PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Copenhagen test and treat hepatitis C in a mobile clinic Study: A protocol for an intervention study to enhance the HCV cascade of care for people who inject drugs (T'N'T HepC)
AUTHORS	Lazarus, Jeffrey; Øvrehus, Anne; Demant, Jonas; Krohn-Dehli, Louise; Weis, Nina

VERSION 1 – REVIEW

REVIEWER	Dr Stuart McPherson Liver Unit The Newcastle upon Tyne Hospitals NHS Foundation Trust Freeman Hospital Freeman Road Newcastle upon Tyne NE7 7DN
REVIEW RETURNED	22-May-2020

GENERAL COMMENTS	This trial protocol is well written, with important objectives that are clearly articulated. I particularly like the design of the study using peers to run the mobile testing unit. This is a good approach and will hopefully help achieve high testing and treatment rates. I have a couple of minor points that the authors may like to consider addressing to enhance the manuscript. 1. It may be helpful to describe in more detail the locations of potential testing locations and particularly the treatment services, perhaps with a simple map. This will give readers a clearer idea of the geography. The closer patients are to treatment services the more likely they are to have treatment (Simpson H, Journal of Public Health 2019) so this may help address this 2. Will incentives be used at any part of the process? If so then please describe or state incentives not used 3. Will there be any attempt to look for reinfections after treatment? Re-infection rates in our region are very high and some patients who are labelled as a treatment failure actually have reinfection eg Patient had treatment for HCV G3 with epclusa and the HCV RNA at 12 weeks was positive treatment suggesting failure, but when genotype tested they were G1a, indicating early reinfection rather than treatment failure Overall a nice study design and I look forward to seeing the results of it in due course.

REVIEWER	Giada Sebastiani McGill University
REVIEW RETURNED	30-May-2020

GENERAL COMMENTS	In this protocol, Lazarus and colleagues present an ongoing study aimed to evaluate the efficacy for testing and linkage to care among people who inject drugs using a peer-based testing at a mobile clinic in Copenhagen, Denmark. The researchers will recruit participants at a community-based, peer-driven mobile clinic, and they will perform a point-of-care HCV antibody test, HCV RNA test and facilitated referrals to designated “fast-track” clinics at a hospital or an addiction centre for treatment. These tests/referral will be administered in the single visit. The primary outcomes for this study are the number of tested and treated individuals. Secondary outcomes include individuals lost at each step in the cascade of care. The study protocol is well written and addresses and important health issue, responding to the WHO call for elimination of HCV by 2030. It focuses on micro elimination in high risk populations, including PWID, homeless and migrants. I have the following comments: 1) I am not sure why an approval from the ethics committee was not required for this study. There is no mention for informed consent throughout the study protocol. This should be thoroughly explained and justified. 2) Inclusion and exclusion criteria for this prospective study are not provided. 3) As the researchers mention, patients will undergo genotype testing, which would represent an additional step into the cascade of care, with increasing possibility of drop out. Patients may be waived the genotype, according to the researchers, however it would be still important to know the genotype as genotype 3 may be associated with need for different treatment, especially in countries where the treatment algorithm is genotype-based, and with higher risk for progressive fibrosis and risk of HCC. This could be considered a limitation of the study protocol. 4) It is not clear whether the liver fibrosis staging will be integrated into the single visit. Do the researchers plan to consider a portable Fibroscan in the single study visit? Quality criteria for reliable Fibroscan examination are missing. The researchers mention that the participant will undergo two Fibroscan examinations? Are patients referred to another clinics/hospital to have the assessment of liver fibrosis? It is known that adding multiple steps in the cascade of care may increase the risk of drop out. Also, the European guidelines recommend combination of two non-invasive tests for liver fibrosis staging in hepatitis C, so will the researchers perform also a APRI/FIB-4 and combine the result with the one from Fibroscan? It would be more efficient instead of adding a second Fibroscan to enlist quality criteria for Fibroscan examination and combine it with FIB-4. Although liver fibrosis staging may not be essential anymore to decide for treatment, it is still recommended for prognostication, risk stratification and initiation of appropriate surveillance (screening for HCC and esophageal varies) in patients with advanced liver fibrosis/cirrhosis. Do the researchers plan to consider a portable Fibroscan in the single study visit? 5) Since the study is already ongoing since 2019, it would be interesting to know how many patients have been already enrolled.

VERSION 1 – AUTHOR RESPONSE

R1

This trial protocol is well written, with important objectives that are clearly articulated. I particularly like the design of the study using peers to run the mobile testing unit. This is a good approach and will hopefully help achieve high testing and treatment rates.
RESPONSE: Thank you very much.

I have a couple of minor points that the authors may like to consider addressing to enhance the manuscript.

1. It may be helpful to describe in more detail the locations of potential testing locations and particularly the treatment services, perhaps with a simple map. This will give readers a clearer idea of the geography. The closer patients are to treatment services the more likely they are to have treatment (Simpson H, Journal of Public Health 2019) so this may help address this
RESPONSE: Thank you for this suggestion. We agree with Simpson's findings. As the testing van is parked by the main train station and the peers facilitate transportation principally to one hospital (where authors LKD and NW work and run a fast-track clinic as we describe in the paper), we do not see a reason to include a map. It is a very simple patient care pathway: diagnosis at the van and care at the hospital.

2. Will incentives be used at any part of the process? If so then please describe or state incentives not used
RESPONSE: There are no incentives.

3. Will there be any attempt to look for reinfections after treatment? Re-infection rates in our region are very high and some patients who are labelled as a treatment failure actually have reinfection eg Patient had treatment for HCV G3 with epclusa and the HCV RNA at 12 weeks was positive treatment suggesting failure, but when genotype tested they were G1a, indicating early reinfection rather than treatment failure
RESPONSE: There will be no re-infection, but it will be reported if found. Text modified in the paper: "The study will further report on barriers experienced along the cascade of care including the percentage of clients without a Danish PIN. Finaly, it will report the number of patients with SVR at EoT and 12 weeks after EoT as well as any cases of re-infection.

"

Overall a nice study design and I look forward to seeing the results of it in due course.

RESPONSE: Much appreciated and thank you again for the helpful review.

R2

In this protocol, Lazarus and colleagues present an ongoing study aimed to evaluate the efficacy for testing and linkage to care among people who inject drugs using a peer-based testing at a mobile clinic in Copenhagen, Denmark. The researchers will recruit participants at a community-based, peer-driven mobile clinic, and they will perform a point-of-care HCV antibody test, HCV RNA test and facilitated referrals to designated “fast-track” clinics at a hospital or an addiction centre for treatment. These tests/referral will be administered in the single visit. The primary outcomes for this study are the number of tested and treated individuals. Secondary outcomes include individuals lost at each step in the cascade of care.
The study protocol is well written and addresses and important health issue, responding to the WHO call for elimination of HCV by 2030. It focuses on micro elimination in high risk populations, including PWID, homeless and migrants.
I have the following comments:
1) I am not sure why an approval from the ethics committee was not required for this study. There is no mention for informed consent throughout the study protocol. This should be thoroughly explained and justified.

RESPONSE: We had many discussions with the authorities. As the purpose of the present study is to assess whether offers of testing in one's own environment can recruit more people to test and get these referred for treatment, the project does not provide new knowledge about humans, which is why the Health Ethics Committee of the Capitol Region of Denmark considered that this is not a health science research project as defined by Danish law and therefore not subject to notification to the Health Ethics Committee.

Ultimately, as noted in the ms “The Health Research Ethics Committee of Denmark (case number H-18058659, dated 17 Dec 2018), and the Danish Data Protection Agency confirmed (4 Jan 2019) that this study did not require their approval.”

2) Inclusion and exclusion criteria for this prospective study are not provided.

RESPONSE: The inclusion criteria has been expanded and the exclusion criteria specified. The text now reads “Study population

The study will include HCV-positive persons aged 18 years and older with a Danish Personal Identification Number (PIN). The subject must have a self-reported history of injecting drugs (active or former) and provide informed consent. We will report on HCV-positive persons without a PIN but exclude them from linkage to care due to the current Danish law. Exclusion criteria: A subject will not be eligible to enroll in the study if any of the following criteria apply: Subject is unable to understand written material or verbal instructions in the study languages (Danish or English) or the subject has participated in the study in the previous 30 days.”

3) As the researchers mention, patients will undergo genotype testing, which would represent an additional step into the cascade of care, with increasing possibility of drop out. Patients may be waived the genotype, according to the researchers, however it would be still important to know the genotype as genotype 3 may be associated with need for different treatment, especially in countries where the treatment algorithm is genotype-based, and with higher risk for progressive fibrosis and risk of HCC. This could be considered a limitation of the study protocol.

RESPONSE: The text has been revised to note that Genotype is determined for all patients, but for patients for whom it would be a barrier to wait 4-6 weeks for the result of a genotype test, pangenotypic treatment will be initiated before the result is available.

4) It is not clear whether the liver fibrosis staging will be integrated into the single visit. Do the researchers plan to consider a portable Fibroscan in the single study visit? Quality criteria for reliable Fibroscan examination are missing. The researchers mention that the participant will undergo two Fibroscan examinations? Are patients referred to another clinics/hospital to have the assessment of liver fibrosis? It is known that adding multiple steps in the cascade of care may increase the risk of drop out. Also, the European guidelines recommend combination of two non-invasive tests for liver fibrosis staging in hepatitis C, so will the researchers perform also a APRI/FIB-4 and combine the result with the one from Fibroscan? It would be more efficient instead of adding a second Fibroscan to enlist quality criteria for Fibroscan examination and combine it with FIB-4. Although liver fibrosis staging may not be essential anymore to decide for treatment, it is still recommended for prognostication, risk stratification and initiation of appropriate surveillance (screening for HCC and esophageal varies) in patients with advanced liver fibrosis/cirrhosis. Do the researchers plan to consider a portable Fibroscan in the single study visit?

RESPONSE: We do consider a portable fibroscan included in the single visit (and after submission, we received the funding for this and expect to initiate use this autumn). The text has been updated in two places to reflect this.

5) Since the study is already ongoing since 2019, it would be interesting to know how many patients have been already enrolled.

RESPONSE: Text added: “As of 10 March 2020, just prior to the declaration of the pandemic, 580 people were tested and 52 individuals were HCV-RNA+. Six additional individuals with HCV infection contacted the service to be linked to care. Of the 52 individuals with chronic HCV infection, 44 were evaluated at the hospital clinic and 39 initiated direct-acting antiviral therapy.

VERSION 2 – REVIEW

REVIEWER	Dr Stuart McPherson Liver Unit, The Newcastle upon Tyne Hospitals NHS Foundation Trust
REVIEW RETURNED	06-Sep-2020

GENERAL COMMENTS	I am happy with the changes

REVIEWER	Giada Sebastiani McGill University
REVIEW RETURNED	25-Sep-2020

GENERAL COMMENTS	In this revised version, the researchers addressed the concerns raised by the reviewers. I find the answers satisfactory. I have no further comment or concern.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
Dr Stuart McPherson

Institution and Country
Liver Unit, The Newcastle upon Tyne Hospitals NHS Foundation Trust

Please state any competing interests or state ‘None declared’:
none declared

Please leave your comments for the authors below
I am happy with the changes

Response: Thank you.

Reviewer: 2
Reviewer Name
Giada Sebastiani

Institution and Country
McGill University

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
In this revised version, the researchers addressed the concerns raised by the reviewers. I find the answers satisfactory. I have no further comment or concern.

Response: Thank you.