CLINICAL STUDY REPORT

ATTIC

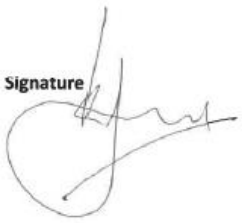
Localized on site testing and treatment of hepatitis C in homeless persons in London: a pilot non-randomised phase 4 interventional clinical trial of grazoprevir and elbasvir ± ribavirin in participants with genotype 1a, 1b or 4 to measure efficacy and adherence to treatment in a homeless population

Sponsor Protocol Code:	KCHATTIC-01
EudraCT Number:	2018-002251-14
ClinicalTrials.gov Identifier:	NCT03797066
REC Number:	18/LO/2094
Investigational Drugs (IMPs):	Grazoprevir and Elbasvir
Indication:	Hepatitis C infection
Development Phase:	4
Study Begin (FPFV):	16/07/2019
Study End (LPLV):	30/11/2020
Report Version & Issue Date:	Version 1.0 dated 11/03/2022
Co-sponsor Name and Address:	King's College Hospital NHS Foundation Trust (KCH) Denmark Hill, London SE5 9RS
Co-sponsor contact details:	
Chief Investigator:	Dr Kosh Agrawal

SIGNATURE PAGE

By signing below I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

Chief Investigator: Dr Kosh Agarwal

Printed name	Signature	Date
K Agarwal		21/Jun/22

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APPENDICES

TABLES

1. Ethics

Independent Ethics Committee or Institutional Review Board
The study protocol and amendments were reviewed and approved by a National Research Ethics Service (London – City and East, REC number: 18/LO/2094).

Ethical conduct of the study
The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

Subject information and consent
The study was designed to assess the feasibility of a test and treat pathway for the management of chronic Hepatitis C among the homeless population in the Southwark and south east London community; with the intention of being adopted / incorporated into clinical practice. Hence, the screening, identification and recruitment of participants was aligned with the current outpatient management plan.

Prior to commencement of recruitment, multiple education and training sessions were held among local clinical commissioning groups, NHS outreach services (including addiction and homeless teams; the hepatitis nursing service; as well as blood borne virus teams) and shelters within the Southwark and Lambeth region. The hepatitis outreach service within Kings College Hospital were all trained (as per GCP) to recruit patients into clinical trials. There was a project coordinator and dedicated study doctors available to support the team. The study delivery was very much a nurse led initiative; and the informed consent process was designed to reflect this.

The clinical teams are involved in providing in-reach services into hostels, shelters and localities identified by the support workers. Rough sleepers/ homeless persons are offered the opportunity to be screened for HCV as part of routine clinical care. Potential study participants were identified from this cohort, and approached at the next interaction with the in-reach team. Participants were also identified and referred by other community services e.g. BBV nurses, substance abuse teams; health inclusion team. If suitable, the health team took the opportunity to discuss clinical trials at the initial interaction.

Patients who returned a positive result; and met main study criteria were provided with patient information sheets. The outreach team nurses discussed the study with potential participants; answering any questions. Study doctors were available for telephonic consultations. Patients were discussed and highlighted in the MDT meeting as a potential study participant. As the main aim was to get patients treated, drugs were pre-dispensed by the hospital pharmacy. At the next interaction, informed consent was obtained by the doctor if present on the mobile bus; or by the hepatitis clinical nurse specialist; with additional telephone consent by the doctor at the same time. The doctor signed the telephone consent form to confirm. The team was hence able to commence treatment with no delay.

2. Data Monitoring

No formal data monitoring committee was convened for this study.

The ATTIC TSC was convened to include a multidisciplinary group of persons who comprised the following members; mostly members of the direct care teams:

- An independent Chair : Dr Matthew Foxton, consultant hepatologist – Chelsea and Westminister NHS Foundation Trust
- Chief Investigator Dr Kosh Agarwal, Consultant Hepatologist – King's College Hospital NHS Foundation Trust
- Members of the TMG: Professor Geoff Dusheiko, Emeritus Professor of Medicine;

Miss Sarah Montague (e.g. study coordinator/trial manager, study statistician, data manager etc)

- Independent clinician(s) or Scientist(s) with relevant experience: Dr Sam Douthwaite, consultant in infectious diseases; Ms Fenella Jolly, clinical nurse manager, Health Inclusion Team, Guy's and St Thomas NHS Foundation Trust; Mr David Robertson, hepatitis clinical nurse specialist, Kings College Hospital.
- One or two Principal Investigators: Dr Kosh Agarwal (Consultant Hepatologist – King's College Hospital) and Professor Graham Foster (Consultant Hepatologist – Bart's Health)
- Representative of the Funder* (not applicable as the funder has a policy not to be involved in the TSC for an investigator sponsored study)
- Representative of the Sponsor* (King's Health Partners)
- Representative of relevant patient group: Mr Stuart Smith, The Hepatitis C Trust; Mr Noah Sullivan, patient manager Thames Reach.

The TSC on behalf of the Sponsor and Funder had overall responsibility for the design and conduct of the trial and for safeguarding the rights, safety and well being of participants. Responsibilities of the TSC included monitoring recruitment, acceptance, adherence, initial SVR rates, safety and governance of the trial. The group met three monthly and updates were circulated to the study team.

3. Sponsors, Investigators and Trial Sites

Sponsors	
Kings College Hospital NHS Foundation Trust	Amy Holton King's Health Partners Clinical Trials Office F16 Tower Wing, Guys Hospital Great Maze Pond London SE1 9RT T: 02071885732 E: amy.holton@kcl.ac.uk
Chief Investigator	Dr Kaushik (Kosh) Agarwal Institute of Liver Studies Kings College Hospital NHS Foundation Trust Denmark Hill, London SE9 5RS E: kosh.agarwal@nhs.net P: +44 (0) 203 299 4015 F: +44 (0) 203 299 3167

4. Co-Investigator(s), Statistician, Laboratories, Database Management

Professor Geoff Dusheiko Emeritus Professor of Medicine , UCL Medical School, Kings College London, Royal Free NHS Trust Institute of Liver Studies Kings College Hospital Email: geoff.dusheiko@nhs.net	**Dr Kosh Agarwal** Consultant Hepatologist Institute of Liver Studies Kings College Hospital Email: kosh.agarwal@nhs.net

Professor Graham Foster Professor of Hepatology Employer Blizard Institute of Cell and Molecular Science Queen Mary University London 4 Newark Street London Email: g.r.foster@qmul.ac.uk	
Laboratory: Kings Liver Laboratories Institute of Liver Studies, King's College Hospital NHS Foundation Trust	

5. Study Synopsis

Title of clinical trial	Localized on-site testing and treatment of hepatitis C in homeless persons in London: a pilot, non-randomised phase 4 clinical trial of grazoprevir and elbasvir ± ribavirin in participants with genotype 1a, 1b or 4 to measure efficacy and adherence to treatment in a homeless population
Protocol Short Title/Acronym	ATTIC
Study Phase	4
Sponsor name	Kings College Hospital NHS Foundation Trust
Chief Investigator	Dr Kosh Agarwal
Eudract number	2018-002251-14
REC number	18/LO/2094
IRAS project ID:	238572
Medical condition or disease under investigation	Chronic Hepatitis C
Purpose of clinical trial	Direct acting antivirals (DAA) are new medications that have been approved for the management of HCV. These drugs have proven to be very effective in curing the HCV, without the need for interferon injections; which have always been used in the past. There are many combinations of DAAs, which treat specific types of HCV. Persons who test positive for the virus are typically referred to be seen and treated by a specialist hepatitis service based in hospital. This means that individuals may sometimes not attend the hospital to commence treatment; or follow up on their management. The study is designed to explore if testing and treating individuals close to their own "local" setting will be an improvement to the current treatment pathway and encourage better involvement with the health care team; as well as looking at what the health care team can do to ensure participants in

	this test-and-treat trial receive the entire course of drug treatment prescribed to treat their HCV infection. Participants infected with either genotype 1 or 4 HCV infection will be treated with Zepatier, a DAA which works by stopping the hepatitis C virus from (multiplying). The study medication is taken for 12 or 16 weeks depending on the genotype (or strain of HCV). Some participants will be given an additional drug called ribavirin. The study will examine the effectiveness of Zepatier at clearing the hepatitis C virus from the blood and body; and also what particular effects may be experienced by participants who may also be taking treatment for other conditions. Participants affected with other genotypes (not 1 and 4)will be offered standard NHS treatment with the appropriate antiviral combination for these strains.
Primary objective	I. Evaluate sustained virological response rates (SVR 12), assessed by the percentage of participants achieving SVR [defined as HCV RNA <lower limit of quantification when tested by sensitive polymerase chain reaction (PCR)] 12 weeks after the end of all study therapy of the fixed dose combination of elbasvir (ELB) and grazoprevir (GZR); given for 12 or 16 weeks in homeless persons with hepatitis C. II. To demonstrate the utility of immediate diagnosis of infectious and progressive hepatitis C by direct testing for HCV RNA and concurrent staging of the liver disease by transient elastography (fibroscan) or APRI testing in homeless centres.
Secondary objective (s)	I. To demonstrate the comparable safety to other DAA treated populations II. To reduce the viraemic interval in infected homeless persons by introducing a short, directed testing-to-treatment pathways – to virological cure (SVR). III. To evaluate the safety and efficacy of this regimen in homeless participants with hepatitis C, many of whom will be using drugs of potential abuse or will be on Opioid Substitution IV. To reduce the prevalence of viraemic hepatitis C, after a pilot trial of treatment in three to four homeless hostels (depending upon recruitment). V. To evaluate participant knowledge of their hepatitis C status and willingness to engage in a test and treat protocol and to correlate the findings with demographic and sociological data

Trial Design	This was a phase 4, open label, non-randomised study, conducted in hostels and homeless shelters in London; as well as mobile clinics in collaboration with the Hep C trust and the NHS Find and Treat program. Treatment: 12 or 16 weeks of Zepatier, based on genotypes; with Ribavarin for certain subtypes. The study drug was administered as a single tablet; which is a combination of 100 mg of grazoprevir and 50 mg of elbasvir; as outlined below: Genotypes 1a/b and 4: once daily dose for 12 weeks, taken with / without food. Genotype 1a and 4: (HCV RNA> 800,000 iu/ml or baseline NS5A resistance): once daily dose for 16 weeks, taken with / without food. There were NO dose modifications with the study drug. Assessment while on treatment at weeks 4/8/12 and 16 (as required) Follow up at weeks 4/8/12 post treatment completion. It was estimated that patients would be in the study for approximately 30 weeks maximum. Screening 7-14 days, as the intention was to commence treatment within a week of diagnosis. On treatment and follow up as below: Genotypes 1a/b and 4: 24 weeks (12 weeks treatment and 12 weeks follow up) Genotype 1a and 4 (HCV RNA> 800,000 iu/ml or baseline NS5A resistance): 28 weeks (16 weeks treatment and 12 weeks follow up)
Endpoints	The primary endpoint was SVR 12.
Planned number of subjects	100
Summary of eligibility criteria	1. Participants 18 years or older with chronic hepatitis C genotype 1 or 4 were eligible. 2. Able and willing to provide written informed consent. 3. Both interferon treatment naïve and experienced participants included. 4. Participants without cirrhosis, if HCV RNA positive, documented chronic hepatitis C and a FibroScan of ≤ 12.5. 5. Participants with cirrhosis (Fibroscan > 12.5 or APRI > 2) eligible if the serum albumin was > 3.5 g/dl, platelets > 100,000 and INR < 1.5 with no prior history of hepatic decompensation. 6. Participants with well controlled HIV coinfection; should be stabilized on antiretrovirals for which no clinically significant interaction is expected. 7. Participants who are HBsAg positive included; with a requirement for antiviral prophylaxis for hepatitis B. Anti-HBc positive participants included; prophylaxis not given but these clients would require close monitoring of their ALT elevations

IMP, dosage and route of administration	Zepatier, 50/100mg per day, oral
Active comparator product(s)	none
Maximum duration of treatment of a subject	16 weeks
Version and date of protocol amendments	V2.7 28/02/2019

6. Glossary of terms

DAA	Direct acting antivirals
HCV	Hepatitis c virus
HCV Abs	Hepatitis C antibodies (indicates previous or current infection)
HCV RNA	Hepatitis C Ribonucleic acid (indicates current infection also known as viraemia)
CNS	Clinical nurse specialist
POCT	Point of care testing
GCP	Good clinical practice
MHRA	Medicines and Healthcare Regulatory Agency
KCH	Kings College Hospital
PCR	Polymerase chain reaction
SVR	Sustained virological response
RNA	Ribonucleic acid
MDM	Multidisciplinary meeting
TFA	Theoretical framework of acceptability
PWID	Patients who inject drugs
PHE	Public Health England
IVDU	Intravenous drug users

7. Publication (reference)

Online blog:
Treading the path less travelled – A different approach to patient recruitment (Bioscience Today) https://www.biosciencetoday.co.uk/treading-the-path-less-travelled-a-different-approach-to-patient-recruitment/

Abstracts, posters and publications:

1. Montague S, Sevdalis N, Boufkhed S, Curtis M, Sekhon M, Dusheiko G and Agarwal K (2020) High patient acceptability for a Hepatitis C Mobile Outreach Service targeting 'vulnerable' homeless communities – an important component for elimination? *Journal of Hepatology.*
2. Allan Rob, Montague Sarah (2020). *London Joint Working Group Annual Conference.* Your role in eliminating hepatitis C in London
3. Montague, S (2019) An evaluation of the implementation of a hepatitis c mobile outreach service for the homeless in south London. *Dissertation MSC Implementation and Improvement Science*, Kings College London.

8. Study period (years)

FPFV: 16/07/2019
LPLV: 28/07/2020

End of Trial: 30/11/2020, Early termination due to various reasons which are outlined in section 19.2

9. Phase of development

Phase 4 non-randomised study

10. Objectives

Primary objectives:

1. To evaluate the percentage of patients achieving sustained virological response (SVR 12), assessed by the percentage of participants achieving SVR [defined as HCV RNA <lower limit of quantification when tested by sensitive polymerase chain reaction (PCR)] 12 weeks after the end of all study therapy of the fixed dose combination of elbasvir and grazoprevir; given for 12 or 16 weeks in homeless persons with hepatitis C.
2. To demonstrate the suitability of immediate diagnosis of infectious and progressive hepatitis C in homeless shelters; by directly testing for HCV RNA and concurrent staging of the liver disease by transient elastography (fibroscan) or APRI testing (AST to platelet ratio index).

Secondary objectives:

1. To demonstrate the comparable safety to other DAA treated populations
2. To reduce the viraemic interval in infected homeless persons by introducing a short, directed testing-to-treatment pathway – to virological cure (SVR).
3. To evaluate the safety and efficacy of this regimen in homeless participants with hepatitis C many of whom will be using drugs of potential abuse or will be on Opioid Substitution
4. To reduce the prevalence of viraemic hepatitis C, after a pilot trial of treatment in three to four homeless hostels (depending upon recruitment).
5. To evaluate participant knowledge of their hepatitis C status and willingness to engage in a test and treat protocol and to correlate the findings with demographic and sociological data

11. Background and Context

There has been a national increase of rough sleeping over the past 10 years. Recent statistics show that in August 2017, there were 1137 rough sleepers in London, who accounted for 24% of the rough sleeping population in England. People experiencing homelessness in London have a very high prevalence of latent tuberculosis infection (16.5%), hepatitis B (11.95) and hepatitis C (13%) infection and co-infection,compounded by poor engagement with care. HCV infection was substantially increased in participants reporting injecting drug use, but even persons without a drug history, levels of HCV infection was higher than the general population. There have been rapid developments in testing and treatment for bloodborne viruses (BBVs, which provide new opportunities for effective diagnosis and management. The introduction of interferon-free regimens of short duration (typically 12 weeks) has the potential to improve engagement with care in this vulnerable population. Direct acting antiviral drugs (DAAs) are better tolerated and have the potential to eliminate the virus. Despite these advances, there are still concerns about treatment in the homeless population due to poor treatment adherence. Traditionally, the treatment of HCV is hospital-based, which results in several barriers to access and treatment. There is a lengthy interval between referral and first specialist appointment, followed by numerous subsequent hospital assessments. Hepatology specialists are also unable or unequipped to manage day to day uncertainties that homelessness presents to a person with HCV infection, which can deter treatment. New models of care are needed to reduce the viraemic interval in infected homeless persons by introducing a short, directed testing-to-treatment pathway.It is also important to determine the current ability of health services to successfully treat those homeless people identified with HCV. This study was been designed to address this uncertainty in the local population, and also determine how service provision can be best integrated with other NHS providers and charitable organisations to improve client engagement with services.

12. Methodology

Conceptual Framework:
There is a great need for locally based interventions to inform services and guide treatment delivery. Although NICE guidelines recommend screening homeless populations for viral hepatitis, general NHS measures to reduce hepatitis C are not translating into a lower prevalence in the homeless. Because homeless individuals are a hard to reach population, research into these marginal groups remains a challenge. Active hepatitis C infection is a significant predictor of mortality; yet treatment rates remain low for an eminently treatable (and transmissible) illness.

We hypothesize that to realise the promise of test and treat strategies with new DAA therapies, rapid ascertainment of viremia and effective treatment within homeless services will be required to reduce the overall prevalence of hepatitis C in at risk populations and homeless centres. Our strategy is to leverage rapid testing and enhanced treatment access with lower cost and greater efficiencies. We aim to bypass complex and inefficient referral algorithms; and to employ a policy of in-reach testing, staging and treatment delivered by trained blood borne virus (BBV) and by in- and out- reach specialist nurses. In this manner, we aim to reduce unnecessary referral delays and "no shows" and improve patient management. Our goal is to demonstrate the achievability of effective co-localised services and their effectiveness in reducing the prevalence of HCV infection in the important but underserved homeless population.

We hypothesise that co-localised services are the most rational strategy to expand testing, staging and treatment that will translate into more meaningful numbers of treated homeless persons; thus reducing incident chronic infection. A successful co-localisation of services will be instrumental in exemplifying models of care for similar community centres. Our proposal to decentralise services in homeless hostels will provide an important test bed for managing the epidemic of hepatitis C and to demonstrate outcomes of test and treatment strategies.

Trial Duration:
24 months proposed duration of study, terminated early due to poor recruitment.

Definition of Trial Time Measurements:
The study patient interactions and consequent investigations is outlined in the schedule of events in the table below.
Participant involvement in the study would conclude with the SVR 12 visit (in patients receiving 12 weeks of treatment at week 24, in patients receiving 16 weeks of treatment at week 28). No further follow up planned and participant would return to routine standard of care follow up.

Table 1: Schedule of events

	Screening visit	TW0	TW4	TW8[e]	TW12 (EOT) [a]	TW16 (EOT) [b]	SVR 4	SVR 12
Eligibility	X							
consent	X							
Medical History	X							
Physical exam	X							
Weight	X							
TE/APRI	X							
Genotype	X							
FBC*	X	X	X	X	X	X	X	X
INR *	X	X	X	X	X	X	X	X

Renal and bone profile ⁎	X	X	X	X	X	X	X	X
Liver profile	X	X	X	X	X	X	X	X
ALT	X	X	X	X	X	X	X	X
HCV RNA*	X	X	X	X	X	X	X	X
HBV serology	X		Only if elevated LFT's		Only if elevated LFT's	Only if elevated LFT's		Only if elevated LFT's
HIV	X							
TB screen [c]	X							
Urinalysis	X	X	X	X	X	X		
Urine Drug screen	X	X	X	X	X	X	X	X
Urine pregnancy test	X	X	X	X	X	X		
Conmeds	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Questionnaire	X							
QoLs		X						X
AFP	X							
Liver US ~	X							
IMP dispensing		X	X	X	X[d]			

⁎ need for sample will be reviewed, depending on baseline results, co-morbidity and clinical presentation
* Cepheid or venous sample
~ Liver US to be undertaken for cirrhotic patients only. Cirrhosis defined as LSM > 12.5 kpa on fibroscan or APRI >2
[a] TW 12 EOT in patients with genotypes 1a/b and 4
[b] TW 16 EOT in patients with genotypes 1a and 4 (HCV RNA >800.000 iu/ml or baseline resistance
[c] TB screen will be undertaken only if results not available within last 6 months, and participants are symptomatic / have history of recent contact with infected persons.
[d] Drugs dispensed to participants receiving 16 weeks of treatment only
[e] Treatment will 8 will be optional. Data collected if patients are reviewed clinically.

Trial Medication:
Zepatier: Grazoprevir and elbasvir available in a two-drug fixed-dose combination containing 100 mg of grazoprevir and 50 mg of elbasvir, in a single tablet**.**

Dosing Regimen:
Treatment delivered as per EMA guidelines in table 2 below:

Table 2: Recommended Zepatier treatment as per EMA

HCV genotype	Treatment and duration
1a	ZEPATIER for 12 weeks ZEPATIER for 16 weeks plus ribavirin[A] should be considered in patients with baseline HCV RNA level >800,000 IU/ml and/or the presence of specific NS5A polymorphisms causing at least a 5-fold reduction in activity of elbasvir to minimise the risk of treatment failure (see section 5.1).
1b	ZEPATIER for 12 weeks
4	ZEPATIER for 12 weeks ZEPATIER for 16 weeks plus ribavirin[A] should be considered in patients with baseline HCV RNA level >800,000 IU/ml to minimise the risk of treatment failure (see section 5.1).

[A] In the clinical studies, the dose of ribavirin was weight-based (< 66 kg = 800 mg/day, 66 to 80 kg = 1,000 mg/day, 81 to 105 kg = 1,200 mg/day, > 105 kg = 1,400 mg/day) administered in two divided doses with food.

13. Number of patients (planned and analysed)

13.1 Planned:
100 - 150

13.2 Analysed

Due to the protracted regulatory processes in the UK; The Access to Treat In the Community (ATTIC) trial received authorisation on the 23rd of March 2019; almost 6 months after the 'go live' date of the KCH mobile outreach service.
Over 712 people were screened by the Hepatitis C Mobile Outreach Clinic since going live at the end of September 2018. Homeless people were approached at 41 different sites across Lambeth, Lewisham, Southwark and Woolwich which included homeless hostels, detoxification and rehabilitation centres, day centres and street outreach (predominantly around the vicinity of Waterloo station but also London Bridge station).

Our initial strategy was to raise awareness of the mobile service both amongst homeless people as well as staff working in the homelessness sector. Initially we focused on visiting day centres, detox and rehabilitation centres and homeless hostels. To complement this effort, we delivered educational talks about HCV and our new model to hostel staff and homelessness organisations (please see appendices for full list of awareness and education sessions and blogs).
When reviewing our screening data it became apparent that serving detox and rehabilitation centres was not an efficient use of resource (no HCV RNA positive patients were identified); thus our strategy changed, shifting to screening street homeless individuals. We maintained our relationships with day centres as they can prove extremely valuable in tracking down patients that have disengaged, been hospitalised or arrested.

When screening street homeless individuals, we focused our efforts around busy train stations primarily Waterloo and London Bridge. Due to the high number of commuters passing through these localities we found communities of homeless people that will regularly visit these localities to solicit or beg. We have observed a higher prevalence of HCV in these individuals but they are often more difficult to engage. Several practical impediments also make recruitment difficult i.e. finding toilet facilities for urine tests etc.

In short: we delivered 158 sessions at 41 different sites across southeast London. We screened 712 persons; 161 of whom were antibody positive. 86 of these persons have tested positive for HCV RNA; with 43 of those either genotype 1a/1b (no genotype 4's have been found).

With respect to the ATTIC study: Informed consent was obtained from 13 patients. Of the 43 HCV RNA positive genotype 1a/1b patients, only 20 were identified after approval of the study. 35 patients had been initiated on treatment via standard of care (16 G1a/1b/4, 2 G2, 14 G3 and 3 unknown genotype due to poor venous access).

Table 3: patient treatment and withdrawal

Patient ID	Treatment completed Y/N	SVR obtained Y/N	Reason for withdrawal/non completion
001	Y	N	Patient lost to follow up
002	Y	Y	
003	Y	Y	
004	Y	N	Patient lost to follow up
005	Y	N	Patient lost to follow up
006	Y	Y	
007	Y	Y	
008	Y	Y	
009	N (treated off study)	N	Refused contraception - withdrawn
010	Y	Y	
011	Y	N	
012	N	N	Withdrawal by subject – went to Southampton to detox
013	Y	Y	

14. Diagnosis and main criteria for inclusion

Diagnosis of chronic hepatitis C.
Inclusion:

- Participants 18 years or older with chronic hepatitis C genotype 1 or 4 were eligible.
- Able and willing to provide written informed consent.
- Both interferon treatment naïve and experienced participants included.
- Participants without cirrhosis, if HCV RNA positive, documented chronic hepatitis C and a FibroScan of ≤ 12.5.
- Participants with cirrhosis (Fibroscan > 12.5 or APRI > 2) eligible if the serum albumin was > 3.5 g/dl, platelets > 100,000 and INR < 1.5 with no prior history of hepatic decompensation.
- Participants with well controlled HIV coinfection; should be stabilized on antiretrovirals for which no clinically significant interaction is expected.
- Participants who are HBsAg positive included; with a requirement for antiviral prophylaxis for hepatitis B. Anti-HBc positive participants included; prophylaxis not given but these clients would require close monitoring of their ALT elevations

15. Test product, dose and mode of administration

Baseline therapy
Participants continued on any standard of care medication, including opioid substitution therapy. There was no non IMP medication delivered as part of the study.
Ribavarin weight based as per standard of care.

IMP
Zepatier administered as a once daily fixed dose combination of elbasvir (50mg) and grazoprevir (100mg).

16. Duration of treatment

Genotypes 1a/b and 4: 12 weeks study treatment and 12 weeks follow up
Genotype 1a and 4: (HCV RNA> 800,000 iu/ml or baseline NS5A resistance): 16 weeks study treatment and 12 weeks follow up with weight - based ribavirin administered.

17. Criteria for evaluation: Endpoints

Primary end-point:
The primary efficacy end point will be the percentage of participants achieving an SVR, defined as an HCV RNA level less than the lower limit of quantitation by sensitive PCR.
Secondary end-point:
Acceptance of the mobile outreach service among the homeless community.

18. Statistical Methods

As this study was a non-randomized, unblinded study and all genotype 1 and 4 patients receive treatment, no comparative statistical test was required to assess the primary objective of overall SVR in this group. A power calculation and sample size was therefore not calculated for this pilot study.
The details below outline the variables to be reviewed, and no separate statistical analysis plan was used.
Primary Outcome:
The percentage of participants achieving an SVR, defined as an HCV RNA level less than the lower limit of quantification by sensitive PCR; by means of a short directed test and treat program in the homeless community.
Secondary Outcomes:
1. Reduction in local prevalence of of viraemic hepatitis C, after a pilot trial of treatment in three to four homeless hostels.
2. Participant knowledge of their hepatitis C status and willingness to engage in a test and treat protocol and correlation of these findings with demographic and sociological data.
3. Impact of a localized test and treat protocol on health related quality of life.
Analysis
Our study was a limited sample observational proof of concept and developmental study in genotype 1 and 4

homeless persons. The analysis focussed on descriptive statistics i.e. calculation of standard deviation, mean and median values.
The intention was to compile completion of treatment data, with careful reflection analysis of adherence by point of care HCV RNA testing. The data was to include end of treatment HCV RNA negativity, post treatment week 12 HCV RNA negativity and monitoring of reinfection rates with documentation of reinfection history. The data was to be calibrated against the period of known viremia prior to treatment.
We had also intended to assess correlation between acceptance of testing, of treatment, and completion of treatment, with a number of demographic and sociological parameters determined at baseline.

The limited data available was analysed by the investigator. The patients were included in the Kings College HepCare database so that real time safety and efficacy results could be obtained for analysis and intervention if required.

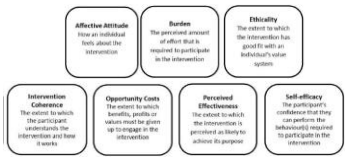
Variables/Time Points of Interest:
The primary efficacy variable is standard for this therapeutic intervention namely undetectable HCV RNA at post treatment week 12. The sensitivity of the Cepheid HCV RNA is equivalent (or slightly greater) than the Roche Amplicor PCR assay. The results in all patients were analysed based on the principles of intention to treat.
Patients who stopped treatment prematurely were considered as treatment failures. The reference SVR 12 rate was pre-specified at 50%, based on previous assessments of pegylated interferon and ribavirin treatment in these genotypes in those with injection drug use.
The time points for HCV RNA are as indicated in the study schedule of events in section 12.The pivotal variable is undetectable HCV RNA at post treatment week 12, as discussed in the objective section and relate to the primary hypothesis.

19. Summary – Conclusions

19.1 Acceptance of HCV mobile service

Summary data can be included here. It is mandatory to provide details on gender and age of the treated subjects at a minimum for EudraCT.

Acceptability of the Hepatitis C Mobile Outreach Clinic was assessed using an adapted theoretical framework of acceptability (TFA) questionnaire as published by Sekhon et al (2017). The TFA (see figure below) shows a multi-faceted framework formed of seven distinct constructs: affective attitude, burden, ethicality, perceived effectiveness, intervention coherence, self–efficacy and opportunity cost.



Each construct of the TFA is measured by one question, and the first question is included to assess the general acceptability of the intervention and to also act as a check of the content validity. Each construct is measured by a 5-point Likert scale.
The survey was composed of three adapted TFA questionnaire to measure the different aspects of the intervention: general service, finger prick blood testing and the peer navigator. Some patient demographics were collected: age, gender, IVDU, HCV diagnosis and treatment status. This information assisted with purposive sampling, ensuring that a variety of different ages, injecting histories and HCV statuses were represented. Patients were not identifiable from this information.
Acceptability was assessed among patients, and staff (as implementors of the service).

Patient participants were recruited between 25/03/2019 and 12/06/2019. It was not feasible to record the uptake rate. Table 4 below describes patient demographics. 77% of patients surveyed were male and 69% of all

patients surveyed reported either past or current intravenous drug use. All patients (100%) had either been infected with HCV in the past or were currently chronically infected with HCV during the period of the survey.

Table 4: Demographic data (HCV acceptance)
[Participants N=13]

	N	%
Gender		
Male	10	76.9
Female	3	23.1
Age		
18-24	0	0
25-34	2	15.4
35-44	9	69.2
45-54	2	15.4
55-64	0	0
>65	0	0
Intravenous drug use		
Yes - current use	8	61.5
Yes - past use	1	7.7
No	4	30.8
Hepatitis C status		
Past infection	0	0
Current infection	13	100
Never infected	0	0
Unknown	0	0

Table 5 below presents the mean rating for each question of the TFA for each aspect of the intervention surveyed. Responses for the overall service were positive, demonstrating high acceptability; and likewise, for the two innovative components of the intervention: finger prick blood testing and the peer navigator. The highest level of acceptability is recorded for question 1 of the overall service survey (4.8, SD= 0.43).

The lowest level of acceptability, with highest levels of variation, is recorded for question 2 of the finger prick blood testing survey (3.5, SD= 1.20). The qualitative commentary for this survey indicates that some participants reported that the finger prick testing is preferable to venous blood collection by traditional phlebotomy however having any blood collected at all is still considered unpleasant and requires too much effort. This was borne out in the actual clinical study where most participants refused any blood taking at study visits.

Table 5: Mean TFA survey results

Table 6 – Item scores for the patient TFA surveys

Theoretical Framework of Acceptability - TFA (Sekhon et al, 2017)	Mean	SD	Median	IQR (Interquartile range 0.25	0.75
Overall service					
Q1) How acceptable did you find the hepatitis c mobile outreach service?	4.8	0.43	5	5.0	5.0
Q2) Did you like or dislike the hepatitis c mobile outreach service?	4.5	0.61	5	4.0	5.0
Q3) How much effort did it take to engage with the hepatitis c mobile outreach service?	4.2	1.28	5	4.0	5.0
Q4) How fair (to all homeless people) is the hepatitis c mobile outreach service?	4.8	0.49	5	5.0	5.0
Q5) The hepatitis c mobile outreach service is likely to improve the chances of homeless people being cured from hepatitis c:	4.4	0.85	5	4.0	5.0
Q6) It is clear to me how the Hepatitis C Mobile Outreach Clinic would help homeless people manage their hepatitis c infection:	4.6	0.56	5	4.0	5.0
Q7) How confident did you feel engaging with the hepatitis c mobile outreach service?	4.5	0.74	5	4.0	5.0
Q8) Engaging with the Hepatitis C Mobile Outreach Clinic interfered with my other priorities:	4.1	1.06	4	4.0	5.0
Finger prick					
Q1) How acceptable is the finger prick test that is offered as part of the hepatitis c mobile outreach service?	4.4	0.73	4	4.0	5.0
Q2) Did you like or dislike the finger prick testing?	3.5	1.20	4	3.0	4.5
Q3) How much effort did it take to receive the finger prick testing?	4.2	1.27	5	4.0	5.0
Q4) How fair (to all homeless people) is having access to finger prick testing as part of the hepatitis c mobile outreach service?	4.5	0.66	5	4.0	5.0
Q5) Finger prick testing is likely to improve patient engagement with the hepatitis c mobile outreach service:	4.4	0.65	5	4.0	5.0
Q6) It is clear to me how finger prick testing would help homeless people manage their hepatitis c infection:	4.2	0.94	4	4.0	5.0
Q7) How confident did you feel about completing the finger prick testing?	4.2	0.87	4	4.0	5.0
Q8) Finger prick testing interfered with my other priorities:	4.4	0.92	5	4.0	5.0
Peer navigator					
Q1) How acceptable do you find the role of having a peer navigator on the hepatitis c mobile outreach service?	4.7	0.58	5	4.5	5.0
Q2) Do you like or dislike having a peer navigator as part of the hepatitis c mobile outreach service?	4.5	0.56	5	4.0	5.0
Q3) How much effort does it take to engage with the peer navigator?	4.3	1.18	5	4.0	5.0
Q4) How fair (to all homeless people) is having access to a peer navigator as part of the hepatitis c mobile outreach service?	4.6	0.81	5	4.0	5.0
Q5) The peer navigator is likely to improve patient engagement with the hepatitis c mobile outreach service?	4.4	0.65	4	4.0	5.0
Q6) It is clear to me how the peer navigator will help homeless people manage their hepatitis c infection:	4.5	0.51	4	4.0	5.0
Q7) How confident did you feel about interacting with the peer navigator?	4.6	0.49	5	4.0	5.0
Q8) Engaging with the peer navigator interfered with my other priorities:	4.2	1.15	5	4.0	5.0

Results demonstrate high levels of acceptability for the overall service and two discrete components assessed. Ergo it is not the healthcare model that patients struggle the most to engage with; it is likely the requirements of the protocol that are too demanding.

19.2 Primary outcome: percentage of participants achieving an SVR

The primary aims of this study were to 1) Evaluate Sustained Virologic Response (SVR) rates, assessed by the percentage of participants achieving an undetectable HCV RNA 12 weeks after completion of DAA therapy (endpoint) and 2) Demonstrate the utility of immediate diagnosis using point-of-care technologies. Patients were to be recruited into a clinical trial to assess SVR. However, although large numbers of patients have been screened and tested, recruitment did not kept pace with planned targets. E.g. As at the 31/3/20, we had screened 712 patients; at 41 different sites across Lambeth, Lewisham, Southwark and Woolwich. Of these 161 tested Antibody positive ; 86 tested RNA positive; with 42 patients initiating treatment (13 of whom participated in the ATTIC study).

Therefore the study faced major challenges. Some of which included the following:

- *The prevalence of hepatitis C may be lower than what was predicted.*

PHE data estimated HCV RNA positivity in the PWID population to be 30%. As previous or current IVDU is high amongst homeless people, HCV RNA positivity was expected to be similarly high. Our testing data, however instead suggests a test-positive rate of between 8-12%.

- *Likelihood patients will drop out during trial.*

We do not want to set our patients up to fail; therefore the team has had to make necessary judgements on adherence to a rigid clinical trial protocol and monitoring. If the person was considered unlikely to adhere to more than 80% of the trial monitoring visits, they were not considered for the formal trial. Building trust in this cohort of patients is difficult and the impositions of a trial versus current low-monitoring treatment could have jeopardised any future engagement with health services.

- *This patient group has several co-morbidities*

Homeless people often suffer from high rates of mental ill health, physical ill health, and drug and/or alcohol misuse and therefore they are likely to not meet the stringent inclusion criteria of the study protocol. Treatment via standard of care (SoC) has been challenging as staff have had to courier medication from homeless day centres to both St Thomas's and St George's Hospital.

- *Protocol restrictions such as the time period allowed between screening and commencing treatment (12 week limit)*

Homeless people are often described as 'chaotic'. Setting up regular appointments is challenging, and tracing is difficult as they often are without mobile phones and frequently move out of area. When found they may not

want to engage as their most important priority is often not related to health issues, and may be linked to drug or alcohol misuse. E.g. some clients are waiting to "score" or have recently taken drugs and therefore do not have capacity to consent to the study or any medical procedures.
Often patients would fall outside of the 12-week screening and consent window by the time they re-engage with the team. Re-bleeding patients again for screening purposes was problematic as these patients are often difficult to bleed (due to IVDU and poor venous access) and attempting to obtain the required volume of blood can be traumatising. Exposure to cold in the winter, further complicates venous access.

- *Requirement for pregnancy testing (and urine drug testing).*

Toilet facilities are seldom available. There is considerable stigma associated with urine testing. Also, NHS SoC procedures do not require pregnancy testing prior to treatment initiation.

19.3 Safety results: AEs / SAEs and SUSARs

There were no SAEs or SUSARs recorded during the study.

Commented [VT1]: do we have a table with SAEs / AEs from teh monitoring visit?

Table 6: Listing of Adverse Events for all patients *(state which version of the MedDRA dictionary or other medical dictionary was used to code the events)*

Record ID	Adverse event	Start Date	End Date	Ongoing:	AE Duration:	Relationship to study treatment	Action taken with study drug	Other action taken	AE Toxicity Grade	AE Serious?
110012	Abdominal discomfort	24-02-2020	18-03-2020	No	23 days	Possibly related	Not discontinued	None	2	No
110006	Itching	24-09-2019	15-01-2020	No	113 days	Unlikely to be related	Not discontinued	None	1	No
110006	Chest pains	09-10-2019	09-10-2019	No	0 days	Unlikely to be related	Not discontinued	Medication Required	2	No
110012	Fracture to right hand	07-04-2020	07-04-2020	No	0 days	Unlikely to be related	Not discontinued	None	Missing/not done	No
110003	Headaches	13-08-2019	19-08-2019	No	6 days	Possibly related	Not discontinued	None	2	No
110003	Fever	24-09-2019	25-09-2019	No	1 day	Unlikely to be related	Not discontinued	None	1	No
110013	Rash	10-03-2020	24-03-2020	No	14 days	Possibly related	Not discontinued	None	1	No

110010	Swollen lower leg	16-06-2020		Yes	ongoing	Unlikely to be related	NA	None	1	No
110010	Inflammed groin	16-06-2020		Yes	ongoing	Unlikely to be related	NA	None	2	No
110008	Tiredness	31-12-2019		Yes	ongoing	Possibly related	Discontinued study drug	None	3	No
110008	Sweaty palms	31-12-2019		Yes	ongoing	Unlikely to be related	Discontinued study drug	None	3	No
110007	Sight loss both eyes	01-01-2998		Yes	ongoing	Unlikely to be related	Not discontinued	None	1	No
110013	Vomitting	10-03-2020	10-03-2020	No	0 days	Unlikely to be related	Not discontinued	None	1	No
110003	Tiredness	13-08-2019	30-08-2019	No	17 days	Possibly related	Not discontinued	None	2	No
110012	Black out (whilst drunk)	07-04-2020	07-04-2020	No	0 days	Unlikely to be related	Not discontinued	None	2	No
110012	Found 'passed out' at a bus stop	22-02-2020	23-02-2020	No	1 day	Unlikely to be related	Not discontinued	None	1	No

110013	Black out/collapse	26-02-2020	27-02-2020	No	1 day	Possibly related	Not discontinued	None	Missing/not done	Missing/not done

Table: Listing of Serious Adverse Events for all patients

Within the per protocol population (n= 13), a total of 17 AEs, including 0 SAE, were identified as treatment-emergent and included in the safety analysis. Summary tables for AEs and SAEs are presented in the appendix of this synopsis.

Overall, 7 patients (54%) patients experienced at least one AE. The proportion that experienced at least one SAE was 0% (n=0).

Incidence of adverse drug reactions (ADRs): 6 / 17 AEs (35 %) were assessed as possibly related to at least one study drug and 0 / 13 patients (0 %) experienced ADR.

There were 0 Serious Adverse Reactions (SARs), 0 unexpected SARs and 0 SUSARs.

20.4 Conclusion

Unfortunately, a rigid clinical trial protocol with a DAA regimen, utilising an approved treatment regimen that has been delivered successfully and safely worldwide for many thousands of patients, including IVDU, and which is incorporated into international treatment guidelines has become outmoded. Regrettably the funder's stipulation for a formal, research approved clinical trial became asynchronous with treatment models for hepatitis C.

When written in 2016 the protocol reflected the need for exploratory parameters in a uniquely underserved population. However, by 2019/2020 when the study was being delivered, the goal posts had shifted rapidly toward widespread testing and elimination. Lowering barriers for standard of care, had become the norm, thus changing practice and service models. The emphasis for management of HCV shifted to minimal monitoring and ready access to treatment. Placing a higher appointment and blood monitoring burden on a cohort of patients known for chaotic and transitory lifestyles was out of keeping with the needs of the homeless population, and hampering rather than assisting treatment, cure and thus a reduction of transmission, and gain of health.

It became apparent that a clinical trial is not an ideal method to meet the models of control of hepatitis C in the homeless population. The onset of the SARS-CoV-2 pandemic presented further challenges to homeless persons and certainly hindered hepatitis screening efforts. The outreach service was terminated in March 2020 and consequently recruitment halted , coinciding with the NIHR decision to halt recruitment to clinical trials across the UK. Careful consideration of the clinical risks to staff and patients, and the slow rate of recruitment resulted in a decision to terminate the study prematurely.

21. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated 02/Jun/2022.

APPENDICES