PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Home-based hepatitis C self-testing in people who inject drugs and men who have sex with men in Georgia: a protocol for a randomized controlled trial
AUTHORS	Shilton, Sonjelle; Stvilia, Ketevan; Japaridze, Maia; Tsereteli, N.; Usharidze, Dali; Phevadze, Shota; Jghenti, Miranda; Mozalevskis, Antons; Markby, Jessica; Luhmann, Niklas; Johnson, Cheryl; Nabeta, Pamela; Ongarello, Stefano; Reipold, Elena; Gamkrelidze, Amiran

VERSION 1 – REVIEW

REVIEWER	Sabin, Caroline UCL Medical School
REVIEW RETURNED	29-Nov-2021

GENERAL COMMENTS	The authors define the protocol for a trial to investigate the efficacy of self-testing for HCV among MSM and PWID in Georgia in comparison to a standard testing route. Whilst this is an interesting trial, I found the structure of the manuscript very hard to follow as information that was needed to judge earlier stages of the protocol was often not provided until much later in the manuscript (for example, the content of the two follow-up surveys). I also had several concerns about the definition of the primary endpoint, the sample size calculations and the population that would be analysed. More importantly, it was very unclear whether this trial was the pilot trial that is mentioned in the Introduction section, or whether this is now complete and the present protocol is for the full trial. Towards the end, it does become apparent that this is the full-scale evaluation of the intervention and the pilot has been completed – but the manuscript does lack detailed information on the outcomes of the pilot trial and how they have fed into the protocol development. Overall, therefore, greater clarity on the status of this proposed trial is required. Specific comments 1. The study is described as a ‘factorial randomized controlled trial’ but I can’t see what makes it a factorial design. As I understand it, the trial is a parallel trial of three arms for MSM and two arms for PWID (with randomisation essentially being stratified by risk group). As such, each participant is only randomised once and there is no ‘combination’ of interventions. 2. I assume that the HCV self-tests provide a result that can be accessed within a short time at home? As all tests differ, and there is often confusion between self-testing and self-sampling approaches, it might be helpful to describe the tests in more detail.

	In particular, if tested under the control setting, then would participants get their result straight away or would they have to return for a follow-up visit? How will the study investigators monitor whether tests have been performed and results reported? Is this only through self-report with the survey or will some proof be required that the test has been completed? 3. The purpose of the two surveys was unclear to me – what information will be collected in these two surveys? I can see that information is provided much later in the document on this, but this should be provided earlier, particularly in relation to the secondary endpoints. 4. Those reporting a positive HCV test will be referred to further HCV testing and those with confirmed active infection will be linked to HCV treatment and care – how? How is HCV care provided in Georgia? Will all participants with a positive result receive free DAA treatment or will they have to pay for this? If so, what is the motivation for testing? 5. Participants may withdraw from the study or be withdrawn – but what is the value of following participants up, particularly if they complete the test immediately and (if necessary) engage with the appropriate care services. What would these participants be asked at the second survey, say? And I would have thought that many people who choose not to take the test would also not complete the follow-up surveys – if these people are all excluded, then how reliable will the resulting test rates be? 6. Please describe the community involvement in the development of the supporting tools that are provided to participants? Assuming this is not the pilot trial, then how have the tools been modified from the pilot versions? 7. What information will be given to participants before they are randomised? Will they know that they might receive a ST or could be referred to a clinic for standard testing? If participants sign up to the trial with the hope of receiving a ST, then is there a danger that they may be disappointed when they do not receive this and then 'withdraw'? How will expectations be managed? 8. Sample size – The authors state that the trial has a 'margin' of 20% - what is meant by a 'margin' here? Usually we refer to margins in the context of 'margins of error' (ie. the variation) but it appears that they actually see this as the clinically relevant difference in testing rates that they hope to detect as significant - no rationale is provided for this size of effect. The reported sample size calculation also assumes a one-sided test, but as it is never possible to rule out the possibility that testing rates could be lower in the intervention arms, a two-sided test would be recommended. And, as noted above, loss-to-follow-up here is likely to be informative as the person has probably chosen not to take the test. Should this not, therefore, be incorporated as part of the primary endpoint in some way? 9. Safety analyses – whilst I appreciate that this is a standard test, surely the intervention here is the use of the test in a self-testing context rather than the use of the test per se. So if a person receives a positive result and attempts suicide as a result (say) then this would be a very negative safety outcome. The authors

	state that ‘social harms relating to self-testing will be evaluated by a community stakeholder group’ – but what do they mean by this? 10. Primary analyses will be performed in the per protocol population –why? If the person has complied with the protocol then they will have completed the test by definition – so by only including this group, the proportion completing a test is likely to be highly exaggerated. I would have thought that in this situation, an ITT analysis would be most important (as in any superiority trial). 11. There is no data monitoring committee planned – who will provide independent oversight for the trial? For example, if testing rates through one of the arms are substantially lower and this becomes obvious very early in the trial, then is it ethical to continue the trial? Who would monitor and make that decision? Data monitoring committees are not only there to monitor AEs but could help with this. 12. Study limitations – the authors note that most of Georgia’s population have already been tested for HCV and may be more motivated to seek repeat testing – so what evidence do they have that this ST approach will reach those who are at greatest need (ie. those at higher risk of HCV infection who haven’t previously been tested)?

REVIEWER	Seyler, Thomas European Monitoring Centre for Drugs and Drug Addiction
REVIEW RETURNED	03-Jan-2022

GENERAL COMMENTS	Objectives: The aim is "to assess the impact and acceptability of an online programme offering home delivery of HCVST to PWID and MSM in Georgia". The authors could specify further the objectives in terms of the indicators they intend to build and analyse (differences in testing rates?). Related to the primary indicators, is it the 'impact' or the 'effectiveness' of self-testing on testing rates that is being estimated? Methods: a more detailed plan of analysis would be useful. For example, the secondary endpoints could be described in more detail: numerator, denominator, ratio or difference when making comparisons across groups, etc. It is not clear how the authors will deal with loss to follow-up and participants not willing to share results, and how they will take this into account when estimating secondary endpoints. Ethics: The record linkage between different databases using the national ID could be explicitly described. Limitations: the authors say that the "study participants will be prospectively recruited through an existing HIV self-testing programme". So it seems that the study population has been in contact with self-testing before. Yet this selection bias is not mentioned.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Reviewer: 1
Prof. Caroline Sabin, UCL Medical School Comments to the Author:
The authors define the protocol for a trial to investigate the efficacy of self-testing for HCV among MSM and PWID in Georgia in comparison to a standard testing route. Whilst this is an interesting trial, I found the structure of the manuscript very hard to follow as information that was needed to judge earlier stages of the protocol was often not provided until much later in the manuscript (for example, the content of the two follow-up surveys). I also had several concerns about the definition of the primary endpoint, the sample size calculations and the population that would be analysed. More importantly, it was very unclear whether this trial was the pilot trial that is mentioned in the Introduction section, or whether this is now complete and the present protocol is for the full trial. Towards the end, it does become apparent that this is the full-scale evaluation of the intervention and the pilot has been completed – but the manuscript does lack detailed information on the outcomes of the pilot trial and how they have fed into the protocol development. Overall, therefore, greater clarity on the status of this proposed trial is required.

Dear Prof. Caroline Sabin,
Thank you for your very helpful review which has raised important aspects for us to address to improve our manuscript. Please find our point-by-point responses below.

Specific comments
Reviewer 1 comment 1:
1. The study is described as a 'factorial randomized controlled trial' but I can't see what makes it a factorial design. As I understand it, the trial is a parallel trial of three arms for MSM and two arms for PWID (with randomisation essentially being stratified by risk group). As such, each participant is only randomised once and there is no 'combination' of interventions.

Response:
Thank you, we have removed the word factorial and updated accordingly in the text which now reads "This is a randomized controlled trial comparing home-delivery of HCV self-tests to referral to standard of care community-based HCV testing sites in PWID and MSM in Tbilisi or Batumi, Georgia. Six study HCV sites in Tbilisi and five in Batumi will participate as outlined in Table 1"

Reviewer 1 comment 2:
2. I assume that the HCV self-tests provide a result that can be accessed within a short time at home? As all tests differ, and there is often confusion between self-testing and self-sampling approaches, it might be helpful to describe the tests in more detail. In particular, if tested under the control setting, then would participants get their result straight away or would they have to return for a follow-up visit? How will the study investigators monitor whether tests have been performed and results reported? Is this only through self-report with the survey or will some proof be required that the test has been completed?

Response:
Thank you.
Re: control: We clarify that in the control setting the participants will be receiving the professional use test which is, under the national program is usually administered by RDT and the result given same day.
We have updated the text in the study design section, the bolded text is the addition "Participants in the control arm will receive information about standard of care professionally administered HCV

testing at one of the study sites."

Re: monitoring test and result report: we clarify that the for the self-test arms the information as to if the test has been performed is based on self-report. If participants in the self-test arms self-report a positive HCV ST RDT result they are prompted to go to their nearest clinic to under go a professionally administered HCV RDT. In the control group the participant enters in their self-report of result in the follow up #1 and in addition the clinics will report back to study staff those participants in the control arm who attended the clinic for professional use test.

Reviewer 1 comment 3:
3. The purpose of the two surveys was unclear to me – what information will be collected in these two surveys? I can see that information is provided much later in the document on this, but this should be provided earlier, particularly in relation to the secondary endpoints.
Response:
Thank you. We had originally structured the manuscript following the order of the SPIRIT checklist. We have now updated the order and have created a section 'Data Collection' directly after 'Study Design' We have moved the text describing the information in these surveys to directly after 'Study Design' in the manuscript. We have included the full surveys as supplementary annexes. We have added additional text in the 'Data Collection' section to explain the purpose of the two surveys which is to ascertain if the participant has completed the test or not. Those who do not complete at least one survey will be considered lost to follow up. Considering the incentive that is provided to participants on completion of survey we are not anticipating a high loss to follow up (the survey responses include; did the test, did not do the test. Of those who report completing the test they have the option to provide the result or decline to provide the result)

"The purpose of the follow up surveys is to collect from the participant if they have completed the test, and if completed what the result of the test was, to collect information on risk behaviours to assess if any change in risk behaviours may have taken place during the study, and the gather feedback on how the participants felt about the testing process. "

Reviewer 1 comment 4:
4. Those reporting a positive HCV test will be referred to further HCV testing and those with confirmed active infection will be linked to HCV treatment and care – how? How is HCV care provided in Georgia? Will all participants with a positive result receive free DAA treatment or will they have to pay for this? If so, what is the motivation for testing?
Response:
Yes, all testing and DAA treatment is provided for free in Georgia through their National Elimination Program. Have added the following bolded text in the 'Study Design' section.
"Any individual reporting a positive HCV self-test will be referred to further HCV testing. Those confirmed to have active HCV infection will be linked to HCV treatment and care which is provided for free through the Georgian National Elimination program. "

Reviewer 1 comment 5:
5. Participants may withdraw from the study or be withdrawn – but what is the value of following participants up, particularly if they complete the test immediately and (if necessary) engage with the appropriate care services. What would these participants be asked at the second survey, say? And I would have thought that many people who choose not to take the test would also not complete the follow-up surveys – if these people are all excluded, then how reliable will the resulting test rates be?
Response:
Thank you, the value of following up participants are 3 fold; first, this survey is what is used to understand if participants where able to complete the testing process. It is participants who do not complete any follow up survey that would be considered LTFU.

Second; it may be the case that the participant was not able to complete the test during the first survey window due to being busy both in the self-testing arm and in the control arm, if the participant answers did not do the test they are invited to state why they did not do the test. This information may be useful to the Georgian National Program when planning of the scale up HCVST nationwide to better tailor their program, as well as the answers in the control group may give the Georgian National Program better insight into how to structure their facility-based testing, for example if many people respond that the clinic hours were not convenient the GNP may consider flexible facility hours and etc.
Third; the surveys provide a space for the participant to report their risk behaviors to understand if there is any change over time, how it is currently structured respondents' complete information about risk behaviors in the baseline, follow up 1, and follow up 2 survey which allows for 3 time points.
As responding to the survey in incentivized (and participants get the incentive no matter if they completed the test or not) we are not expecting that those who don't take the test won't complete the surveys, preliminary data from the first 100 enrolled are indicating that participants complete the survey regardless of if they completed the test or not.

Reviewer 1 comment 6:
6. Please describe the community involvement in the development of the supporting tools that are provided to participants? Assuming this is not the pilot trial, then how have the tools been modified from the pilot versions?
Response:
The instructions for use for the self-test have been optimized from the previous feasibility and acceptability study. We also conducted several reviews of study materials among potential end users and have added this text in the "Patient and public involvement"
"Representatives and target end users from the MSM and PWID organizations have reviewed and commented on an information overview sheet that is provided with the self-tests. Prior to finalization of the data collection forms and website interface we piloted the forms and interface with 41 potential end users from MSM community and 19 potential end users from PWID community. We incorporated the feedback into the final design of the data collection tools and website interface."

Reviewer 1 comment 7:
7. What information will be given to participants before they are randomised? Will they know that they might receive a ST or could be referred to a clinic for standard testing? If participants sign up to the trial with the hope of receiving a ST, then is there a danger that they may be disappointed when they do not receive this and then 'withdraw'? How will expectations be managed?
Response:
As per ethics guidance from the National Ethics Board all participants are provided information that they might receive a ST or might be referred to a clinic for standard testing. So far out of the 138 participants who were eligible and consented for the study 3 have withdrawn and have not re-enrolled.

Reviewer 1 comment 8:
8. Sample size – The authors state that the trial has a 'margin' of 20% - what is meant by a 'margin' here? Usually we refer to margins in the context of 'margins of error' (ie. the variation) but it appears that they actually see this as the clinically relevant difference in testing rates that they hope to detect as significant - no rationale is provided for this size of effect. The reported sample size calculation also assumes a one-sided test, but as it is never possible to rule out the possibility that testing rates could be lower in the intervention arms, a two-sided test would be recommended. And, as noted above, loss-to-follow-up here is likely to be informative as the person has probably chosen not to take the test. Should this not, therefore, be incorporated as part of the primary endpoint in some way?
Response:

One of the primary objectives of the trial is "to assess that the proportion of participants who report completing the HCV antibody testing in the intervention group is superior to that of the participants in the control group by a margin of 20%". The 20% margin indicates the margin for the superiority comparison to be considered successful –under the assumption that the percentage of participants to complete the testing will be higher in intervention arm than in the control arm. The analysis will be performed with a one-sided test as its power is higher in a case where a difference is expected in one direction –as it is the case for this trial.

Reviewer 1 comment 9:
9. Safety analyses – whilst I appreciate that this is a standard test, surely the intervention here is the use of the test in a self-testing context rather than the use of the test per se. So if a person receives a positive result and attempts suicide as a result (say) then this would be a very negative safety outcome. The authors state that 'social harms relating to self-testing will be evaluated by a community stakeholder group' – but what do they mean by this?
Response:
There is information on the selftest.ge portal that directs participants to a chat line if a person is having any concerns, feeling any mental stress, or experiencing any social harms during their participation in the study. In addition, the organizations involved in the study have strong connections to the communities included in this study, organization staff are in regular communication with their beneficiaries and have been sensitized to be actively probing for any potential social harms during the study. If any social harms are uncovered, either through the chat line or the regular communication they will be escalated as per the social monitoring structure illustrated in Figure 2.

Reviewer 1 comment 10:
10. Primary analyses will be performed in the per protocol population –why? If the person has complied with the protocol then they will have completed the test by definition – so by only including this group, the proportion completing a test is likely to be highly exaggerated. I would have thought that in this situation, an ITT analysis would be most important (as in any superiority trial).
Response:
The primary endpoint will be evaluated by comparing the proportion of participants who perform one test with those who complete a follow-up. In this way we will obtain data on the two groups and be able to compare the proportions in a meaningful way. We would like to clarify that PP (Per-Protocol): all participants in ITT who fully complied with the protocol (i.e.: primary endpoint variable is available) in this case means participants who have completed at least one of the follow up surveys, meaning they have reported if they have or have not taken the test, in this context this does not mean participant who have completed the test.

Reviewer 1 comment 11:
11. There is no data monitoring committee planned – who will provide independent oversight for the trial? For example, if testing rates through one of the arms are substantially lower and this becomes obvious very early in the trial, then is it ethical to continue the trial? Who would monitor and make that decision? Data monitoring committees are not only there to monitor AEs but could help with this.
Response: Given that the intervention is a change in how testing is delivered, rather than a test itself, the investigators felt that an external data monitoring committee wouldn't be required. A Monitoring Plan is in place and data will be reviewed at 3-month intervals, and decisions made by the study steering committee

Reviewer 1 comment 12:
12. Study limitations – the authors note that most of Georgia's population have already been tested for HCV and may be more motivated to seek repeat testing – so what evidence do they have that this ST approach will reach those who are at greatest need (ie. those at higher risk of HCV infection who

haven’t previously been tested)?
Response: FIND, in partnership with NCDC has completed two previous HCVST feasibility and acceptability studies in Georgia, in these studies among the MSM group 74% reported that they had never tested previously for HCV and among PWID group 46% had never tested previously. This indicates that both groups, particularly the MSM group may be at high risk (as MSM are at higher risk globally than ‘general population’ for HCV) and not previously reached.

Reviewer: 2
Dr. Thomas Seyler, European Monitoring Centre for Drugs and Drug Addiction Comments to the Author:
Objectives: The aim is "to assess the impact and acceptability of an online programme offering home delivery of HCVST to PWID and MSM in Georgia". The authors could specify further the objectives in terms of the indicators they intend to build and analyse (differences in testing rates?). Related to the primary indicators, is it the 'impact' or the 'effectiveness' of self-testing on testing rates that is being estimated?

Reviewer 2: Comment 1: Methods: a more detailed plan of analysis would be useful. For example, the secondary endpoints could be described in more detail: numerator, denominator, ratio or difference when making comparisons across groups, etc. It is not clear how the authors will deal with loss to follow-up and participants not willing to share results, and how they will take this into account when estimating secondary endpoints.
Response: Thank you. We are not expecting a substantial number of loss to follow up as responding to the survey is incentivized (and participants get the incentive no matter if they completed the test or not). We are not expecting that those who don’t take the test won’t complete the surveys, preliminary data from the first 100 enrolled are indicating that participants complete the survey regardless of if they completed the test or not and, given the anonymous nature of the online reporting, have been forthcoming in fully answering the survey questions. Participants can answer that they have completed the test but would not like to disclose the result. To highlight that
• ITT (Intention-To-Test): all participants who sign the informed consent form (ICF).
• MITT (Modified-Intention-To-Test): all participants in ITT who were randomized to HCV self-testing (Arm 1 to Arm 5).
• PP (Per-Protocol): all participants in ITT who fully complied with the protocol (i.e.: primary endpoint variable is available)
We have updated table 2 to include statistical analysis methods which includes more details on descriptive analysis of secondary outcomes. Including the numerators and denominators that will be used (MITT and PP). To highlight that PP in this case means participants who have completed at least one follow up survey (reporting if they have or have not completed the test).

Reviewer 2 comment 2Ethics: The record linkage between different databases using the national ID could be explicitly described.
Response: Thank you. We have added the following text in the Data Management section
“There is only one study database with no direct links with any other databases. In terms of following participants along the continuation of care offered by the National Elimination Program, the NCDC study team will, with consent from participants, attain the ID numbers of individuals who test positive in the control group, as well as those in the intervention groups who attend to a clinic for a professional use RDT after completion of a self-test. This ID number will allow NCDC study staff to follow their progress in the national HCV database which captures all diagnostic and treatment data of the National Elimination Program.”
Reviewer 2 comment 3Limitations: the authors say that the "study participants will be prospectively recruited through an existing HIV self-testing programme". So it seems that the study population has been in contact with self-testing before. Yet this selection bias is not mentioned.

Response: Thank you, we have updated the text to" Study participants will be prospectively recruited through an existing HIV self-testing online platform". We would like to clarify that we are not recruiting among participants of an existing HIV self-testing program but rather, to facilitate integrated care, are building on the existing online platform to include HCV self-testing as opposed to creating a separate vertical program platform for HCV self-testing alone.

VERSION 2 – REVIEW

REVIEWER	Sabin, Caroline UCL Medical School
REVIEW RETURNED	07-Feb-2022

GENERAL COMMENTS	I do think this protocol is now clearer after the restructuring. However, the analysis of the primary endpoint remains unclear - I can see the rationale for a one-sided test, and understand that the margin of 20% relates to the argument that the new approach would be considered an improvement only if at least 20% better than the existing standard. However, the actual hypotheses to be tested (ie. the null and alternative hypotheses) remain somewhat unclear and no details are provided as to the statistical method that will be used to test this. It might help if the authors could give some examples of how results would be interpreted if, say, a significant difference of 15% was seen between the two arms.

VERSION 2 – AUTHOR RESPONSE

Feedback from reviewer 1: Prof. Caroline Sabin, UCL Medical School Comments to the Author:
I do think this protocol is now clearer after the restructuring. However, the analysis of the primary endpoint remains unclear - I can see the rationale for a one-sided test, and understand that the margin of 20% relates to the argument that the new approach would be considered an improvement only if at least 20% better than the existing standard. However, the actual hypotheses to be tested (ie. the null and alternative hypotheses) remain somewhat unclear and no details are provided as to the statistical method that will be used to test this. It might help if the authors could give some examples of how results would be interpreted if, say, a significant difference of 15% was seen between the two arms.

Response: Thank you, we really appreciate your thorough comments in the last round of review which enabled us to improve our manuscript. We have added further detail in the 'sample size and statistical analysis section'
"In our settings, the superiority test is a (one-sided) hypothesis test where the null hypothesis is that the outcome in the intervention arm is not better than in the control arm, so rejecting the null hypothesis will support the evidence of the anticipated superiority of the intervention arm."

The primary outcome of the trial is to prove the superiority in the intervention arm vs control regarding the proportion of participants reporting completion of the HCV AB testing, with a margin set at 20%.
In our settings, the superiority test is a (one-sided) hypothesis test where the null hypothesis is that the outcome in the intervention arm is not better than in the control arm, so rejecting the null hypothesis will support the evidence of the anticipated superiority of the intervention arm.
This can be formalized as:
H0: Pi – Pc <= Delta

HA: Pi – Pc > Delta
Where Delta is our chosen margin of significance and P (i = intervention, c = control) represent the estimated proportions in the two arms.
The actual test will be implemented with a Z-test in R with the package TwoSampleProportion.NIS, .
Preliminary results from the first 700 enrolled participants indicates that uptake in the HCVST arms is ranging from 25% to 38% increase in uptake of HCVST in the intervention (HCVST) arms compared to the SoC.