PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	WHISPER or SHOUT study: Protocol of a cluster-randomised controlled trial assessing mHealth sexual reproductive health and nutrition interventions among female sex workers in Mombasa, Kenya
AUTHORS	Chersich, Matthew; Ampt, Frances; Mudogo, Collins; Gichangi, Peter; Lim, Megan; Manguro, Griffins; Jaoko, Walter; Temmerman, Marleen; Laini, Marilyn; Comrie-Thomson, Elizabeth; Stoové, MA; Agius, Paul; Hellard, Margaret; L'Engle, Kelly; Luchters, Stanley

VERSION 1 - REVIEW

REVIEWER	Ioannis Patrikios European University Cyprus School of Medicine Nicosia, Cyprus
REVIEW RETURNED	22-May-2017

GENERAL COMMENTS	The abstract is missing major important info... mostly in "methods"; and the English language needs professional assistance

REVIEWER	RAPHAEL W. LIHANA KENYA MEDICAL RESEARCH INSTITUTE NAIROBI KENYA
REVIEW RETURNED	23-May-2017

GENERAL COMMENTS	This is a well thought out and designed study that will address the gaps and concerns in contraception among sex workers and how they can be effectively utilized to achieve desirable outcomes. This protocol can be reproduced in other settings where sex work, undesired outcomes and related socioeconomic issues have played out against populations. It would therefore serve to answer several other questions that may arise if acceptance for full implementation is granted.

REVIEWER	Alexander Jenson Johns Hopkins Hospital Department of Emergency Medicine United States of America
REVIEW RETURNED	04-Jun-2017

GENERAL COMMENTS	Overall: This is a well designed research protocol for a study that is needed in a high risk group. The use of WHISPER and SHOUT groups as controls for each other is innovative, and the cluster

	randomization protocol seems sound. This article is very useful in examining a well-designed study protocol. Introduction: No significant changes. Methods/Analysis: Pg 8 Line 40 - where would unscheduled visits take place? Is there a physical location where FSW can come to receive care? How would they notify study staff if they were pregnant? Pg 8 Line 43 - will there be any secondary measures of risky sexual behavior? Uptake of LARCs, which you mention in the introduction? These seem like a possible intermediate to the outcomes that you suggest, and should also be assessed. In addition, it would allow for you to analyze proximate causes for the changes in the outcomes (ie unintended pregnancies down among people who obtain LARCs during the study period, but no change in HIV/syphilis rates) Pg 9 Line 7 - How will you measure malnutrition? What anthmpometry measurement? Adult MUAC? Pg 10 line 9 - how are "pull" prices paid so as to ensure than participants do not pay the SMS costs? up front or reimbursed? Pg 11 - Line 55 - randomization is to WHISPER or SHOUT correct? Please clarify. Pg 12 line 10 - please make clearer regarding randomization - is each CLUSTER randomized, or the individual FSW within the cluster? This is paragraph is somewhat unclear, and should be simplified. Pg 12 line 17 - how close are these individual venues? I can imagine 2 bars next to each other where there could still be message sharing. Is there any geographic attempts to separate each arm spatially? Data Analyses: Pg 14 line 50 - 42% seems optimistic for the reduction in anemia prevalence from SMS data. Was any thought given to expanding the sample size to detect a smaller odds reduction? Particularly because there is no data on the efficacy of mHealth interventions for reducing anemia. I worry that the sample size will not be large enough to detect a possible intervention. Discussion: No significant changes necessary.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
The abstract is missing major important info... mostly in "methods"; and the English language needs professional assistance
Response: Please note comments above in relation to the level of English in this manuscript.
With regards to the abstract, we have made minor amendments to the abstract, without compromising its brevity. Please let us know if further changes are desirable, and if so, we would appreciate more detailed suggestions as to what additional information is desired.

Reviewer 2
This is a well thought out and designed study that will address the gaps and concerns in contraception among sex workers and how they can be effectively utilized to achieve desirable outcomes. This protocol can be reproduced in other settings where sex work, undesired outcomes

and related socioeconomic issues have played out against populations. It would therefore serve to answer several other questions that may arise if acceptance for full implementation is granted.

Response: Thank you for this encouraging feedback. Please note that full implementation of this study has indeed been approved by ethical review committees in both Kenya and Australia (page 14, lines 16-19).

Reviewer 3
This is a well designed research protocol for a study that is needed in a high risk group. The use of WHISPER and SHOUT groups as controls for each other is innovative, and the cluster randomization protocol seems sound. This article is very useful in examining a well-designed study protocol.

Response: Thank you for your helpful review and for highlighting the points that needed clarification in our manuscript. We have addressed each in turn below.

Introduction:
No significant changes.

Methods/Analysis:
Pg 8 Line 40 - where would unscheduled visits take place? Is there a physical location where FSW can come to receive care? How would they notify study staff if they were pregnant?

Response: FSWs attend the study clinics on their appointment days but can also attend at any other time if they have questions or concerns (unscheduled visits). In the manuscript, we have clarified where the unscheduled visits take place (page 7, line 28), and that they are open daily (page 11, line 21).

Pregnancy is detected by either of the following methods:
- Urinary testing at six and 12 months, and at unscheduled visits if women attend concerned that they are pregnant or requesting a test (page 7, lines 27-29; page 12, table 2)
- Self-report: the six- and 12-month questionnaires include questions on the number of pregnancies in the last six months and the outcome(s) of any pregnancies (page 7, lines 29-30; page 12, line 8)

The latter method has been clarified by addition of the text on line 30, page 7.

Pg 8 Line 43 - will there be any secondary measures of risky sexual behavior? Uptake of LARCs, which you mention in the introduction? These seem like a possible intermediate to the outcomes that you suggest, and should also be assessed. In addition, it would allow for you to analyze proximate causes for the changes in the outcomes (ie unintended pregnancies down among people who obtain LARCs during the study period, but no change in HIV/syphilis rates)

Response: We agree that measures of sexual behavior, in particular uptake of LARCs and other contraceptives, are important intermediate outcomes and proximate determinants of pregnancy incidence (illustrated in the logic model on page 23). We have specified on page 7 (line 34) that prevalence of LARC and dual method use are included in the secondary outcomes that will be examined as part of the SRH intervention.

Pg 9 Line 7 - How will you measure malnutrition? What anthmpometry measurement? Adult MUAC?

Response: Thank you for pointing out this omission. Malnutrition will be measured by body mass index (BMI <18.5kg/m2 for underweight and BMI ≥25 kg/m2 for overweight) and MUAC. This has been amended on page 8 (lines 5 and 6). Anthropometry measures are also described on page 12

(lines 19-20).

Pg 10 line 9 - how are "pull" prices paid so as to ensure than participants do not pay the SMS costs? up front or reimbursed?

Response: No costs are incurred by participants for accessing pull messages, as stated on page 9 (line 6-7). The study has a contract in place with VOTO Mobile which ensures that the study bears the cost of pull messages, regardless of how many times the pull system is accessed during the trial.

Pg 11 - Line 55 - randomization is to WHISPER or SHOUT correct? Please clarify.
Pg 12 line 10 - please make clearer regarding randomization - is each CLUSTER randomized, or the individual FSW within the cluster? This is paragraph is somewhat unclear, and should be simplified.

Response: Randomisation is indeed undertaken at the cluster level, and each cluster is assigned to either the WHISPER or SHOUT arm of the trial. We hope that the modifications on pages 10 (line 39) and 11 (lines 6-9) make this clear.
The primary purpose of cluster randomisation was to limit contamination between trial arms which would be more likely to occur if randomisation was at the individual subject level; this is outlined in the limitations section (page 3, lines 15-18).

Pg 12 line 17 - how close are these individual venues? I can imagine 2 bars next to each other where there could still be message sharing. Is there any geographic attempts to separate each arm spatially?

Response: We did not attempt to separate each arm spatially because we wanted to sample the venues randomly. Spatial separation of the trial arms could result in confounding, for example if sex workers or clientele frequenting specific areas practiced higher risk sex, resulting in higher rates of pregnancy in those areas.

We agree that randomly selecting venues very close together (e.g. next door or on the same street) could increase the risk of contamination. However, in practice this has not occurred and is very unlikely for two reasons. First, a small proportion of venues was selected from the sampling frame (106 out of 760 venues). Second, our sampling frame covers a large geographical area; the larger boundaries used to define the regions of Kisauni and Changamwe account for more than 2/3 of Mombasa (i.e. an area of at least 200km2). The recruiters have to travel large distances to attend many of the prescribed venues. Therefore, we anticipate that the risk of contamination due to closely-located venues is lower than the risk posed by potential confounding resulting from non-random selection of venues.

Data Analyses:
Pg 14 line 50 - 42% seems optimistic for the reduction in anemia prevalence from SMS data. Was any thought given to expanding the sample size to detect a smaller odds reduction? Particularly because there is no data on the efficacy of mHealth interventions for reducing anemia. I worry that the sample size will not be large enough to detect a possible intervention.

Response: The sample size for the overall trial was calculated based on the anticipated parameters of the SRH intervention (WHISPER), as described on p13 (lines 21-22). It is true that there is a risk that this will result in the nutrition study (SHOUT) being underpowered. However, this is the first study to estimate prevalence of anaemia among female sex workers and will provide preliminary data on whether mHealth is a feasible means of addressing malnutrition and anaemia in this population. In addition to the primary outcome of anaemia prevalence, secondary outcomes such as the difference in mean haemoglobin will also be important and may be more easily compared between the two

groups. Finally, interim data collected at enrolment indicates that the prevalence of anaemia is likely to be considerably higher than estimated from the literature. If this is true, it will increase the power of the study to detect a change in anaemia prevalence between the groups.

Discussion:
No significant changes necessary.