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)	A protocol for a randomized controlled trial of a couples-focused intervention to improve engagement in HIV care
AUTHORS	Tabrisky, Alyssa; Coffin, Lara; Olem, David; Neilands, Torsten; Johnson, M

VERSION 1 – REVIEW

REVIEWER	Natalie Leblanc University of Rochester School of Nursing USA
REVIEW RETURNED	15-Mar-2020

GENERAL COMMENTS	Protocol and study is relevant and timely. Some items for consideration and refinement include: 1. What is meant by excellent medication adherence? This is noted as an outcome. A clear definition is warranted. 2. Not clear why LGBTQ are exclusively specified given that Black/ and other POC populations are challenged to engage across the care continuum regardless of sexuality. 3. What are the plans in place to ensure a diverse population of participants. If the target population are exclusive to gay men, protocol should indicate this. 4. Should differences in treatment regiments be accounted for on the outcome? If so/or not - a comment addressing this would be useful to include.

REVIEWER	Karl Technau Empilweni Services and Research Unit, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
REVIEW RETURNED	23-Apr-2020

GENERAL COMMENTS	The manuscript titled:" A protocol for a randomized controlled trial of a couples-focused intervention to improve engagement in HIV care" presented by Tabrisky et al is reviewed below. The authors present an interesting and well written protocol paper which describes their ongoing study assessing a couples-focused intervention as the intervention in a randomized controlled trial. The study is presented comprehensively and seems to be

	appropriate and able to address important questions around adherence and engagement support for people living with HIV. There are a few points presented below that should be addressed/considered to possibly improve the manuscript: 1) It may be worth adding the consort checklist, particularly looking at the randomization and blinding points otherwise all seems to be well covered. 2) The aim of the study is mentioned in the abstract in line 4 of page 3 as well as in the subsection “Aim of the study” on page 5. Given that the enrolment particularly seeks out individuals with evidence of poor adherence or suboptimal engagement, I would suggest that mentions of the aim include this fact, i.e. that the study is not on all PLHIV but those with evidence of poor engagement. 3) Primary aim on page 5: “among HIV-infected sexual and gender minorities” should be phrased better to refer rather to people who are living with HIV rather than minorities being infected? 4) Page 3, “Strengths and Limitations of the study”. Overall I think the study is very well designed and thoughtfully conceived. I do think however that the authors could use this opportunity to expand the section of strengths and limitations. Please also clarify the point on “laboratory-confirmed HIV viral load” – the way it is written I cannot say whether the authors list this as a strength or a limitation, this may be an example of addressing it in more detail and seeing how it could be both a strength and a weakness. 5) Page 4, line 47-48, “Partners may have…” – I think I understand what the sentence means but I suggest writing it more clearly, e.g. explaining how a caretaker role may prevent a person from taking care of themselves. Both options may be possible silencing the self as well as looking after oneself to ensure the partner has support. 6) The statistics section makes sense but is above my level of expertise and may need review by someone else in order to confirm that it is appropriate. Minor: 1) The protocol paper is mostly not written in first person so line 27-29 on page 12 feels like a deviation from this. 2) Please correct Table 2 “other’s’ “

REVIEWER	Dr A M Rehman LSHTM, UK
REVIEW RETURNED	11-Jun-2020

GENERAL COMMENTS	The authors describe an ongoing study to improve engagement in HIV care in the San Francisco region among sexual and gender minorities (SGM) and their partners. The protocol describes many of the trial procedures well. The proposed statistical analysis is detailed and considers potential bias and how to correct for that. I have a few comments to address detailed below. 1. The population being studied is clear, those identifying as SGM, living with HIV and in a primary relationship; the inclusion criteria and analysis population are not completely clear, and this translates into the description of the primary outcome, analysis and the sample size calculations. a. Sero-discordant couples are eligible for the study, and the primary outcome can only be assessed in the PLWH. However, are SGM-discordant couples allowed, or must both members of the couple identify as SGM? If SGM-discordant couples are ineligible, can the authors provide comment on whether the

	enrolled population matches the target population, and potential bias from this definition? 2. Please add more detail over how the primary outcome is defined. a. Please provide details of which assay is used. b. Confirm whether the primary outcome is undetectable infection (page 16, line 13) or virologic suppression (page 6, line 35)? The term virologic control (page 5, line 43) is non-specific and should be changed to reflect a more specific definition. c. Please also provide details on how values below the lower limit of detection will be treated. 3. The authors have conducted power calculations under a number of different assumptions. a. Either a Table or Figure would complement the description in the text. b. Please expand how to interpret effect size estimates of 0.20 and 0.50; this might be considered in terms of proportions. c. What is the assumed proportion with the primary outcome in the "control" arm? d. Given the study includes sero-discordant couples (and potentially SGM- discordant couples), how are the varying numbers of dyads versus single participants dealt with in the sample size calculations [refer to point above regarding the analysis population]? 4. Please state type of analysis which will be performed in terms of "intention to treat" and "per protocol". Prior to the planned adjustments for potential bias (multiple imputation), will an unadjusted intention to treat analysis or a modified intention to treat analysis be performed? 5. Definitions for secondary analysis (specific aim 2) are not provided (page 17, lines 19-22) and specific aim 3 (page 18, lines 7-14). Please either provide definitions here, or describe when these will be defined, for example will they be defined in a statistical analysis plan, decided prior to final data analysis. 6. If relevant, please provide details of interim analyses, or state that none will be carried out. 7. Please provide the allocation ratio. 8. Please state who was blinded to outcome assessment, and whether the study biostatistician is blinded to treatment allocation or unblinded. 9. Please state if there have been any changes to the trial outcomes since the study commenced. 10. Was any blocking or stratification used in the randomisation?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

Comment: "*What is meant by excellent medication adherence? This is noted as an outcome. A clear definition is warranted."*

Response: The reviewer has identified an important aspect of the study around medication adherence. A definition of the term "excellent medication adherence" has been added to the manuscript, which is rooted in the validated measure of medication adherence employed in the study.

Comment: "*Not clear why LGBTQ are exclusively specified given that Black/ and other POC populations are challenged to engage across the care continuum regardless of sexuality."*

Response: As mentioned in the paper, sexual and gender minorities represent a high-risk population for poor clinical outcomes and increased risk of HIV transmission. The authors acknowledge that individuals outside of the targeted community are also at risk of poor clinical outcomes and risk of HIV transmission. The background information about the risks of HIV infection in sexual and gender minorities outlines the importance of the DuoPACT Study focusing on addressing the barriers in the marginalized population.

Comment: "*What are the plans in place to ensure a diverse population of participants. If the target population are exclusive to gay men, protocol should indicate this."*

Response: The inclusion criteria for the study includes individuals who identify as a sexual and/or gender minority as indicated in Table 1: Inclusion and exclusion criteria. Recruitment methods centered around sexual and gender minorities are outlined in the manuscript to ensure there is a diverse population of participants. The target population is all sexual and/or gender minorities where one or both partners are living with HIV. The recruitment venues sources and images are designed to reflect diversity related to race, ethnicity, age, and gender identity of the greater San Francisco Bay Area.

Comment: "*Should differences in treatment regiments [sic] be accounted for on the outcome? If so/or not - a comment addressing this would be useful to include."*

Response: We clarify that differences in treatment regimens are not part of the analysis plans. We will, however, report the treatment regimens of participants in the sample description. -

Reviewer #2:

Comment: "*It may be worth adding the consort checklist, particularly looking at the randomization and blinding points otherwise all seems to be well covered."*

Response: We appreciate the reviewer's suggestion. However, the authors decided that the tables provided were sufficient enough to cover the import aspects of the study.

Comment: "*The aim of the study is mentioned in the abstract in line 4 of page 3 as well as in the subsection "Aim of the study" on page 5. Given that the enrolment particularly seeks out individuals with evidence of poor adherence or suboptimal engagement, I would suggest that mentions of the aim include this fact, i.e. that the study is not on all PLHIV but those with evidence of poor engagement."*

Response: The reviewer has identified confusion in the language about the focus of the study. The study is focused on poor engagement of PLHIV. The authors have reviewed and revised all language around the aims of the study to better specify the focus is on PLWHIV that have evidence of poor healthcare engagement.

Comment: "*Primary aim on page 5: "among HIV-infected sexual and gender minorities" should be phrased better to refer rather to people who are living with HIV rather than minorities being infected?"*

Response: We appreciate the acknowledgement of confusion in this specific sentence. We have revised this language to "people living with HIV who identify as sexual or gender minority".

Comment: "*Page 3, "Strengths and Limitations of the study". Overall I think the study is very well designed and thoughtfully conceived. I do think however that the authors could use this opportunity to expand the section of strengths and limitations. Please also clarify the point on "laboratory-confirmed HIV viral load" – the way it is written I cannot say whether the authors list this as a strength or a limitation, this may be an example of addressing it in more detail and seeing how it could be both a strength and a weakness."*

Response: Thank you for pointing out that it does not clarify whether it is a strength or limitation. We clarify that the use of laboratory ascertained viral load is a strength over other studies that rely on either self-reported viral load data (prone to reporting bias) or health record extraction (prone to missing or suboptimally-timed data).

Comment: "*Page 4, line 47-48, "Partners may have…" – I think I understand what the sentence means but I suggest writing it more clearly, e.g. explaining how a caretaker role may prevent a person from taking care of themselves. Both options may be possible silencing the self as well as looking after oneself to ensure the partner has support."*

Response: We appreciate the feedback and have revised the sentence to improve clarity.

Comment: "*The statistics section makes sense but is above my level of expertise and may need review by someone else in order to confirm that it is appropriate."*

Response: No changes warranted, but please see responses to reviewer 3.

Comment: *"The protocol paper is mostly not written in first person so line 27-29 on page 12 feels like a deviation from this."*

Response: The sentence has been revised to maintain first person throughout the manuscript.

Comment: *Please correct Table 2 "other's'."*

Response: The grammatical error has been corrected.

Reviewer #3:

Comment: "*The population being studied is clear, those identifying as SGM, living with HIV and in a primary relationship; the inclusion criteria and analysis population are not completely clear, and this translates into the description of the primary outcome, analysis and the sample size calculations.*
a. Sero-discordant couples are eligible for the study, and the primary outcome can only be assessed in the PLWH. However, are SGM-discordant couples allowed, or must both members of the couple identify as SGM? If SGM-discordant couples are ineligible, can the authors provide comment on whether the enrolled population matches the target population, and potential bias from this definition?"

Response: We have clarified in the revised manuscript that only one member of the couple must identify as SGM for the couple to be eligible for the study, which allows greater representation of the range of couple configurations in the area.

Comment: *Please add more detail over how the primary outcome is defined.*

Response: We have added more detail that the primary outcome is suppressed viremia, as operationalized as a viral level below the detectable lower limit of the assay.

Comment: *Please provide details of which assay is used.*

Response: We now clarify the assay used for the primary outcome: "HIV-1 RNA quantitative real-time PCR."

Comment: *Confirm whether the primary outcome is undetectable infection (page 16, line 13) or*

virologic suppression (page 6, line 35)? The term virologic control (page 5, line 43) is non-specific and should be changed to reflect a more specific definition.

Response: We have clarified that the primary outcome is suppressed viremia, as operationalized as a viral level below the detectable lower limit of the assay.

Comment: *Please also provide details on how values below the lower limit of detection will be treated.*

Response: These values are coded as "suppressed viral load."

Comment: *The authors have conducted power calculations under a number of different assumptions.*
a. Either a Table or Figure would complement the description in the text.
b. Please expand how to interpret effect size estimates of 0.20 and 0.50; this might be considered in terms of proportions.
c. What is the assumed proportion with the primary outcome in the "control" arm?
d. Given the study includes sero-discordant couples (and potentially SGM- discordant couples), how are the varying numbers of dyads versus single participants dealt with in the sample size calculations [refer to point above regarding the analysis population]?

Response: We now include a table showing the various assumptions under which we performed our power analyses. The table included raw proportion differences (labeled *Pdiff* in the table) in addition to standardized effect size estimates to aid in interpreting the effect size estimates. We also note here that a standardize effect size of .20 may be considered small whereas a standardized effect size of .50 may be considered medium. Our standardized effect sizes ranged from .30 to .41, which are between the benchmarks for small and medium standardized effects, respectively, so our study is powered to detect effect sizes that are between small and medium for the primary analysis. The minimum raw proportion differences ranged from 10% to 20%. Since the proportion in the control arm was unknown, it was varied across three possible values: low (30%), medium (50%), and high (80%). We have also elaborated on how the power analysis addresses inclusion of single participants from sero-discordant couples vs. dual participants from sero-concordant dyads.

Comment: "*Please state type of analysis which will be performed in terms of "intention to treat" and "per protocol". Prior to the planned adjustments for potential bias (multiple imputation), will an unadjusted intention to treat analysis or a modified intention to treat analysis be performed?"*

Response: We have clarified that the proposed primary inferential analyses will be conducted via the intention-to-treat (ITT) principle in that they will include all participants who are randomized. Multiple imputation will be used in conjunction with the proposed primary analysis because the primary analysis uses generalized estimating equations (GEE), which assumes a more restrictive missing data mechanism (covariate dependence) than the missing-at-random (MAR) mechanism assumed under multiple imputation. However, as a sensitivity analysis we will perform an unadjusted analysis on non-imputed data. We do not plan to use modified intention-to-treat analyses in this study. The proposed secondary exploratory analyses will be defined in a statistical analysis plan prior to the final data analysis, as recommended by the reviewer (see next comment and our response), and thus may be either intention-to-treat or per-protocol depending upon the requirements of the analysis.

Comment: "*Definitions for secondary analysis (specific aim 2) are not provided (page 17, lines 19-22) and specific aim 3 (page 18, lines 7-14). Please either provide definitions here, or describe when these will be defined, for example will they be defined in a statistical analysis plan, decided prior to final data analysis."*

Response: We have clarified in the revised manuscript, now stating that these exploratory analyses will be defined in a statistical analysis plan decided prior to the final data analysis.

Comment: "*If relevant, please provide details of interim analyses, or state that none will be carried out."*

Response: We have clarified in the revised manuscript that no interim analyses are planned.

Comment: "*Please provide the allocation ratio."*

Response: We have clarified that the allocation ratio is 1:1.

Comment: "*Please state who was blinded to outcome assessment, and whether the study biostatistician is blinded to treatment allocation or unblinded."*

Response: We have clarified that the primary outcome is carried out by a third-party laboratory that is blinded to treatment allocation.

Comment: "*Please state if there have been any changes to the trial outcomes since the study commenced."*

Response: We have clarified that there have been no such changes to trial outcomes.

Comment: "*Was any blocking or stratification used in the randomisation?"*

Response: We have clarified that stratification based on couple-level serostatus (sero-concordant or discordant) is used in the randomization procedure with randomly-permuted block sizes of 2, 4, and 6.

VERSION 2 – REVIEW

REVIEWER	Karl-Gunter Technau Empilweni Services and Research Unit, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
REVIEW RETURNED	05-Aug-2020

GENERAL COMMENTS	The original query was: Comment: "Primary aim on page 5: "among HIV-infected sexual and gender minorities" should be phrased better to refer rather to people who are living with HIV rather than minorities being infected?" The authors responded: Response: We appreciate the acknowledgement of confusion in this specific sentence. We have revised this language to "people living with HIV who identify as sexual or gender minority". When I read it in the tracked changes document the change seems not to have yet been effected where it still says "… HIV-infected …minorities". I suggest rephrasing to: 1. Evaluate the efficacy of DuoPACT on virologic control among people living with HIV in primary relationships who are part of sexual and gender minorities? or similar

VERSION 2 – AUTHOR RESPONSE

Reviewer 1.

Comment: "*What is meant by excellent medication adherence? This is noted as an outcome. A clear definition is warranted."*

Response: A detailed definition of the term "excellent medication adherence" has been added to the methods section. This operationalization is rooted in the validated measure of medication adherence employed in the study. The new text is as follows:

"Less than excellent medication adherence is operationalized as reporting anything other than excellent on a validated single item adherence rating scale that asks 'Thinking back over the past 30 days, how would you rate your ability to take your HIV medications as prescribed?' Response choices include excellent, very good, good, poor, and very poor, with responses validated with viral load and electronic adherence measurements." Supporting citations are provided.

Reviewer 2.

Comment: "Primary aim on page 5: "among HIV-infected sexual and gender minorities" should be phrased better to refer rather to people who are living with HIV rather than minorities being infected?"

Response. We appreciate the feedback and have made changes to the language describing the target population.

Reviewer 3. Note that the numbers of the comments refer to those that the reviewer indicated needed additional response from the prior review.

1. **Comment:** "*The population being studied is clear, those identifying as SGM, living with HIV and in a primary relationship; the inclusion criteria and analysis population are not completely clear, and this translates into the description of the primary outcome, analysis and the sample size calculations. Sero-discordant couples are eligible for the study, and the primary outcome can only be assessed in the PLWH. However, are SGM-discordant couples allowed, or must both members of the couple identify as SGM? If SGM-discordant couples are ineligible, can the authors provide comment on whether the enrolled population matches the target population, and potential bias from this definition?"*

Response: We have clarified in the revised manuscript that a minimum of one member of the couple must identify as SGM to meet that eligibility criterion.

2. **Comment:** "*Please add more detail over how the primary outcome is defined."*

Response: We have added more detail that the primary outcome is suppressed viremia, as operationalized as a viral level below the detectable lower limit of the assay. More detail has been added to the Study Design to address the primary outcome.

4. Comment: "*Confirm whether the primary outcome is undetectable infection (page 16, line 13) or virologic suppression (page 6, line 35)? The term virologic control (page 5, line 43) is non-specific and should be changed to reflect a more specific definition."*

Response: We have clarified that the primary outcome is suppressed viremia, as operationalized as a viral load below the detectable lower limit of the assay. We no longer use the term “virologic control,” which we agree lacks specificity.

5. Comment: “*Please also provide details on how values below the lower limit of detection will be treated.”*

Response: These values are coded as “suppressed viral load.”

6. Comment: *The authors have conducted power calculations under a number of different assumptions.*
a. Either a Table or Figure would complement the description in the text.
b. Please expand how to interpret effect size estimates of 0.20 and 0.50; this might be considered in terms of proportions.
c. What is the assumed proportion with the primary outcome in the “control” arm?
d. Given the study includes sero-discordant couples (and potentially SGM- discordant couples), how are the varying numbers of dyads versus single participants dealt with in the sample size calculations [refer to point above regarding the analysis population]?

Response: We now include a table showing the various assumptions under which we performed our power analyses. The table includes raw proportion differences (labeled *Pdiff* in the table) in addition to standardized effect size estimates to aid in interpreting the effect size estimates. We also note here that a standardize effect size of .20 may be considered small whereas a standardized effect size of .50 may be considered medium. Our standardized effect sizes ranged from .30 to .41, which are between the benchmarks for small and medium standardized effects, respectively, so our study is powered to detect effect sizes that are between small and medium for the primary analysis. The minimum raw proportion differences ranged from 10% to 20%. Since the proportion in the control arm was unknown, it was varied across three possible values: low (30%), medium (50%), and high (80%). We have also elaborated on how the power analysis addresses inclusion of single participants from sero-discordant couples vs. dual participants from sero-concordant dyads.

VERSION 3 – REVIEW

REVIEWER	Karl-Gunter Technau University of the Witwatersrand
REVIEW RETURNED	31-Oct-2020

GENERAL COMMENTS	In my opinion all concerns have been adequately addressed