RESEARCH ARTICLE


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Abstract

Background: The COPCOV study (chloroquine/ hydroxychloroquine prevention of coronavirus disease), which started recruitment in April 2020, is a multi-country double-blind, randomised, placebo-controlled trial which is being conducted in healthcare facilities involved in coronavirus disease 2019 (COVID-19) case management. COPCOV aims to recruit healthcare workers and other staff employed in facilities managing people with proven or suspected COVID-19.

Methods: We conducted a series of engagement sessions, each involving a short presentation of the study, a section where attendees were asked to express if they would be interested in participating in such a study and which information they would need to change their
view and an open Q&A section. Answers were transcribed and coded into themes by two independent investigators. Themes were derived from the data. The aims were to assess the feasibility of the study at the respective sites, to identify context-specific ethical issues, to understand concerns potential participants might have, to fine tune research procedures and to refine COPCOV information materials. They complemented other site-specific engagement, communication and public relation activities such as press releases and websites.

**Results:** From 16th March 2020 to 20th January 2021, 12 engagement sessions were conducted in Thailand, Laos, Vietnam, Nepal and the UK involving 213 attendees in total. The sessions were designed to encourage potential participants and research professionals not directly involved in the project to interact with those who planned the study and those conducting it. Many attendees were keen to join the study while others had concerns. Questions raised revolved around the social value and study rationale; safety of trial medications and risk-benefit balance; study design and commitments.

**Conclusions:** These sessions helped us refine information materials, identify misunderstandings about the study as well as complement site feasibility assessments. Our experience strongly supports the use of participatory practices prior to conducting clinical trials.

**Keywords**
Good participatory practice, public engagement, Coronavirus Disease 2019 (COVID-19), prevention, clinical trials, bioethics

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This article is included in the Coronavirus (COVID-19) collection.
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Competing interests: WS, JJC, EAA, SUS, MM, SV, CW, BH, VS, NJW and PYC are investigators or otherwise involved in the COPCOV study; Chloroquine/hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT04303507; 11/03/2021).

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**Introduction**

Good participatory practice and COVID-19 trials

In the context of a novel and rapidly spreading outbreak such as coronavirus disease 2019 (COVID-19), it is essential for clinical research to be planned, approved and carried out as quickly and as effectively as possible. Indeed, since the start of the outbreak stakeholders have aimed to mobilise vast resources and streamline regulatory practices, stimulating a response of unprecedented proportions in the scientific community. At the time of writing, over 300 new papers on COVID-19 are being published daily with a total of over 150,000 publications\(^3\). However, in this race against time, it is essential that all key ethical issues intrinsic to clinical research are not overlooked and that the interests of potential participants and other stakeholders are safeguarded. In addition to the scrutiny by ethics committees and regulatory bodies, good participatory practice (GPP), or variations of it, patient and public involvement and community engagement, have been highlighted in various guidance documents as important tools\(^4\).

GPP helps develop pertinent research projects, in which the design and implementation are shaped by local views, beliefs and practices. GPP is also an important tool to assess feasibility and improve recruitment, retention and adherence in research activities\(^4\).

The COPCOV study

COPCOV (chloroquine/hydroxychloroquine prevention of coronavirus disease), is a randomised, placebo-controlled pre-exposure prophylaxis study to determine whether chloroquine or hydroxychloroquine prevents COVID-19\(^5\). It is being conducted in healthcare institutions around the world where proven or suspected COVID-19 cases are found. Participants are being recruited among unvaccinated healthcare workers and other persons at risk of contracting COVID-19. At the time of the engagement sessions, vaccines were not widely available yet. Participants are randomised to receive either the intervention, consisting of chloroquine or hydroxychloroquine (depending on local regulations and availability) or placebo.

All participants continue to take the usual precautions for protection against the virus. Participants take the study drugs each day for a period of three months and are followed closely to see how well the drug is tolerated, whether they contract the infection, and if they do, whether they develop mild or more severe COVID-19. If a participant develops COVID-19, they will be treated according to local treatment guidelines.

Due to the use of hydroxychloroquine/chloroquine for rheumatological conditions and for malaria, both as prophylaxis and in mass drug administration, there are a large amount of data supporting the safety of long-term administration of these drugs\(^6\). However, no conclusive evidence of benefit in COVID-19 pre-exposure prophylaxis has so far been produced. Similarly, no other chemoprophylactic agents have found repercussions for the COPCOV trial and other trials using hydroxychloroquine. Other milestones pertinent to the COPCOV study were the announcement that chloroquine/hydroxychloroquine is not effective for the treatment of active COVID-19 by the World Health Organisation (WHO) on July 4\(^{th}\) 2020 and the positive results of the first studies of vaccines against COVID-19 in late 2020\(^9\)–\(^11\).

In the present paper we describe the engagement activities that took place as part of the development and implementation of the COPCOV study from March 2020 to January 2021 and share some insights and reflections from our experience. The specific objectives of these engagement activities were to assess feasibility of the study at the respective sites, to identify potential context-specific ethical issues, and to understand concerns participants might have. The engagement sessions were also aimed to help fine tune our research procedures and refine COPCOV information materials. These activities complemented other site-specific engagement activities, consultations with public advisory groups, communication and public relation activities such as press releases and websites. The sessions were based on the theoretical framework of GPP.

**Methods**

**Study design**

From 16\(^{th}\) March 2020 to 20\(^{th}\) January 2021, 12 engagement sessions were conducted in Thailand (4 sessions), Laos (1 session), Vietnam (1 session), Nepal (5 sessions) and the UK (1 session). The details of each session are summarized in Table 1. The locations of the engagement events were purposively selected based on geographical spread, availability of facilitators and other feasibility factors including COVID-19 restrictions. The number of sessions per location varied according to the judgement of local facilitators who took into consideration the need to include a wide range of potential participants and to provide an environment conducive for participants to express their views.

**Ethical considerations**

The protocol of the COPCOV study listed public engagement activities as part of the study. The protocol was approved by the following ethics committees: Oxford Tropical Research (OxTREC, reference number 25-20) and Mahidol Faculty of Tropical Medicine (FTM-EC, reference number TMEC 20-17). In accordance with the approved protocol, attendees were informed that the findings of these engagement sessions would be included into reports and, in some of the sessions, recorded for note taking by local facilitators who took into consideration the need to include a wide range of potential participants and to provide an environment conducive for participants to express their views.
Table 1. Overview of sessions

<table>
<thead>
<tr>
<th>Site and session number</th>
<th>Attendees, number</th>
<th>Facilitators and relationship to attendees</th>
<th>Attendees, background</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-The Mahidol-Oxford Tropical Medicine Research Unit (MORU), Bangkok, Thailand</td>
<td>70</td>
<td>2 physicians, 1 public engagement staff  - Co-working relationship</td>
<td>Researchers and academic staff, physicians, administrative staff (breakdown unknown)</td>
</tr>
<tr>
<td>2-Mahidol University, Faculty of Tropical Medicine (FTM), Bangkok, Thailand</td>
<td>5</td>
<td>1 physician  Co-working relationship</td>
<td>Nurses (4)  Admin staff (1)</td>
</tr>
<tr>
<td>3-MORU Health Research and Interest Group (HREIG)</td>
<td>9</td>
<td>3 physicians  1 public engagement staff No relationship</td>
<td>General public, not employed in the healthcare sector (9)</td>
</tr>
<tr>
<td>4-Chiangrai Clinical Research Unit (CCRU) Chiangrai, Thailand</td>
<td>4</td>
<td>1 research nurse, 1 physicianCo-working relationship</td>
<td>Research nurses (2)  Lab technicians (2)</td>
</tr>
<tr>
<td>5-The Horton Hospital, Oxford University Hospitals (OUH) NHS Foundation Trust, Banbury, United Kingdom</td>
<td>15</td>
<td>1 physician, 1 medical student  Co-working relationship</td>
<td>Nurses (5)  Physicians (5)  Clinical support workers/Nursing assistants (5)</td>
</tr>
<tr>
<td>6-Mahosot Hospital, Vientiane, Laos</td>
<td>25</td>
<td>4 physicians  1 co-working relationship  3 no relationship</td>
<td>Physicians (25)</td>
</tr>
<tr>
<td>7-Chiangrai Prachanukroh Hospital, Chiangrai, Thailand</td>
<td>25</td>
<td>1 research nurse, 1 physician No relationship</td>
<td>Nurses (3)  Physicians (17)  Public health officers (2)  Other (2)</td>
</tr>
<tr>
<td>8-Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam</td>
<td>11</td>
<td>1 public engagement coordinator  2 physicians No relationship</td>
<td>Nurses (7)  Physicians (3)  Medical assistant (1)</td>
</tr>
<tr>
<td>9-13 B.P. Koirala Institute of Health Sciences Dharan, Nepal (5 sessions in total)</td>
<td>58 (total)</td>
<td>1-3 Physicians (depending on session) No relationship</td>
<td>Unreported (12)  Nurses or nurse aids (35)  Data managers (1)  Medical officers/physicians (10)</td>
</tr>
</tbody>
</table>

Procedure

The sessions were conducted face-to-face, with the exception of one session that was conducted online. The following authors were facilitators of one or more sessions: PYC (MSc, PhD), CP (MD), NK (BSc), SU (MPH, PhD), HTM (BSc), MM (MD), EAA (MBBS, PhD), SKS (MD, DM), BH (MD, PhD), CJW (MBBS, PhD). All facilitators were trained by the head of engagement of the COPCOV study (PYC). All those presenting the study and answering questions had previous research or clinical experience and biomedical training and were familiar with the study protocol and COVID-19. At the beginning of each session facilitators introduced themselves, their professional background and explained their roles with respect to the COPCOV study.

Sessions were facilitated by researchers working at the study sites, in some cases they had official duties at the institutions on site. See Table 1 for a breakdown of locations and number of participants and dates of the engagement sessions as well as the relationship between attendees and facilitators. The number of
participants in each session was based on feasibility factors, including COVID-related restrictions. The duration of each session and the number of sessions per site also took into account when data saturation was reached. Facilitators advertised the sessions directly or liaised with representatives or collaborators of the partner institutions who in turn invited healthcare workers and researchers to attend each session. Sessions were aimed at one or more healthcare worker groups and researchers but other interested individuals were free to join, there were therefore no strict inclusion or exclusion criteria.

The COPCOV engagement team conducted engagement sessions in Bangkok and encouraged study staff at potential study sites to do the same, proposing a general format that could be adapted to local requirements: Participants of the sessions were briefed on the COPCOV study design and procedures (10–20 minutes) and asked two predefined questions in the local language: 1) “Would you take part in such a study and why?” and 2) “What additional information would strengthen or make you change your decision?”. These questions were posed primarily to stimulate discussions rather than to quantify the proportion of those who would versus those who would not take part. Participants were given up to five minutes to write their answers (or questions) down individually. This step was important to encourage all participants to voice their opinions and to provide anonymity. This was followed by a question-and-answer session and open discussions. In some sessions, additional questions were posed to attendees to facilitate discussions. All sessions were conducted by facilitators who were familiar with COVID-19, the COPCOV study, and spoke the local language.

Data management
Participant responses were either written on sticky notes or spoken out directly. Sticky notes were then collected by the facilitators. Depending on the available time, a variable proportion of issues were discussed by the participants together with facilitators and involved researchers. Detailed notes were taken during the discussion session. Session reports were compiled by facilitators and moderators at each site and included the number of participants divided by profession, the duration, the transcription of the statements on sticky notes or spoken out as well as questions asked and the answers given. No patient identifying or demographic data (with the exception of profession) was collected.

All responses and questions were compiled into a Microsoft Excel (Microsoft Office professional 2019) spreadsheet and then coded by two members of the team (CP and PYC). Discrepancies were discussed until consensus was reached. We used the thematic analysis approach. The analysis was inductive in nature.

Results
We conducted a total of 13 sessions involving 222 participants. No participant characteristics other than their profession was recorded. As participation was voluntary, there was a risk for selection bias towards participants interested in the project. Each session lasted between 45 and 90 minutes. Many participants were keen to join the study while others had concerns. The responses to the pre-defined questions and open discussions were grouped into three broad themes. Each of the themes are discussed in turn below: social value and study rationale, safety and risk benefit balance, study design and commitments.

Social value and study rationale
During each session, there was considerable interest in the rationale of the study. While many participants saw the need for the study, others questioned the rationale, both in terms of choice of trial medications and the need for a prevention trial.

A participant from Vientiane, Laos said he would participate in the trial “to prove if chloroquine can be used or not for the prevention of COVID-19” (April 2020). The need to protect oneself was also cited as a reason to participate in the study, e.g., “increase chance to protect myself and others” (Bangkok, TH, Nov 2020) and “may reduce severity of COVID in me” (Banbury, UK, Mar 2020), was a common statement.

A participant from Dharan, Nepal, who also saw the need said “there is no other options so far, such as no vaccine” (Nov 2020). This was despite the fact that vaccines were already close to approval and rollout at the time in the UK and USA. This participant recognised that it would take several months to years before a vaccine could be available to the wider community in Nepal.

Many statements and questions concerning evidence and rationale referred to the limited amount of evidence or perceived lack of plausible efficacy of chloroquine/ hydroxychloroquine on SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2): “I want to see case study that has been experimented on all genders, all ages and experiment with patients with underlying diseases” (Chiangrai, TH, Apr 2020) or “[…] we do not have any confirmation if chloroquine can be used for the prevention of COVID-19” (Vientiane, LA, Apr 2020).

Other concerns were related to the media e.g., “Media influence that chloroquine is not effective for COVID prevention” (Dharan, NP, Nov 2020).

In addition to questions on the rationale of the trial medications, participants also questioned the need of a prevention trial e.g., when asked “what information would change your decision?”, a participant who said he was not interested in the study answered, “if it was aimed at treatment rather than prophylaxis” (Banbury, UK, Mar 2020).

Where disease incidence was low and where personal protective equipment (PPE) was widely available, many felt that a prevention trial was not needed e.g., “[…] would these people not be taking extra precautions like PPE? Will there be high enough risk of infection to determine the difference between the group[s]?” (Bangkok, TH, Mar 2020) and “I can use other methods to prevent myself from covid-19” (Vientiane, LA, April 2020).

Despite emphasising that the COPCOV study is a prevention trial, some participants also talked about treatment e.g. “I want to know the treatment of COVID-19” (Vientiane, LA, April 2020).
Concerns about safety and risk-benefit balance
An issue that was widely raised was that of safety of the trial medications. In some instances, concerns were expressed in broad terms: “need more info[rmati]on on side effects and risks of the drugs” (Banbury, UK, Mar 2020) or “afraid of side effects” (Bangkok, TH, Mar 2020). In other cases, participants referred to specific side effects of chloroquine and hydroxychloroquine such as cardiovascular, ocular, hepatic or renal adverse effects. This worry was exacerbated after the article by Mehra et al. was published in the Lancet on the 22nd of May 2020 (the article was later retracted). In Vietnam, where the engagement session was held a few weeks after the publication of the Mehra et al. paper, none of the participants in the workshop were interested to join the study. “Some paper showed that chloroquine is not effective for COVID-19 patients, this drug can even cause some side effects, especially on cardiovascular system” (Ho Chi Minh City, VN, June 2020).

In some cases, participants viewed that the risk of the side effects outweighed the risk of getting infected. Consider this quote, “I worry about side effects, and I think the chance of getting infection is low” (Chiangrai, TH, April 2020).

Participants were also interested in the management of adverse events and complications or of COVID-19: “how can we minimise the danger of side effects?” (Bangkok, TH, May 2020) or “management approach if […] side effect[s] occur.” (Chiangrai, TH, Apr 2020).

A handful of participants perceived that participating in the study would increase the risk of contracting or transmitting COVID-19: “it would put my family members at risk” (Bangkok, TH, March 2020) or “having children in case anything happens to me” (Banbury, UK, Apr 2020). One participant expressed this concern in more detail, worrying that follow-up visits would increase contact with potentially infected people: “there will be a group of [other] people coming, it might be [at a] follow-up [visit] […] It probably increases the risk to contact […] or not? […]” (Chiangrai, TH, Mar 2020).

Study design and commitments
Participants were also interested in the procedural details of the study such as “when does the study start?” (Vientiane, LA, Apr 2020), “How many visits/ attendances required, Any exclusion criteria?” (Banbury, UK, Mar 2020). Critical views on certain design choices were also brought up: “3 months duration sounds too long” (Bangkok, TH, Mar 2020) or “There could be many confounding factors between control and placebo” (Chiangrai, TH, Apr 2020).

These questions reflected both a desire to find out more about the study and understand the rationale of the procedures as well as concerns over research-related burdens and commitments. Examples of worries specific to the latter: “I worry that I would be given a placebo which has no effect” (Chiangrai, TH, Mar 2020), and “I want to join but because there are many procedures to do, such as checking temperature every day, reporting symptoms every day, and must take medicine every day, therefore, I may not have time to participate” (Chiangrai, TH, Mar 2020).

Discussion
Implications on the COPCOV trial
In this paper, we report our findings from twelve engagement sessions organised to follow a specific format as described above in geographically diverse locations between March 2020 and January 2021. The issues considered important, as derived from statements on desire to participate or not to COPCOV and open questions by attendees, were highly variable depending on location and timing. The information gathered provided important insights to improve the ethical and operational aspects of the COPCOV study.

By conducting engagement sessions of this type, investigators confirmed that the safety of the trial medications were of key importance to potential participants. Many such worries could have been prompted by media reports particularly after the publication of a likely fraudulent paper stating that hydroxychloroquine was found to increase mortality in COVID-19 patients8.

Our engagement sessions also identified some delicate themes. One worrying misunderstanding was that participants thought they might be at higher risk of contracting COVID-19 by joining the study. This could mean that some may have thought that the trial would challenge participants by infecting them with the virus. Another example was the confusion between the concepts of treatment and prevention, so some participants did not understand the rationale for conducting a prevention trial like COPCOV after preliminary data from the RECOVERY trial showed that hydroxychloroquine was ineffective in the treatment of patients hospitalised with severe COVID-1912. COPCOV studies chloroquine and hydroxychloroquine for the prevention of COVID-19 before an individual is exposed or infected, which is substantially different from the treatment of patients that already have COVID-19 or treatment of individuals who have already been exposed to an infected contact.

These drugs could still be of benefit while we wait for the world’s population to be vaccinated. Chloroquine/hydroxychloroquine could also be beneficial in future pandemics, where vaccines would not be instantly available, or if the efficacy of vaccines decreased during the current pandemic.

These sessions were helpful in facilitating the refinement of COPCOV study key messages on the COPCOV trial website and participant information materials. In addition to updating print information, the COPCOV team collaborated with an animation team to produce a video explaining the difference between prevention and treatment in the context of COVID-19. Webinars and information booths at medical conferences were also organised.

These engagement sessions complemented the routine good clinical practice and quality-focused site assessments at potential
study sites. The desire to participate in the COPCOV study varied, so the sessions were helpful in evaluating potential study sites and contributed to the decision of excluding two sites (Chiangrai, TH and Ho-Chi-Minh, VN), saving considerable time and resources. In the context of COVID-19, even if reliable data on the status of the epidemic is widely available, it is difficult to anticipate how potential subjects feel about its spread, its handling by local authorities and the need for preventive medication. Taking the examples of Vientiane (Laos) and Chiang Rai (Thailand) which are 600km apart, both sessions were conducted roughly at the same time and both cities had relatively low local SARS-CoV-2 transmission, yet 78% of participants in Vientiane compared to none in Chiang Rai said they would like to participate in the study. It is possible that views at the national, local, or even at the hospital level might have influenced these striking differences. In Vietnam, at the time of the engagement session (June 2020), none of the participants were interested in enrolling in COPCOV.

It is possible that the endorsement of the project by a highly-regarded figure, as was the case in Vientiane, might have contributed to the positive attitude towards the project. Interestingly, a participant in Chiangrai who was sceptical said if a “medical professor who we respect also participates in this study” she/he might change her/his mind.

Strengths and limitations
As engagement activities may influence any phase of research, including the choice of research topics, study design and recruitment strategies, their impact is likely to be strongest when started early in the course of a study.13,14 For the COPCOV trial, these sessions were organised prior to the study being launched at the respective sites. This was possible because of existing working relationships between the sites and the COPCOV core team. Additionally, the primary target population of COPCOV consisted of healthcare workers, it was therefore possible to engage participants relatively easily and it was not necessary to explain research concepts in detail, as most participants were familiar with them already, which is unlikely to be the case for most clinical trials.

In the case of a large multi-centre trial with a relatively fixed design such as COPCOV, the potential for any single engagement activity in shaping significant aspects of the trial such as study design, and choice of control group, is limited. It is therefore a risk that participants might feel their concerns are unanswered. The limitations must be made clear to participants but they should also not be an excuse for not engaging with communities. It is the responsibility of the researchers to define which aspects can be adapted, explain this to engagement session participants and make sure there are sufficient resources and will to make the necessary changes after receiving feedback.15

Our engagement sessions were designed to obtain quick feedback from potential participants of the COPCOV study and not for in-depth discussions on the major aspects of the trial such as study design and choice of control groups. The latter discussions were conducted with funders, site investigators, ethics committees and key stakeholders in the relevant countries. Rather, our engagement sessions were designed to help us identify the priorities, concerns and attitudes of potential participants, refine information materials, identify site specific issues not otherwise identified by site investigators and ethics committees. These sessions did not replace but complemented and informed in-depth informed consent sessions with potential COPCOV participants. Detailed discussions and training were also held with site staff during site initiation meetings, where detailed discussions on study procedures took place.

We did not conduct these engagement activities at all participating sites. This was primarily due to the feasibility and practical reasons such as availability of experienced engagement staff. However, other forms of engagement took place at each site, following local guidelines. The specific findings of engagement other than that described in our methods are not reported here.

Conclusions
Our engagement sessions raised very important issues, helped improve COPCOV key messages, re-assessed site-specific feasibility, reviewed certain safety aspects and facilitated embedding the views of the target population in the study. By conducting sessions at different timepoints and using a shared but flexible format it was possible to adapt to the changes in the pandemic and in our understanding of it and anticipate difficulties. Additionally, having a designated member of the study team responsible for engagement activities allowed for concerted efforts and for the uptake of relevant findings. Our experience strongly supports the use of participatory practices and shows that even for large multi-centre trials and during a pandemic, organisational hurdles can be overcome. The fruits are well-worth the efforts.

Data availability
Underlying data

This project contains the following underlying data:
- COPCOV_engagement_questions.pdf (participant responses noted in the sessions)

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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This paper has some potential but as it stands it falls short of reporting good participatory practice. Firstly, the introduction is very short and does not delve into the debates around GPP. There is much literature on the subject, presenting different methods of GPP for clinical trials. The methods section describes the engagement sessions but does not suggest this is a research study. Whilst the attendees were given information that the findings from the sessions would be included in reports, they did not give informed consent for this to be a data collection exercise, as far as I can see.

The findings are about the data from the sessions as if this was a data collection exercise. I had expected to see the findings reporting on how the engagement exercise impacted on trial procedures as well as communication about the trial.

The findings, rather than draw on the debates about GPP, were mainly conjecture and included some findings not reported in the findings section. For example, the sentence "..the participants thought that the trial would challenge participants by infecting them with the virus".

There is some discussion about the limits of a single engagement exercise on influencing trial design, but I think this gets lost in the summary of the findings. This section should be expanded to discuss how better engagement could be set up at design stage of trials.

Overall, I think the paper should acknowledge that the participants were educated in medicines as most were health care workers. This means that their concerns about testing drugs were based on good knowledge. I think the authors would better use this to exemplify the limits of such engagement approaches and rather discuss more effective engagement taking into account the difficulties of engaging rapidly during a pandemic.

Is the work clearly and accurately presented and does it cite the current literature?
Is the study design appropriate and is the work technically sound?  
No

Are sufficient details of methods and analysis provided to allow replication by others?  
No

If applicable, is the statistical analysis and its interpretation appropriate?  
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?  
No

Are the conclusions drawn adequately supported by the results?  
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Anthropology of epidemics and clinical trials

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.