visits. Missed pills will be recorded in the CRF. Investigators will retrospectively document any missed pills in the period between treatment start to enrolment.

15.9 Medication destruction/return and Recall

IMP which is not used by a participant or is found to have breached its conditions for use should be returned to pharmacy and destroyed according to local guidelines. Returned and destroyed IMP must be documented.

15.10 Prescription of IMP / Placebo/NIMP

Participants will initially start treatment on the NHS programme, and will be prescribed according to local procedures, checked and signed by authorised personnel. Treatment will be logged on BlueTeq. Upon entering the study, prescriptions of study drug must be signed by study investigators authorised by the delegation log.

The Trial Pharmacy will be provided with a delegation log detailing which investigators are authorised to sign prescriptions.

15.11 Preparation and labelling of IMP

The drugs sofosbuvir/velpatasvir is a fixed dose combination tablet which does not need any preparation.

15.12 Preparation and Administration of IMP

Sofosbuvir/velpatasvir should be taken orally, swallowed whole, with or without food. Due to its bitter taste, the film-coated tablet should not be chewed or crushed. It should preferably be taken at the same time each day.

Missed doses should be managed according to drug SmPC instructions. If sofosbuvir/velpatasvir is missed, another tablet should be taken within 18 hours of the missed dose, and the next due dose taken at the usual time. If the missed dose is more than 18 hours, then the missed dose should be omitted and the next due dose taken at the usual time.

If the subject has vomiting within 3 hours of taking sofosbuvir/velpatasvir, they should take another tablet. If vomiting occurs after 3 hours of the dose, they should take the next due dose at the usual time.

If the subject accidentally takes more than the recommended dose, they should contact the study team before taking the next due dose.

Adherence to dosing will be monitored during study visits.

15.13 Dosage schedules

Sofosbuvir/velpatasvir should be taken as one tablet per day, preferably at the same time daily, for total 12 or 24 weeks.

15.14 Dispensing of IMP

Dispensing will be according to guidelines in place within the Trust and Clinical Trial Pharmacy, who are responsible for dispensing in line with their local dispensing procedures and excursion management normal practices.

Drugs dispensed as NHS treatment but used after a participant has enrolled (a period of no more than 4 weeks) will be recorded only in the NHS pharmacy. Drugs dispensed as IMP by the Trial Pharmacy must be logged to allow tracking of study drugs. All trial pharmacists must have documented training for this trial.

A dispensing label with study specific information will be applied, the Batch and expiry number must not be obscured.

15.15 Dosage modifications

Dose modification of sofosbuvir/velpatasvir is not permitted. There are no stopping rules based on virological outcome but discontinuation may occur at the discretion of investigator or at participant request to withdraw. Participants who do not achieve end of treatment virological response are not permitted to extend treatment within this study.

15.16 Known drug reactions and interaction with other therapies

Refer to clinical particulars within SmPC for contraindications, special warnings, interaction with other medicinal products, and other undesirable effects.

Velpatasvir is an inhibitor of drug transporter P-glycoprotein, breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1 and OATP1B3. Co-administration with medicinal products which are substrates of these transporters may increase the exposure of such medicinal products.

Sofosbuvir and velpatasvir are substrates of drug transporters P-gp and BCRP. Velpatasvir is also a substrate of drug transporter OATP1B. *In vitro,* slow metabolic turnover of velpatasvir by CYP2B6, CYP2C8 and CYP3A4 was observed. Medicinal products that are potent inducers of P-gp or potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g. rifampicin, rifabutin, St. John's wort, carbamazepine, phenobarbital and phenytoin) may decrease plasma concentrations of sofosbuvir or velpatasvir leading to reduced therapeutic effect of sofosbuvir/velpatasvir. The use of such medicinal products with Epclusa is contraindicated. Medicinal products that are moderate P-gp inducers or moderate CYP inducers (e.g. oxcarbazepine, modafinil or efavirenz) may decrease sofosbuvir or velpatasvir plasma concentration leading to reduced therapeutic effect of Epclusa. Co-administration with such medicinal products is not recommended with Epclusa. Co-administration with medicinal products that inhibit P-gp or BCRP may increase sofosbuvir or velpatasvir plasma concentrations. Medicinal products that inhibit OATP, CYP2B6, CYP2C8, or CYP3A4 may increase plasma concentration of velpatasvir. Clinically significant medicinal product interactions with Epclusa mediated by P-gp, BCRP, OATP, or CYP450 inhibitors are not expected; Epclusa may be co-administered with P-gp, BCRP, OATP and CYP inhibitors.

15.17 Prior and Concomitant medication

To avoid drug-drug interactions, the following list of concomitant medications are not permitted, according to product SmPCs. Participants taking these medications must have discontinued prior to starting sofosbuvir/velpatasvir (this is expected to be in line with standard care practice).

In accordance with the SmPC of Epclusa (sofosbuvir/velpatasvir) concomitant use of the following medications are contraindicated:

Anticonvulsants - carbamazepine, phenytoin, phenobarbital, oxcarbazepine
Antimycobacterials – rifampicin, rifabutin, rifapentine
Antiretrovirals - efavirenz
St John's wort
Modafinil
Proton-pump inhibitors should be avoided and if necessary, sofosbuvir/velpatasvir should be taken with food and administered 4 hours before proton pump inhibitor, at maximum doses equivalent to 20mg omeprazole per day.
Amiodarone should be avoided and if necessary, close monitoring is required

The following medications should be co-administered with caution:

Digoxin
Amiodarone
Rosuvastatin (do not exceed 10mg), other statins consider dose reduction
Antacids (e.g. aluminium hydroxide) – separate administration by 4 hours
H2 antagonists – administer simultaneously or staggered from sofosbuvir/velpatasvir, at a dose not exceeding the equivalent of 40mg famotidine twice daily
Dabigatran
Tenofovir

For management of other concomitant medications, refer to SmPC, EASL practice guidelines and http://hep-druginteractions.org/

15.18 Trial restrictions

No dietary restrictions are required for the trial. Concurrent alcohol or recreational drug use is not an exclusion for this trial, but the subject's suitability to enrol or continue within the study will be at the discretion of investigators.

15.19 Assessment of compliance

Compliance will be monitored via pill counting and checking returned empty bottles during study visits. Missed pills will be documented in CRF. Investigators will reiterate dosing schedule and the importance of compliance for efficacy. Participants are considered lost to follow up if there is no end of study visit at post treatment week 12+4 weeks.

There is no provision for supplying additional IMPs which are lost or damaged during the trial. Participants should continue on the study but doses missed due to insufficient drug supply should be recorded as missed doses. Investigators can dispense the next due prescription early to cover for lost or damaged medication. According to local pharmacy policy, if surplus/ replacement medication is available (for example if another patient withdraws from treatment), this can be supplied as IMP for a study participant, provided the medication has not been dispensed from pharmacy, and the usual storage and packaging requirements are complied with.

Any study IMP which is dispensed and unused by the participant will be recalled and destroyed in the site pharmacy. For participants who withdraw during study treatment, they may be eligible to continue treatment on the NHS programme according to their usual clinician's judgement and local Trust guidelines.

15.20 Name and description of each Non-Investigational Medicinal Product (NIMP)

There are no Non-IMPs which need to be supplied together with the IMP. Medications required for the management of IMP adverse events or concurrent medical conditions are permitted. Investigators are responsible for checking contraindications and drug-drug interactions.

15.21 Arrangements for post-trial access to IMP and care

At the end of study participants will be returned to their usual health care practitioner. This includes participants who fail to achieve SVR12 after completing the study IMP. There is currently no established re-treatment options for study participants or for patients treated with standard of care.

16 Equipment and Devices

No medical device is under investigation for the study.

List of medical equipment required for the study but not under investigation:

- phlebotomy kit
- urinary pregnancy test (beta hCG)

These will be standard NHS kit and will be maintained according to site guideline or usual practice.

17 Pharmacovigilance

17.1 General Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death. • Is life-threatening. • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity. • Consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI): • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product. • In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

17.2 Site Investigators Assessment

The Principal Investigator is responsible for the care of the participant, or in his/her absence an authorised medic within the research team is responsible for assessment of any event for:

- Seriousness
  Assessing whether the event is serious according to the definitions given in section 17.1.

- Causality
  Assessing the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

- Expectedness
  Assessing the expectedness of all SARs according to the definition given. If the SAR is unexpected, then it is a SUSAR.

- Severity
  Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

    - **Mild**: Some discomfort noted but without disruption of daily life
    - **Moderate**: Discomfort enough to affect/reduce normal activity
    - **Severe**: Complete inability to perform daily activities and lead a normal life

17.3 Reference Safety information

Reference Safety Information (RSI) is the information used for assessing whether an adverse reaction is expected.

Please refer to the following SmPC:

Epclusa 400mg/100mg film coated tablets – last updated 13/7/2016 (Gilead Sciences)

17.4 Notification and reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is documented in the participant's medical notes and CRF and the participant is followed up by the research team.

Recording of AEs should start from the first day of randomisation, to the post treatment 12 week visit. Since participants have commenced treatment on standard NHS care at the time of enrolment, events which occurred prior to enrolment are retrospectively documented.

Serious adverse events which occur during IMP use (i.e. treatment week 13 to 24) and until end of trial (post-treatment week 12) need to be reported. SAEs occurring during treatment but prior to IMP use need to be recorded in medical notes and CRF, but not reported.

17.5 Notification of AEs of special interest

Adverse events relating to hepatic decompensation (i.e. development of ascites, encephalopathy, variceal bleeding) are of special interest. These events are expected from the natural progression of the underlying condition being treated, but are of particular relevance in patients with compensated or decompensated cirrhosis, due to reports of decompensation in patients with advanced liver disease treated with DAA therapies.

In addition, cardiac arrhythmias in particular severe bradycardia and heart block have been observed with sofosbuvir when used with concomitant medications which lower heart rate (note amiodarone is prohibited).

Therefore the occurrence of the above adverse events, if graded as serious, should be reported according to the procedures detailed in the section 'Notification and reporting for SAE/SUSAR'. AESIs which are not graded as serious are recorded as for other AEs and do not require reporting.

17.6 Adverse events that do not require reporting

In clinical trials treatment emergent adverse events associated with sofosbuvir/velpatasvir were reported at similar frequencies to placebo-treated patients. The most frequent events (at $\geq$10%) were headache, fatigue and nausea. Therefore no SAEs are considered 'expected' and SAEs should be reported as detailed in 17.4.

17.7 Notification and Reporting of Serious Adverse Events & SUSARs

All Serious Adverse Event (SAEs) will be recorded in the participants' notes, the CRF, the sponsor SAE form and reported to the sponsor (Joint Research Management Office) within 24 hours of the PI or co-investigators becoming aware of the event. Nominated co-investigators (as listed will be authorised to sign the SAE forms in the absence of the PI at the participating sites. The sponsor will not consider a SAE 'valid' unless there is written evidence of that the SAE has been medically assessed by the PI or delegated qualified medic (see JRMO SOP 26a - Phamacovigilance reporting for CTIMPs).

Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur during the trial will be reported to the JRMO within 24 hours of the PI or co-investigator becoming aware of the event. SUSARs should be reported to the sponsor (JRMO) within 24 hours. The sponsor will report SUSARs fatal or life-threatening SUSARs as soon as possible, but no later than 7 days after you are first aware of the reaction. Any additional relevant information must be sent within 8 days of the report.

You must report non-fatal or non-life-threatening SUSARs as soon as possible but no later than 15 days after you are first aware of the reaction.

17.8 Sponsor Medical Assessment

Sponsor has delegated the responsibility for oversight of IMP safety profile and medical assessment of SAEs and SUSARs to the CI. The CI must review all SAEs within 24 hours of receipt. This review should encompass seriousness, relatedness and expectedness. Day 0 for all SUSARs is when the SAE/SUSAR is received by the CI and /or coordinating team and /or sponsor whichever is first.

It is expected that the CI will achieve oversight of IMP safety profile through trial committees as per section 28.0.

It is noted that the CI can upgrade an event to 'related' or 'unexpected' but cannot downgrade the PI assessment of an event to 'unrelated' or 'expected'.

If there is disagreement between CI and PI assessment, it is the CI's responsibility to liaise with the Site PI before CI's final decisions.

The CI and PI assessment can differ.

17.9 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30. The measures should be taken immediately to protect the safety of trial participants. The MHRA can be informed retrospectively of the measures taken.

The CI has an obligation to inform both the MHRA and Research Ethics Committee **in writing within 3 days**, in the form of a substantial amendment. The sponsor (JRMO) must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

17.10 Procedures for reporting blinded SUSARs

NA

17.11 Pregnancy

If a participant or the female partner of a male participant becomes pregnant whilst involved in the study, it should not be considered an SAE or AE but requires reporting, monitoring and follow up. The sponsor should be notified immediately (within 24 hours of site becoming aware of the pregnancy) using the sponsor pregnancy form. The pregnancy reporting procedure will be the same as for SAE.

The CI in conjunction with the site PI will determine if the fetus has been exposed to the IMP. The PI has responsibility to ensure that the pregnancy is form is completed and submitted to the Sponsor within agreed timelines. The initial report should be within 24 hours and follow up information submitted when it becomes available, up to the time of birth.

The PI must follow up the pregnancy until delivery as well as after birth if clinically appropriate. Any events to the mother or child that occur during this time that could be considered an SAE must be reported to the sponsor in line with section 17.7 utilising the sponsor SAE reporting form.

Pregnant female participants should be withdrawn from the treatment, but if willing can be follow up for primary outcome measure. Male participants can continue on the study.

Requirements for contraception during and following the use of the IMPs are documented within their SmPC and therefore do not need to be reported to the manufacturer.

18.0 Annual reporting

Development Annual Safety Update (DSUR)
The DSUR will be written by the CI (using Sponsor template) and submitted to the sponsor for review prior to submission to the MHRA. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the "notice of acceptance letter" from the MHRA. As delegated Sponsor Medical Assessor the CI will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial. REC will be sent a copy of the DSUR.

Annual Progress Report (APR)
The APR will be written by the CI (using HRA template) and submitted to the sponsor for review prior to submission to the REC. The APR is due within 30 days of the anniversary date of the "favourable opinion" letter from the REC.

19.0 Statistical and Data Analysis

19.1 Sample size calculation

The planned sample size is 60 participants - with 30 participants in each of two treatment arms. This is based on the assumption of a 30% difference in the primary outcome measure (proportion of patients who achieve SVR12) between the two treatment arms, where SVR in the 12 week treatment arm is 65%, and 95% in the 24 week treatment arm. All outcomes are measured on an intention to treat basis.

Estimates of SVR rates for patients with slow treatment response (week 2 HCV detectable) is derived from post-hoc analyses of cohort studies or clinical trials. For genotype 3 patients with decompensated cirrhosis treated with sofosbuvir and NS5A inhibitor (daclatasvir or ledipasvir) with or without ribavirin, SVR was 65% for patients viraemic at week 2 [14]. There is no data available for this subgroup treated with sofosbuvir/velpatasvir. For all genotype 3 patients with decompensated cirrhosis, SVR was 50% after 12 weeks of sofosbuvir/velpatasvir [16], and 91% for patients with compensated cirrhosis [15]. Another study showed that a combination of 3 negative factors in genotype 3 patients dropped SVR after 12 weeks of sofosbuvir/velpatasvir to 85%, from 95% if only 2 negative factors were present [18].

Given the trial cohort will contain compensated and decompensated patients, the SVR after 12 weeks is estimated at 65%. The study assumes an SVR of 95% with the extended arm, in order for the margin of improvement to be clinically and statistically significant, as well as cost-effective to justify the increased drug costs. This is a realistic assumption given 12 weeks of sofosbuvir/velpatasvir in genotype 3 patients without negative factors (i.e. without cirrhosis) achieved SVR of 97% [15]. This study will demonstrate if treatment extension can overcome the impact of negative treatment factors on SVR.

To detect a true difference between the two treatment arms (if one exists) with 80% power and 95% confidence level, 24 participants are required as a minimum in each arm. The study will recruit 60 participants to allow for withdrawals or those lost to follow up.

Study participants will undergo block randomisation such that at any time during the study, roughly equal numbers will be recruited into both arms, allowing for interim analysis as necessary. An interim analysis may be performed when about 50% of planned recruitment has taken place, to assess safety and efficacy, whether the study sample needs to be altered. This will be determined by the Chief Investigator and/or the Trial Steering Committee.

19.2 Planned recruitment rate

The study plans to recruit 60 participants from 5 London sites in 9 months. Each site therefore has to recruit 12 patients, at a rate of less than 2 patients per month.

There are estimated 10,000 HCV infected individuals in England who have cirrhosis. Around 45% may be infected with genotype 3. The study target group is enriched within London where there is a high immigrant population (where genotype 3 HCV prodominates) and a concentration of patients with cirrhosis or advanced liver disease, currently over 30% of treated patients nationally have cirrhosis. At Royal London Hospital (one of the study sites), approximately 3 new patients with genotype 3

HCV are identified to start treatment each week. Amongst patients treated within the Expanded Access Programme, around 50% of patients did not achieve undetectable HCV after 2 weeks of treatment. In a phase 3 trial of 12 weeks of sofosbuvir/velpatasvir, which did not include the hardest to treat patients with decompensated cirrhosis, 38% did not achieve undetectable HCV at treatment week 2, and this is expected to be higher for a cohort including decompensated cirrhosis [20].

Sofosbuvir/velpatasvir is due to become routinely available as NHS treatment in the upcoming months. The number of prescriptions for high cost interferon-free therapies for genotype 3 patients is determined by the treatment centre's 'run rate'. Participating sites have indicated that the number of subjects required for recruitment is within their run rate allowance.

Given the entry criteria for the study match the NHS eligibility criteria for sofosbuvir/velpatasvir use, identification of suitable patients for recruitment, using the NHS treatment network, will be straightforward. Chosen study sites are all experienced HCV treatment and clinical trial centres, with a good track record of recruitment for regional and international studies.

Based on the low discontinuation rate on the Expanded Access Programme in England, where real world patients with advanced liver disease were treated [14], the study does not anticipate premature treatment or study withdrawal to be a major problem. The study will recruit patients who adhered to 90% of their treatment at screening, to eliminate the risk of early drop outs.

Currently there are no competing clinical trials for the study population but this may change throughout the duration of the trial. However most clinical trials will involve experimental IMPs while this study uses treatment which patients have already consented to start. The study and treatment schedule requirements are similar to that within routine NHS treatment, therefore we anticipate the study will be considered favourably by patients.

19.3 Statistical analysis plan (SAP)

All statistical analysis will be performed as specified *a priori* on the whole study population (intention to treat), with post-hoc analysis performed as appropriate. These are detailed below.

19.4 Summary of baseline data and flow of patients

Demographic and baseline characteristics will be summarised using standard descriptive methods. Data will include gender, self-identified ethnicity, age, previous treatment experience, body mass index, baseline (pre-treatment) HCV RNA level, week 2 HCV RNA level, genotype of HCV infection, baseline laboratory values (haemoglobin, platelet count, creatinine, ALT, bilirubin, albumin) and liver severity score (MELD score) generated from the above baseline laboratory values.

Categorical data will be summarised by proportions and continuous data summarised by mean, median and range.

Flow of patients will be reported according to CONSORT guidelines.

19.5 Primary outcome analysis

The proportion of patients receiving 12 and 24 weeks of sofosbuvir/velpatasvir with undetectable HCV RNA (below limit of quantification up to 15iu/mL) in serum at 12 weeks (+4 weeks) after end of treatment (sustained virological response SVR12).

SVR12 will be calculated on intention to treat, i.e. all randomised participants who received at least one dose of study drug will be included. Patients randomised will have completed at least 90% of sofosbuvir/velpatasvir at screening (between treatment week 8-12). Patients randomised to 24 weeks must have taken at least one dose of the extension phase treatment. Comparison of proportions will be analysed by Chi-square test.

19.6 Secondary outcome analysis

Secondary endpoints - safety analysis

- proportion of patients requiring study treatment discontinuation
- proportion of patients with serious adverse events (SAEs) during study period (ie treatment period + follow up)

Secondary endpoint - quality of life

- Short-Form Health Survey (SF36) scores at the end of treatment and 3 months post-treatment for both treatment arms. Score range from 0-100, with the highest score representing best quality of life. For each treatment arm, group mean scores at both time points, as well as the change from end of treatment to post-treatment, will be analysed.

To evaluate the tolerability of extended treatment, it is important that any randomised participant who takes at least one dose of the extended phase treatment is included in the analysis.

Comparison of proportions will be analysed by Chi-square test. Comparison of means of continuous variables will be analysed by T-test.

19.7 Subgroup analyses

Subgroup analysis, with consideration to sample size, will be performed as appropriate. Important subgroups include gender, previous HCV treatment history, and whether compensated or decompensated cirrhosis (randomisation will be stratified by this baseline factor).

19.8 Adjusted analysis

Adjusted analysis or other post-hoc analysis will be performed as appropriate.

19.9 Interim analysis and criteria for the premature termination of the trial

An interim analysis of efficacy and safety will be considered through discussion with the Trial Steering Committee when about half the planned sample size is recruited to evaluate if there is an indication to discontinue the trial, alter the sample size, or replace participants who withdraw.

19.10 Subject population

All data will be reported on an intention to treat basis such that all randomised participants who received one dose of study drug will be included (entry criteria dictates all participants have adhered to 90% of treatment at the point of screening). Per protocol analysis will be analysed and reported as appropriate, for instance if there is an unexpectedly high treatment discontinuation or lost to follow up rate. For per protocol analysis, participants who adhered to 90% of their treatment according to randomisation will be included.

19.11 Procedure(s) to account for missing or spurious data

To reduce missing data on the primary outcome, SVR12 will be defined as HCV RNA <15iu/mL from 12 to 16 weeks after end of treatment. This widens the window when SVR12 can be reported. A negative HCV RNA at any point after 12 weeks post-treatment is clinically considered to be a sustained virological cure. Negative HCV RNA at less than 12 weeks post-treatment will be considered non-SVR12.

Non SVR12 will be differentiated by true viral relapse or missing data due to lost to follow up, to allow per-protocol analysis.

Given data is time point specific, data outside of the defined window cannot be carried forward to replace missing data.

19.12 Other statistical considerations.

NA

19.13 Economic evaluation

This study will not formally evaluate cost effectiveness and cost increment per QALY of the two treatment durations, but will evaluate treatment costs based on drug costs alone per successful treatment (SVR12)

20.0 Data Handling & Record Keeping

20.1 Confidentiality

The Principal Investigator has a responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) and all subsequent amendments as defined in the JRMO SOP 20 Archiving.

The Chief Investigator and the study team will adhere to these parameters to ensure that the Participant's identity is protected at every stage of their participation within the study. To ensure this is done accordingly, at time of consent each participant will be allocated a unique screening number by either the PI or a member of the study team before undergoing any screening procedures.

The trial will be conducted in compliance with the requirements of the Data Protection Act 1998. All investigators and trial site staff must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

20.2 Data Custodian Details

The Chief Investigator, Professor Graham Foster, Blizard Institute, Queen Mary University of London, is the 'Custodian' of the research data. The study will not collect identifiable information. Unique study identifiers will be used for study documents. A participant ID log will be kept in the Investigator Site File with the Principle Investigator. For purposes of monitoring and audit, original source files containing identifiable data may be inspected by third parties (i.e. the Sponsor or regulatory bodies, and not any other organisation or commercial company). Participants will sign consent to permit access to identifiable data for such purposes. Identifiable data will not leave the study site.

Any publication relating to the study will contain no identifiable data. Research data will be kept for 20 years in accordance to the Sponsor's policy.

20.3 Pseudononymisation

The study will use identifiers for participants consisting of ABC-00, where the first three letters are abbreviated for the study site, and the number will be successive participants screened at the site. These details will be used on CRFs and for study correspondence leaving the study site, such as with the Sponsor.

20.4 Transferring/Transporting Data

Data containing identifiable information will not be stored on any portable device. Data transferred between sites will contain pseudoanonymised identifiers only. Electronic transfer of data must be in accordance with the UK Data Protection Act 1998.

20.5 Data collection tools and source document identification

Data reported on the CRF/eCRF will be derived from source documents. Researchers delegated with the completion and return of eCRF are responsible for the accuracy of completed data.

Data will be entered at each site on an electronic CRF (eCRF) onto a web-based database. Any data collected via CRF/eCRF for the study belongs to the study Sponsor. The Sponsor will not have access to source data, except during monitoring or audit, but will have access to the anonymous data entered into the database.

20.6 Source Data

Source data is defined as all information in original records of clinical findings, observations and other trial activities necessary for the reconstruction and evaluation of the study. These may contain identifiable information and will be stored in confidential conditions and will not leave the study site. Depending on the site they may be paper medical notes or electronic health records. Their maintenance and storage will be in accordance to the site NHS Trust guideline or policy. A trial monitor may inspect the source data. A source data list will be provided to each site as part of the Investigator Site File to aid consistent monitoring.

Note participants will complete a set of Quality of Life questionnaires, which will be completed in paper form by participants, and transcribed by the study team onto eCRF. ECRF data will be processed using licensed Health Outcome Scoring Software to generate summary scores for each participant during data analysis. These summary scores will be statistically analysed as detailed in the SAP.

20.7 Case Report Form

CRF will be entered electronically onto a trial web-based database, direct from source documents, by investigators/ study nurse.

Paper CRFs will be available in case of technical failures.

20.8 Data handling and record keeping

CRFs will be electronically stored and managed by an authorised database (Discover*e*) which is hosted on a secure served Cerner, a system commissioned by the Sponsor for the secure and confidential handling of data. The system will comply with the requirements and processes specified in SOP 38. It will enable quality control of data (drop down, or fixed range variables, in preference to free text where possible), audit trail, and secure data back up.

Training of staff on the use of eCRF and the data management system will be documented.

20.9 Access to Data, Source Data and Documents

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Only members of the health care team directly related to the care of the participant will have access to the participant's medical records.

21.0 Archiving

During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and Trust Policy that the records are kept for a further 20 years.

Site files from other sites must be archived for 20 years at the originating site external site and cannot be stored at the BH Modern Records Centre or within QMUL.

Destruction of essential documents will require authorisation from the Sponsor.

Following submission of the end of study report, the Sponsor will authorise archiving. The sites will archive their Investigator's Site Files. The trial database which contains the eCRF will be archived securely within the system server.

22.0 Monitoring, Audit and Inspection

22.1 Monitoring

A Trial Monitoring Plan will be developed and agreed by the Sponsor and Chief investigator based on the sponsors trial risk assessment, this will include on site monitoring. Monitoring procedures are detailed in the Trial Monitoring Plan.

22.2 Auditing

Sponsor retains the right to Audit any trial, trial site or central facility. In addition, any part of the trial may be inspected by the regulatory bodies and funders where applicable.

22.3 Notification of Serious Breaches to GCP and/or the protocol

The Site Principal investigator is responsible for reporting any serious breaches to the sponsor (JRMO) **within 24 hours.**

The Chief Investigator is responsible for reporting any serious breaches to the sponsor (JRMO) **within 24 hours**.

The sponsor will work with the CI to investigate any potential breach and notify and report to the MHRA (as applicable) within 7 working days of becoming aware of the serious breach.

A serious breach is a breach likely to affect to a significant degree:

- the safety or physical or mental integrity of the trial participants
- the scientific value of the study

If the above should occur, the sponsor will be notified immediately.
The sponsor will notify the licensing authority in writing of any serious breach of

- the conditions and principles of GCP in connection with the study
- the trial protocol

within 7 days of being aware of the breach

22.4 Compliance

The CI will ensure that the trial is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and any subsequent amendments of the clinical trial regulations, current Research Governance Framework, GCP guidelines, the World Medical Association Declaration of Helsinki (1996), the Sponsor's SOPs, and other regulatory requirements as amended.

22.5 Non-Compliance

Planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials. Unintentional deviations must be adequately documented and reported to the CI and Sponsor.

Non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which need to be escalated.

CI and the coordinating team should assess the non-compliances and action a timeframe in which they need to be dealt with. This assessment should include the need to escalate to the sponsor. Any event with the potential to affect participant safety or data integrity should be reported to the sponsor within 24 hours of the Coordinating team becoming aware.

Where applicable corrective and preventative actions APA should be assigned. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the Sponsor will agree an appropriate action, including an on-site audit.

22.6 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments

Before any site can enrol participants into the trial, the Principal Investigator or designee will apply for NHS permission from the site's Research & Development (R&D) department.

For any amendment that will potentially affect a site's NHS permission, the Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D).

NA

23.0 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The study is funded by the National Institute for Health Research (NIHR) via a Doctoral Research Fellowship grant.

Drugs used in this study are funded by NHS England.

Competing interests from all PIs at participating sites will be reported.

24.0 Ethical and Regulatory Considerations

Before the start of the trial, approval will be sought from the Research Ethics Committee (REC) and MHRA for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.

Decision whether an amendment constitutes a minor or substantial amendment lies with the sponsor.

Substantial amendments that require review by the Sponsor and REC and MHRA (where relevant) will not be implemented until the REC and or MHRA grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites).

All correspondence with the Sponsor, REC and MHRA will be retained in the Trial Master File at the lead site and Investigator Site File at each site.

The Chief Investigator will notify the REC, MHRA and Sponsor of the end of the study.

25.0 Peer review

See report from Dr William Alazawi, Senior Lecturer and Consultant Hepatologist, Queen Mary University of London.

26.0 Public and Participant Involvement

Public and participant will be invited to review participant related documents, and to take part in the Trial Steering Committee. Their involvement in TSC is desirable but not compulsory.

27.0 Indemnity

Professor Graham Foster of Queen Mary University of London is the Chief Investigator. Queen Mary University of London is also sponsoring this study and has arranged for suitable indemnity to be in place for this study.

27.1 Amendments

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, the sponsor must submit a valid notice of amendment to the licencing authority (MHRA) and to the REC for consideration. The MHRA and/or the REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC.

If applicable, other specialist review bodies (e.g. CAG) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

Amendments also need to be notified to NHS R&D departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D (e.g. a change to the funding arrangements). For studies with English sites processed in NIHR CSP the amendment should be submitted in IRAS to the lead CRN, which will determine whether the amendment requires notification to English sites or may be implemented immediately (subject to REC/MHRA approval were necessary)

Protocol amendments will be made after review between PIs and the CI and/or the Trial Steering Committee. These will be submitted through IRAS to relevant stakeholders such as REC and the JRMO. All amended study documents must be tracked for version number and dated. Decision on whether an amendment is substantial or non-substantial will be determined by the JRMO.

27.2 Access to the final trial dataset

The CI and those delegated to data analysis and reporting, such as investigators or statistician, will have access to the final trial dataset. The Trial Steering Committee also has access.

28.0 Trial Committees

The trial will be managed by a Trial Steering committee consisting Principal Investigators taking part in the study, the study management team, statistician and 2 independent medical peers. The committee will review data management, safety, and trial progress and will have the authority to terminate the study if they believe that its continuation poses unacceptable risks to patients. The committee will have a charter agreed by sponsor, CI and committee members. This charter outlines the roles and responsibilities of the committee, frequency of meetings, the documentation and dissemination of the meeting records and any decisions made.

29.0 Publication and Dissemination Policy

29.1 Publication

Publications will occur at the end of the study. The sponsor and the funder (NIHR) retains the rights to review all publications prior to submission or publication. The CI is responsible for ensuing accuracy of any publication from this study.

The full study report will be accessible via Eudra CT and Clinical trials.gov if applicable.

29.2 Dissemination policy

All publications from the study will be published with joint authorship which will include all members of the study teams at the multiple sites. No member of the study team may publish any data from

the study without the express consent of the management committee and any publications will be co-authored by all members of the study teams.

All publications will acknowledge the sponsor and the funder.

30.0 References

[1] Public Health England (2015). Hepatitis C in the UK 2015 report [online]. Available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/448710/NEW_FINAL_HCV_2015_IN_THE_UK_REPORT_28072015_v2.pdf

[2] Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014; 370:1899-1898

[3] Afdhal N, Reddy KR, Nelson D, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014; 370:1483-1493

[4] Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014 May 22; 370(21): 1973-82

[5] Zeuzem S, Dusheiko G, Sulupere R, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. NEJM 2014; 370:1993-2001

[6] Gilead Sciences. Summary of Product Characteristics Harvoni. Last update 2 Aug 2016

[7] Bristol Myers Squibb. Summary of Product Characteristics Daklinza. Last update 19 Sept 2016

[8] Gilead Sciences. Summary of Product Characteristics Epclusa. Last update 13 Jul 2016

[9] Gane EJ, Hyland RH, An D, el al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. Gastroenterology 2015 Nov; 149(6):1454-1461

[10] Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology 2015 Apr;61(4):1127-35

[11] Leroy V, Angus P, Bronowicki JP, et al. All-oral treatment with daclatasvir plus sofosbuvir plus ribavirin for 12 or 16 weeks in HCV genotype 3-infected patients with advanced fibrosis or cirrhosis: the ALLY-3+ phase 3 study. 66th AASLD San Francisco Nov 13-17, 2015

[12] Sulkowski M, Gardiner D, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014;370:211-221

[13] Welzel TM, Herzer K, Ferenci P, et al. Daclatasvir plus sofosbuvir with or without ribavirin for the treatment of HCV in patients with severe liver disease: interim results of a multicentre compassionate use program. 50th EASL Vienna Apr 22-26, 2015

[14] Foster, G.R., Irving, W.L., Cheung, M.C. et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016; 64: 1224-1231

[15] Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015;373:2608-2617

[16] Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618-2628

[17] Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1,2,4,5, and 6 infection. N Engl J Med 2-15;373:2599-2607

[18] Reau N, Agarwal K, Patel Keyur, et al. Sofosbuvir/Velpatasvir for 12 Weeks Results in High SVR12 Rates in Patients With Negative Predictors of Response to Treatment: an Integrated Analysis of Efficacy From the ASTRAL-1, ASTRAL-2, and ASTRAL-3 Studies. DDW San Diego May 22-24, 2016

[19] Kowdley KV, Nelson DR, Lalezar JP, et al. On-treatment HCV RNA as a predictor sof sustained virological response in HCV genotype 3 infected patients treated with daclatasvir and sofosbuvir. Liver Int DOI 10.111/liv.13165

[20] Alqahtani S, Zeuzem S, Bourgeois S, et al. On-Treatment HCV RNA as a Predictor of SVR12 in Patients With Genotype 1-6 HCV Infection Treated With Sofosbuvir/Velpatasvir for 12 Weeks: An Analysis of the ASTRAL-1, ASTRAL-2, and ASTRAL-3 Studies. EASL Barcelona Apr 13-17, 2016

[21] Goossens N and Negro F. Is genotype 3 of the hepatitis C virus the new villain? Hepatology 2014 Jun;59(6):2403-12

[22] European Association for Study of Liver. Clinical practice guidelines: management of hepatitis C virus infection. J Hepatol 2014 Feb;60(2):392-420

[23] EASL Recommendations on treatment of hepatitis C 2016 J Hepatol article in press

[24] Dyson JK, Hutchinson J, Harrison L, et al. Liver toxicity associated with sofosbuvir, an NS5A inhibitor and ribavirin use. J Hepatol 2015 Aug 29 [epub ahead of print]

[25] Welker MW, Luhne S, Lange CM, et al. Lactic acidosis in patients with hepatitis C virus related cirrhosis and combined ribavirin/sofosbuvir treatment. J Hepatol 2015 Nov 30 [epub ahead of print]

[26] Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011 Sep 15;365(11):1014-24

[27] Maasoumy B, Vermehren J, Welker MW, et al. Clinical value of on-treatment HCV RNA levels during different sofosbuvir-based antiviral regimens. J Hepatol 2016 Sept;65(3):473-82

[28] Dahari H, Halfon P, Colter SJ. Resurrection of response-guided therapy for sofosbuvir combination therapies. J Hepatol 2016 Sept;65(3):462-464

This protocol is based on JRMO CTIMP Protocol Template June 2015 version 4.0.