OPEN PEER REVIEW

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Peer Review Report for "Hepatitis C Treatment Among People Who Use Drugs in an Office-Based Opioid Treatment Program Versus a Syringe Exchange Program: A Real-World Prospective Clinical Trial"

Author(s): Andrew Seaman, Wren Ronan, Lauren Myers, Haven Wheelock, Melinda Butler, Lisa Nelson, Beth E. Williams, Atif Zaman

Review Timeline:

Submit Date:	22 Mar 2021
Revised Date:	22 Oct 2021
Accepted Date:	22 Oct 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0)

14 Apr 2021

Dear Editor,

I read the manuscript entitled “Hepatitis C treatment among people who use drugs in an office-based opioid treatment program versus a syringe exchange program: a real-world prospective clinical trial”. This is an interesting work in which the authors tried to compare the virologic response rate to the treatment (SVR12) with elbasvir/ grazoprevir among PWID on medications for opioid use disorder (MOUD, n=25), those on a syringe services program (SSP, n=25), and a community standard group (n=50) in Portland, Oregon. The rates of SVR12, adherence and treatment completion among SSP group were much lower than MOUD and standard groups.

In my opinion, this research is a one-arm trial rather than a standard trial. The same intervention i.e. elbasvir/ grazoprevir medications, was applied for three groups of HCV-positive patients.

My comments:

- Reference number should not be presented in the ABSTRACT (line 7).

- There are some mistakes on abbreviating of words:
o The spelled out form of HCV was not correct (“Hepatitis C virus” not “Hepatitis C”).
o Some words have not been spelled out in the first use in the ABSTRACT and/ or main text (such as MOUD, SVR12, APRI).
o Some terms have been abbreviated despite being mentioned only once (FQHC).
o Some words have been spelled out for several times (SSP, PP).
o In a few cases, reference numbers have been given instead of abbreviated forms (lines 44 and 66).
- There are contradictions in almost all of measures reported as numbers and/or percentages in the ABSTRACT and the measures presented in Results section of the main text.
- The keywords in the end of ABSTRACT should be given based on the MeSH database (https://www.ncbi.nlm.nih.gov/mesh).
- Reference number was started with 2 in Background section!
- There are different definition for the variable of ‘medication adherence’ in the ABSTRACT (missing ≤7 doses), main text (greater or less than 90% pills taken), and Table 2 (greater than or equal to 90 % pills taken)!
- Based on data used for sample size calculation (lines 97-101), SVR12 rate would be 75% in the safety net clinic patients (not 70%).
- What about HCV viral load? Did you measure it? If measured, was it different among three groups?
- Were the trial registered in the formal registries? If yes, please write the registration number and name of registry.
- Both absolute and relative effect sizes are need. It is suggested to present the number of participants (denominator) and affected cases (numerator) in addition to the percentages in the RESULTS section (lines 121-125, 127-131).
- For each primary and secondary outcome, the estimated effect size and its precision (95% CI) should be reported in the text and the relevant tables.
- I strongly recommend to report odds ratios (ORs) where you used logistic regression to identify variables predicting the outcome.
- Having an APRI score less than 0.7 has been declared as an inclusion criteria (line 66) but the studied groups have been categorized based on score <0.7 and >0.7 in Table 1.
- In Table 1, the sum of SSP members for variable of Race/ Ethnicity is 24. What about 25th case?!
- In Table 1, please revise the wrong classifications of variables i.e. Established primary care (< 1 and >=1) and APRI Score (< 0.7 and >=0.7)
- Could you write the values of numerators and denominators for the percentages in all cells of Table 2? There are some incorrect numbers!
- Using logistic regression should be mentioned in the title of Table 3.
- In lines 132, you said that last drug use < 6 months was statistically more likely to achieve SVR12 but its p-value is 0.129 (Table 3).
- In figure 1, please define how many cases were not enrolled due to ‘other lab exclusion’ in MOUD group (n = 9?).
- Please write the percentages on each of the 6 columns in figure 2.
- It is difficult for me to understand the sentence in lines 160-161 (“The disparity in SVR12 in real world, non-incentivized studies to incentivized clinical trials may suggest the need

161 for implementation of incentives for DAA dispensation and SVR12 labs into usual clinical care"). Could you rephrase it to be easier for understanding your mean?
- In lines 171-177, the reasons of enrollment excluding were discussed but the reported numbers and frequencies are different from those were given in Figure 1.
- In line 177, please clarify what the word of 'this' refers to.
- Do you say that the MOUD and SSP groups are interventions (line 182)? They are two study groups that experienced the same intervention. Please rewrite it correctly.
- Finally, the authors' conclusions are not related directly to their findings.

Heidar Sharafi: Associate Editor | **Revision** (0) 1 May 2021

Dear EIC,

This is an interesting study providing valuable evidence on HCV care among marginalized population of people who use drug, however, the presentation of study, especially the results should be improved before consideration for publication:

1. While the manuscript has been prepared by native English speakers, it suffers from high standard of academic writing. There are issues pointed by one of the reviewers. I can add few more:
a. Using appropriate term for referring the study population. While it included as "people who inject drug" in title, it has been talked regarding PWID in the abstract and manuscript body. While some it is evident that the participants are using drugs, it is not mentioned that they are exclusively selected from those with active drug injection. This ambiguity should be resolved.
b. "eradication model". I am not sure if it is referring to "elimination of HCV". I am confident authors are aware of difference between elimination and eradication.
c. I know authors are well aware of the definition of "ITT" and "PP" terms and concepts, however, these are not well-defined for the readers. Personally, I cannot configure the definition for ITT included as "ITT SVR12 was defined as those who initiated E/G, completed HCV Ribonucleic Acid (RNA) polymerase chain reaction testing at the SVR12 timepoint and were found to be undetectable."
d. Role of the funding source should be excluded from manuscript and it can be included in the footnotes as the publisher asked in the submission.
e. The paragraph regarding the ethics considerations can be moved under "Study design and settings" subheading.
f. I recommend authors to present structure the Results section under subheadings.
g. "Granular adherence". I am not sure if it is frequently used.
h. In conclusion, "... limiting volume of blood, and rapid, and simplified treatment ...". It is not written in an academic context. Maybe authors meant "limiting blood sampling volume/number". Regarding rapid treatment, I have no idea.
i. Figure needs a footnote defining the abbreviations.
j. Tables need more details and definitions. The abbreviations should be spelled out for each table. The units should be added such year for age. The statistical for each comparison in tables should be mentioned in the table footnote. Some qualitative variables have missing % such as those with 0 value and those for "drug of choice".

k. The data presented by figure 2 are duplicated in Table 2. I suggest to remove Figure 2.
L. There is no consistency in presentation of P values: P = 0.007, P < 0.05, P <0.01, P < 0.0001, P = 0.129, Not significant
m. I believe the manuscript needs a great revision regarding its academic presentation and even language expression. I recommend authors to have help of someone expert in academic writing to improve the presentation of manuscript and its readability greatly.

2. I have a great concern regarding the study design and its presentation. The two groups of SSP and MOUD are highly overlapped in their characteristics. I recognized they have enrolled from two different clinics, however, it is not clear if these two clinics offers different services, one only SSP and one only MOUD. Are the participants received all the HCV care services in these two centers? or they were referred to other centers? Wrapping up my concern, I cannot how these two arms work and what is the difference between these two arms except the partial difference in the characteristics of the participants in the two arms. If the difference is not wide, I recommend to present it as a single arm study.

3. I have a concern regarding the AHC control. Are they included as study participants? Have they consented to participate? What was the objective to include them? What are the matched inclusion and exclusion criteria?

4. I recommend to remove the data regarding RAVs. Including the data of RAVs (and including it as a secondary outcome) makes it more complicated in terms of methods presentation and results interpretation.

5. It has been included that SVR was assessed 24 weeks treatment initiation. I consider it as 12 weeks after treatment completion.

6. How the treatment dispensed? For clarification, we need more details on treatment dispensation.

Finally, I am happy to receive the authors response to this peer-review and expect to have another round of peer-review.

Regards

Seyed Moayed Alavian: EIC | **Revision** (**0**) 1 May 2021

Dear Authors,

Thanks for submitting your manuscript. Please follow the reviewers' and editor's comments and submit a revision.

Regards,
EIC

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Response to Reviewers

Manuscript Title: Hepatitis C treatment among people who use drugs in an office-based opioid treatment program versus a syringe exchange program: a real-world prospective clinical trial

To: Editor-in-Chief of Hepatitis Monthly

Dear Dr. Alavian

Thank you for the opportunity to respond to reviewer comments on our manuscript entitled, *"Hepatitis C treatment among people who use drugs in an office-based opioid treatment program versus a syringe exchange program: a real world prospective clinical trial"* for consideration for publication in Hepatitis Monthly. We appreciate ongoing consideration for publication and feel the reviewer's clear and helpful suggestions have strengthened the revised manuscript. The following are the responses to all the reviewer's comments, point by point:

Reviewer 2:

Reviewer 2: I read the manuscript entitled "Hepatitis C treatment among people who use drugs in an office-based opioid treatment program versus a syringe exchange program: a real-world prospective clinical trial". This is an interesting work in which the authors tried to compare the virologic response rate to the treatment (SVR12) with elbasvir/ grazoprevir among PWID on medications for opioid use disorder (MOUD, n=25), those on a syringe services program (SSP, n=25), and a community standard group (n=50) in Portland, Oregon. The rates of SVR12, adherence and treatment completion among SSP group were much lower than MOUD and standard groups.
In my opinion, this research is a one-arm trial rather than a standard trial. The same intervention i.e. elbasvir/ grazoprevir medications, was applied for three groups of HCV-positive patients.
Author Response: We agree with the reviewer that this is a single intervention trial. However, the intervention is implemented in two separate clinical settings among patients engaging in care in two completely different treatment modalities (harm reduction vs treatment-`oriented substance use disorder care). Population and clinical settings are common ways of differentiating trial arms in real-world, non-randomized clinical trials. In this case, it is the population/setting that is the intervention, not the study drug.

Reviewer 2: Reference number should not be presented in the ABSTRACT (line 7).

Author Response: This has been corrected.

Reviewer 2: There are some mistakes on abbreviating of words:
o The spelled out form of HCV was not correct ("Hepatitis C virus" not "Hepatitis C").
o Some words have not been spelled out in the first use in the ABSTRACT and/ or main text (such as MOUD, SVR12, APRI).
o Some terms have been abbreviated despite being mentioned only once (FQHC).
o Some words have been spelled out for several times (SSP, PP).
o In a few cases, reference numbers have been given instead of abbreviated forms (lines 44 and 66).

Author Response: MOUD was spelled out in the abstract. FQHC abbreviation is now removed. Superfluous SSP definitions were removed. The authors were unable to find cases of reference numbers being used in lieu of abbreviations. We corrected the remaining abstract abbreviation errors, as follows:

Line 2: "Hepatitis C Virus (HCV)"

Line 15: "Sustained Virologic Response at 12 weeks (SVR12)"

Line 12: "aspartate aminotransferase to platelet ratio (APRI)"

Reviewer 2: There are contradictions in almost all of measures reported as numbers and/or percentages in the ABSTRACT and the measures presented in Results section of the main text.

Author Response: We apologize for the significant oversite in our editing process. The following corrections were made:

-Line 19 (Abstract): “adherence (missing ≤7 doses) in 100% (25/25) vs 68% (17/25)”

-Lines 19-20 (Abstract): “treatment completion 100% (25/25) vs 64% (16/25)”

-Line 20 (Abstract): “SVR12 rates were 96% (24/25) vs 60% (15/25)”

-Line 21 (Abstract): “SVR12 was achieved in 94% (47/50).”

-Line 21-22 (Abstract): “There were two virologic failures or re-infections in the SSP group”

Reviewer 2: The keywords in the end of ABSTRACT should be given based on the MeSH database (https://www.ncbi.nlm.nih.gov/mesh).

Author Response: The keywords have been replaced by MeSH Major Headings.

Reviewer 2: Reference number was started with 2 in Background section!

Author Response: Apologies for not catching this Endnote failure; corrected in the manuscript.

Reviewer 2: There are different definition for the variable of ‘medication adherence’ in the ABSTRACT (missing ≤7 doses), main text (greater or less than 90% pills taken), and Table 2 (greater than or equal to 90 % pills taken)!

Author Response: Definition harmonized to >90% pills taken as definition for adherence. This was the metric used in the final data analysis and the oversite was in the description for different versions of the paper. This was addressed in the manuscript, as follows:

-Line 19: “good adherence (>90% pills taken)”

-Line 120-121 (Methods): “good medication adherence (defined as greater than 90% pills taken)”

Reviewer 2: Based on data used for sample size calculation (lines 97-101), SVR12 rate would be 75% in the safety net clinic patients (not 70%).

Author Response: This was confirmed by the authors and updated in the manuscript.

Reviewer 2: What about HCV viral load? Did you measure it? If measured, was it different among three groups?

Author Response: We used a quantitative HCV RNA PCR for all baseline HCV confirmation and SVR12 confirmation. We did not include quantitative viral load data in the manuscript as, with the exception of 8 weeks vs 12 weeks of SOF/LED where 6 million IU predicts similar response at 8 vs 12 weeks in non-cirrhotics, the authors are unaware of any data suggesting baseline quantitative viral load predicts treatment outcome. This study used only E/G for treatment and, as such, we did not see the value of including viral load data.

Reviewer 2: Were the trial registered in the formal registries? If yes, please write the registration number and name of registry.

Author Response: We regret the omission. Updated in the manuscript, as follows:

-Line 73-74: “This trial was registered with clinicaltrials.gov, NCT03093415.”

Reviewer 2: *Both absolute and relative effect sizes are need. It is suggested to present the number of participants (denominator) and affected cases (numerator) in addition to the percentages in the RESULTS section (lines 121-125, 127-131).*

Author Response: We agree with this recommendation and have made the following changes in the results section, w/ effect size representation changes italicized.

> -Lines 144-150 (Results): “By design, all in the SSP group injected drugs within the last month and all in the MOUD group were on buprenorphine *(11/25; 44%)* or methadone *(14/25; 56%).* In the MOUD group, *9/25 (36%)* also reported at least one engagement with the SSP during treatment, and *14/25 (56%)* in the SSP group were also on MOUD, 6 of whom (43%) started MOUD during the study period. The academic hepatology group (AHG) was significantly older and had a higher APRI score than the two prospective groups. Only *13/50 (26%)* in the AHG carried substance use diagnoses; active use data were not collected.
>
> -Lines 152-155: In intention to treat (ITT) analysis, *24/25 (96%)* in the MOUD and *15/25 (60%)* achieved SVR12, which was statistically significant ($p<0.0001$). There were two confirmed treatment failures, both in the SSP group, with *24/24 (100%)* of the MOUD group and *15/17 (88%)* of the SSP group achieving SVR12 in per protocol analysis (Fig. 2, Table 2).
>
> -Lines 157-160: When combined, *41/50 (82%)* completed treatment in the SSP and MOUD cohorts (defined as taking >90% total regimen), *25/25 (100%)* and *17/25 (68%)* in the MOUD and SSP groups, respectively. Granular adherence and treatment completion rates were unknown in the AHC comparison but presumed by filling last prescription *50/50 (100%).*
>
> -Lines 160-162: Participants on MOUD, Adherence > 90%, and those completing therapy were all statistically more likely to achieve ITT SVR12. Housing status and recent drug use was not associated with SVR12. At least one minor side effect was noted by *33/50 (66%)* of patients in the prospective arms and more commonly reported in the SSP than MOUD group, *18/25 (72%) vs 15/25 (60%),* respectively.”

Reviewer 2: *For each primary and secondary outcome, the estimated effect size and its precision (95% CI) should be reported in the text and the relevant tables.*

I strongly recommend to report odds ratios (ORs) where you used logistic regression to identify variables predicting the outcome.

Author Response: Changes incorporated in the revised manuscript. In table 2, the authors disagreed that adding 95% CIs would make sense statistically. However, in Table 3, we agree that adding ORs and 95% CIs added value and these were amended as requested.

Reviewer 2: *Having an APRI score less than 0.7 has been declared as an inclusion criteria (line 66) but the studied groups have been categorized based on score <0.7 and >0.7 in Table 1.*

Author Response: The inclusion criteria define the fibrosis inclusion criteria as “low fibrosis, defined as an Aspartate Aminotransferase Platelet Ratio Index (11) of less than 0.7(12-14) or transient elastography (FibroScan) or Fibrosure suggesting metavir fibrosis score of F2 or less…” (Lines 63-65). Thus, participants were included if they met either criteria, and leaving some to have an APRI score of >0.7 to be included if the other fibrosis assessment measure was F2 or less.

Reviewer 2: *In Table 1, the sum of SSP members for variable of Race/ Ethnicity is 24. What about 25th case?!*

Author Response: These data were double checked and Table 1 updated for accuracy. There were 2 participants in the SSP group identifying as “Other / Declined.” This was corrected in Table 1.

Reviewer 2: *In Table 1, please revise the wrong classifications of variables i.e. Established primary care (< 1 and >=1) and APRI Score (< 0.7 and >=0.7)*

Author Response: It is unclear to the authors what reviewer 2 means by “wrong classifications of variables” with regard to the “Established Primary Care” variable. These were individuals who had either a. not

established primary care, b. established primary care for < 1 year, or c. established primary care for > 1 year. We feel these representations are accurate, though would be happy to reassess if the reviewer can provide more clarity. With regard to the APRI score classifications, we believe this reflects a misunderstanding of the inclusion criteria by the reviewer, addressed at the top of page 4 of this document.

Reviewer 2: *Could you write the values of numerators and denominators for the percentages in all cells of Table 2? There are some incorrect numbers!*

Author Response: Thank you, the lack of denominators created confusion when comparing the ITT and PP analyses. All numbers were accurate. However, with the definition of the PP analysis as the % of all participants who completed SVR12 testing who had a non-detectable RNA, the denominator (# of participants with completed SVR12 lab data) should have been reported. This was an oversight and has been corrected for all cells in Table 2.

Reviewer 2: *Using logistic regression should be mentioned in the title of Table 3.*

Author Response: Agreed. Table 3 title changed to “Predictors of SVR12 (MOUD and SSP Groups) by Logistic Regression

Reviewer 2: *In lines 132, you said that last drug use > 6 months was statistically more likely to achieve SVR12 but its p-value is 0.129 (Table 3).*

Author Response: Thank you, this was an oversight. This has been corrected to read:

> -Lines 160-162: “Participants on MOUD, Adherence, and those completing therapy were statistically ….”

Reviewer 2: *In figure 1, please define how many cases were not enrolled due to ‘other lab exclusion’ in MOUD group (n = 9?).*

Author Response: Yes, 9 participants were not enrolled due to ‘other lab exclusion.’ This was corrected in the manuscript, figure 1.

Reviewer 2: *Please write the percentages on each of the 6 columns in figure 2.*

Author Response: Percentages added.

Reviewer 2: *It is difficult for me to understand the sentence in lines 160-161 (“The disparity in SVR12 in real world, non-incentivized studies to incentivized clinical trials may suggest the need 161 for implementation of incentives for DAA dispensation and SVR12 labs into usual clinical care”). Could you rephrase it to be easier for understanding your mean?*

Author Response: Agree this language is confusing. Adapted as follows:

> -Lines 198-201: In addition, real-world, non-incentivized studies have been shown to have lower SVR12 lab completion rates than financially incentivized prospective clinical trials among PWID. Implementing financial incentives to routine HCV treatment in this population may improve engagement and lab completion.

Reviewer 2: *In lines 171-177, the reasons of enrollment excluding were discussed but the reported numbers and frequencies are different from those were given in Figure 1*

Author Response: Agreed there were discrepancies between the text and the flow diagram that occurred during the editing process. The primary data represented in figure 1 were confirmed to be accurate and aligned with the text as follows:

> -Lines 213-219: Out of a total of 300 participants with chronic HCV screened, 250 were unable to make it to enrollment. A total of 82 were excluded by investigator driven constraints, such as

inclusion criteria requiring low fibrosis status, or MOUD or active drug use. However, several factors related to the study drug E/G also contributed. 53 patients were excluded were due to inability to complete the high volume of lab work necessitated by this agent (notably genotype and NS5A resistance testing), 47 due to wrong genotype (exclusively genotype 3), and 8 due to RAVs inconsistent with the study drug. This reflects a total of 36% of the overall screened population.

Reviewer 2: *In line 177, please clarify what the word of 'this' refers to.*

Author Response: This line was edited for clarity, as follows:

-Lines 183-184: The lower ITT SVR12 rate in the SSP group likely reflects multiple factors.

Reviewer 2: *Do you say that the MOUD and SSP groups are interventions (line 182)? They are two study groups that experienced the same intervention. Please rewrite it correctly.*

Author Response: Agreed that the MOUD and SSPs are really both recruitment sites and exposures rather than interventions. This was rewritten as follows:

-Lines 224-226: First, the two study groups were recruited from different sites linked to an exposure (MOUD and SSP engagement), though there was crossover exposure to both MOUD and SSP engagement at both sites.

Reviewer 2: *Finally, the authors' conclusions are not related directly to their findings.*

Author Response: We have modified our conclusion as follows:

-Lines 233-239: This study adds depth and nuance to the existing literature on treatment of chronic HCV in people who use drugs. Our data show that people who use drugs can be successfully treated with DAAs, though those with continued chaotic drug use may struggle to complete lab work confirming HCV cure. Extensive pre-treatment laboratory evaluation – especially when using medications requiring genotype and NS5a resistance testing – remains a barrier to treatment. More research is needed into simplified pre-treatment evaluation, use of pangenotypic regimens, and incentivizing SVR12 lab completion to address these barriers to hepatitis C elimination among people who use drugs.

Associate Editor Comments:

Associate Editor: *Using appropriate term for referring the study population. While it included as "people who inject drug" in title, it has been talked regarding PWID in the abstract and manuscript body. While some it is evident that the participants are using drugs, it is not mentioned that they are exclusively selected from those with active drug injection. This ambiguity should be resolved.*

Author Response: Thank you. PWID are often referred to in the related literature as those with active or previous injection drug use, though agree it would be helpful to more precisely define here. Updated the manuscript as follows:

-Lines 56-58 (Study Design): In this real-world, multi-site prospective open-label trial, we enrolled PWID (defined as people with current or previous injection drug use) with confirmed HCV viremia who were engaged in either an MOUD or an SSP setting.

-Lines 77-78 (Participants): …least 18 years of age; current or previous history of injection drug use;

Associate Editor: *"eradication model". I am not sure if it is referring to "elimination of HCV". I am confident authors are aware of difference between elimination and eradication.*

Author Response: Agreed, and yes, we are aware of the difference between eradication and elimination. Eradication was changed to elimination in the first line of the abstract.

Associate Editor: *I know authors are well aware of the definition of "ITT" and "PP" terms and concepts, however, these are not well-defined for the readers. Personally, I cannot configure the definition for ITT included as "ITT SVR12 was defined as those who initiated E/G, completed HCV Ribonucleic Acid (RNA) polymerase chain reaction testing at the SVR12 timepoint and were found to be undetectable."*

Author Response: We will further clarify these definitions below. We defined ITT SVR to be consistent with the previous landmark studies in this population (now cited Dore et al., 2016; Grebely et al., 2018). Our definition of mPP SVR was chosen as the most useful definition for purposes of interpreting these data, though we recognize that this differs from the convention used more commonly outside of the HCV literature. As such, we have reframed the mPP analysis to a modified PP analysis and more clearly defined this group, as follows:

> Lines 116-123 (Methods): ITT SVR12 was defined as a confirmation of undetectable HCV RNA at least 12 weeks after the end of treatment among participants who initiated E/G. This ITT SVR12 definition was based on previous literature in a similar population. Secondary outcomes were modified per protocol SVR12 (mPP SVR12), treatment discontinuation, good medication adherence (defined as greater than 90% pills taken), and percentage of participants with NS5a RAVs at screening. Modified per protocol SVR12 was defined as those with undetectable HCV RNA 12 weeks after end of treatment, among those initiating E/G who completed SVR12 confirmation labs.

Associate Editor: *Role of the funding source should be excluded from manuscript and it can be included in the footnotes as the publisher asked in the submission.*

Author Response: The following paragraph has been removed from the methods of the manuscript and ensured included in the footnotes:

> -Lines 241-247: **7. Role of the funding source**
>
> This study (including study drugs) was funded through an investigator-initiated grant by Merck & Co., Inc. The funder had no role in the analysis or interpretation of results. All listed co-authors had access to the raw data but these were not shared with or requested by the funder. AZ and AS were responsible for the statistical analysis, manuscript development, and decision to submit for publication.

Associate Editor: *The paragraph regarding the ethics considerations can be moved under "Study design and settings" subheading.*

Author Response: Ethics considerations moved to study design and setting subheading:

> -Lines 69-74: This study was approved by the Oregon Health & Sciences University Institutional Review Board. Informed consent was collected on all participants. All research activities confirmed to the ethical guidance of the 1975 Declaration of Helsinki. This trial was registered with clinicaltrials.gov, NCT03093415.

Associate Editor: *I recommend authors to present structure the Results section under subheadings.*

Author Response: Subheadings inserted.

Associate Editor: *"Granular adherence". I am not sure if it is frequently used.*

Author Response: “Granular” removed.

Associate Editor: *In conclusion, "... limiting volume of blood, and rapid, and simplified treatment ...". It is not written in an academic context. Maybe authors meant "limiting blood sampling volume/number". Regarding rapid treatment, I have no idea.*

Author Response: Please see re-written conclusion in response to final comment by Reviewer 2.

Associate Editor: *Figure needs a footnote defining the abbreviations.*

Author Response: Figures 1 and 2 updated with footnote for definitions.

Associate Editor: *Tables need more details and definitions. The abbreviations should be spelled out for each table. The units should be added such year for age. The statistical for each comparison in tables should be mentioned in the table footnote. Some qualitative variables have missing % such as those with 0 value and those for "drug of choice".*

Author Response: We have updated the tables with definitions, units, statistical comparisons, and qualitative variables, as requested.

Associate Editor: *The data presented by figure 2 are duplicated in Table 2. I suggest to remove Figure 2.*

Author Response: The authors think the additional data including statistical significance and denominators for mPP analysis add value to data representation for these primary outcomes in table 2. Additionally, the visual representation of the ITT and mPP SVR12 rate in Figure 2 also adds value. While typically duplicating data representation is not optimal, we think in this place it is warranted. However, if the editor feels strongly about this, the authors would be willing to remove Fig 2 in final edits.

Associate Editor: *There is no consistency in presentation of P values: P = 0.007, P < 0.05, P <0.01, P < 0.0001, P = 0.129, Not significant*

Author Response: Agreed. P values edited to be discrete values unless p<0.0001.

Associate Editor: *I believe the manuscript needs a great revision regarding its academic presentation and even language expression. I recommend authors to have help of someone expert in academic writing to improve the presentation of manuscript and its readability greatly.*

Author Response: This article was re-reviewed by two separate experts in academic writing and edited for clarity.

Associate Editor: *I have a great concern regarding the study design and its presentation. The two groups of SSP and MOUD are highly overlapped in their characteristics. I recognized they have enrolled from two different clinics, however, it is not clear if these two clinics offers different services, one only SSP and one only MOUD. Are the participants received all the HCV care services in these two centers? or they were referred to other centers? Wrapping up my concern, I cannot how these two arms work and what is the difference between these two arms except the partial difference in the characteristics of the participants in the two arms. If the difference is not wide, I recommend to present it as a single arm study.*

Author Response: We recognized the concerns of the editor regarding the study design and the confusion regarding its presentation. At the core, this is an evaluation of hepatitis C screening and treatment at two different clinical models of care: 1) An office based opioid treatment program (MOUD) and 2) a syringe services program. As such, though there is significant crossover in *exposures* (eg. MOUD and SSP exposures, homelessness, primary care engagement, etc), the testing, enrollment, clinical care (eg. treatment w/ E/G), and monitoring all occurred at the recruitment sites. As such, this is a comparison of different settings to test and treat hepatitis C, not a comparison of different exposures or interventions. This bears clinical importance, as most MOUD programs and SSPs are not testing for or treating hepatitis C, though individuals who participate in these services are increasingly being treated by external providers. In essence, the question is not who should we treat, but where should we / can we treat.

The manuscript was adapted for clarity as below:

> -Lines 66-67 (Study Design): … This study was designed to assess efficacy of screening and treatment within MOUD treatment programs as compared to SSPs.

-Lines 90-92(Participants): As this study was designed to assess the role of the treatment site rather than individual exposures, participants in the MOUD group were not excluded if they engaged with an SSP, and those in the SSP group were not excluded if they were taking MOUD.

-Lines 224-231(Limitations): First, the two study groups were separated primarily by site of clinical engagement (MOUD and SSP settings), though there was crossover exposure to both MOUD and SSP engagement at both sites. While our data allow some comparisons of HCV treatment outcomes from these different clinical settings, our ability to assess the role of MOUD or SSP engagement on HCV treatment outcomes is limited. Additionally, the small sample size was powered sufficiently to detect a difference in the primary outcome between recruitment sites but not to detect meaningful differences in individual predictors of participants completing treatment or achieving SVR12.

Associate Editor: *I have a concern regarding the AHC control. Are they included as study participants? Have they consented to participate? What was the objective to include them? What are the matched inclusion and exclusion criteria?*

Author Response: At the time this study was designed, there were very few examples of treatment of people actively using drugs from the US literature. Inclusion of this community comparison group was intended to provide a local comparator for treatment outcomes among a “standard” community treatment site. It was recognized that the populations would be different. These individuals were analyzed retrospectively through chart review and matched to all inclusion/exclusion criteria except injection drug use history. They did not undergo full informed consent, as approved by our institutional review board. The manuscript was updated for clarity, as follows:

-Lines 63-66: These prospective cohorts were compared to a community comparison retrospective cohort in an academic hepatology clinic (AHC) who received treatment with E/G over the same time period as the MOUD and SSP groups were enrolled.

-Lines 70-72: Informed consent was collected on all participants in the prospective trial. The retrospective community control group analysis was performed without individual consent, in accordance to institutional review board guidance.

-Lines 93-95: The AHC retrospective comparison group analysis employed the same inclusion and exclusion criteria as the prospective sites, except for the requirement for a history of injection drug use due to missing data.

Associate Editor: *I recommend to remove the data regarding RAVs. Including the data of RAVs (and including it as a secondary outcome) makes it more complicated in terms of methods presentation and results interpretation.*

Author Response: Completely agree that this is confusing with regards to results presentation. However, percent RAVs at screening was a pre-specified outcome for the trial, as written in the clinical trials registry and we feel it is best to leave it listed in the methods as is. We removed NS5a resistance from the secondary outcomes table and listed it in the participants subheading of the results, as follows:

-Lines 141-142: Only 3% (8/300) were excluded due to RAVs inconsistent with the study medication.

Associate Editor: *It has been included that SVR was assessed 24 weeks treatment initiation. I consider it as 12 weeks after treatment completion.*

Author Response: This was poorly worded. SVR12 was assessed 12 weeks after treatment completion. Amended as follows:

-Lines 98-99: We assessed participants at screening, enrollment, weeks 2, 4, 8, and 12 of therapy, and 12 weeks after treatment completion (SVR12).

Associate Editor: *How the treatment dispensed? For clarification, we need more details on treatment dispensation.*

Author Response: Study procedures were edited to include dispensation process:

> -Lines 108-109: Medications were dispensed at enrollment and weeks 2, 4, and 8 of treatment in individual pill bottles separate from other medications.

Sincerely yours,
[Blinded for Review]

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Heidar Sharafi: Associate Editor | **Revision** (1) 22 Oct 2021

Dear EIC,

Authors correctly addressed the peer-review comments. I have no more comments.

AE

Seyed Moayed Alavian: EIC | **Revision** (1) 22 Oct 2021

Dear Authors,

Thank you for submitting the revised manuscript. I am delighted to inform that your manuscript is accepted for publication in Hepatitis Monthly journal.

Regards,
EIC