Good participatory practice for coronavirus disease 2019 (COVID-19) research: the case of a COVID-19 prevention study [version 3; peer review: 1 approved, 1 approved with reservations]


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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 COVID-19 case management. Participants are staff employed in facilities managing people with proven or suspected COVID-19. As part of the study, we conducted a series of engagement sessions. The
Aims were to assess the feasibility of the study, to identify context-specific ethical issues, to understand possible concerns, to fine tune research procedures and to refine the COPCOV information materials.

Methods: The COPCOV study was approved by relevant institutional review boards. The sessions described in this paper were part of the study. We conducted a series of engagement sessions, each involving a short presentation of the study, a section where attendees were asked to express their willingness to participate in such a study, 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. They complemented other site-specific engagement, communication, and public relation activities such as press releases and websites.

Results and conclusions: From 16\textsuperscript{th} March 2020 to 20\textsuperscript{th} January 2021, 12 engagement sessions were conducted in Thailand, Laos, Vietnam, Nepal and the UK involving 213 attendees in total. Issues raised revolved around the social value and study rationale; safety of trial medications and risk-benefit balance; study design and commitments. These sessions helped us identify concerns people had, which helped us refine information materials 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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Amendments from Version 2

The third version of the article has been uploaded in response to suggestions from the reviewers.

We added a sentence in the ‘Methods’ section to locate the study within current ethics guidelines. In order to add clarity, we moved the aims in the background, so they are now stated just before the methods. We expanded the results paragraph in the Abstract. The ‘Results’ and ‘Conclusions’ paragraphs are now grouped together.

A paragraph was added to the ‘strongs, limitations and lessons learnt’ section explaining the challenges of disseminating findings from public engagement activities that are not specifically designed as research or data collection projects. In the same section, we added a comment on the presence of dedicated public engagement staff embedded within research teams.

The ‘Approvals and Ethical Considerations’ paragraph was expanded to explain questions related to informed consent for subjects being recorded and quoted.

Additional answers to the reviewers questions can be found under the ‘Responses’ section of the reviewer’s report.

Any further responses from the reviewers can be found at the end of the article.

Introduction

Good participatory practice and COVID-19 trials

In the context of a novel and rapidly spreading outbreak such as 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. However, in this race against time to find therapeutics for COVID-19, 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, stakeholder and community engagement, have been highlighted in various guidance documents and literature as important tools.

For example, GPP for emerging pathogens (GPP-EP), inspired by the widely-endorsed GPP guidelines for biomedical HIV prevention trials, provides a set of guidelines on how to effectively engage stakeholders in the design and conduct of prevention and treatment trials for emerging and re-emerging pathogens. The 2016 Council for International Organizations of Medical Sciences (CIOMS) guidelines states that “Researchers, sponsors, health authorities and relevant institutions should engage potential participants and communities in a meaningful participatory process that involves them in an early and sustained manner in the design, development, implementation, design of the informed consent process and monitoring of research, and in the dissemination of its results.”

Engagement around research studies occurs along a spectrum: from reaching out and informing, to consulting, involving, collaborating and formal partnerships. Engagement can be conducted in a variety of ways, such as consultation with community advisory boards, participatory and community drama, participatory visual methods, radio chat shows, holding village meetings and local events.

There are many challenges associated with GPP. The aims of GPP and how to evaluate GPP are not always clear, and the health research and community contexts in which they are conducted are wide ranging. The goals include a combination of instrumental goals and ethical goals such as respecting stakeholders, building relationships, determining appropriate benefits, minimising risks, supporting consent processes, understanding vulnerabilities and researcher obligations, gaining approvals and building legitimacy for research. In practice, however, engagement initiatives in health research often have more than one goal, and the distinction between instrumental and ethical goals are sometimes unclear.

The potential unintended negative impacts should not be overlooked. These include the potential for engagement to be tokenistic, further marginalizing communities who are difficult to reach, and at risk of physical and mental exhaustion from the requirements of engagement that may not always outweigh the expected benefits.

Implementing GPP requires effort, funding, resources, and expertise, but when implemented appropriately it can enhance the impact of trials such as the PREVAIL (Partnership for Research in Ebola Virus in Liberia) and the recently reported RECOVERY (Randomised Evaluation of COVID-19 Therapy) trials. Engagement has also been shown to build trust between the community and members of the study team, strengthen the informed consent process, and help with recruitment into studies. These reasons as well as the collective experience of engaging with communities of the authors are the inspiration of the work reported here.

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. 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 large amounts of data supporting the safety of long-term administration of these drugs. However, no conclusive evidence of benefit in COVID-19 pre-exposure prophylaxis has so far been produced. Similarly, no other chemoprophylactic agents have been proven to be effective. The rationale behind usage is based on in vitro antiviral activity of chloroquine and hydroxychloroquine on severe acute respiratory syndrome coronaviruses (SARS-CoV1 and SARS-CoV2) *in-vitro*. It remains unclear if this will translate into clinical benefit, and we may yet still not find out.

The first COPCOV participant was enrolled in Thailand on 29th April 2020. Within weeks of the study start, COPCOV recruitment was paused hours after an article by Mehra et al. was published (on May 22nd 2020) describing increased mortality in patients receiving chloroquine/hydroxychloroquine. The article was retracted on June 4th 2020 because of concerns about the veracity of the dataset but by that time it had already had profound 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 4th 2020 and the positive results of the first studies of vaccines against COVID-19 in late 2020.

In the present paper we describe a set of 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. We also describe how these engagement activities impacted the COPCOV trial and communication approaches. 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 community advisory boards and public advisory groups, as well as communication and public relation activities such as press releases and websites.

**Methods**

**Design**

From 16th March 2020 to 20th 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) with potential COPCOV participants. 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.

**Approvals and ethical considerations**

The protocol of the COPCOV study listed public engagement activities as part of the study. The protocol was approved by the Oxford Tropical Research (OxTREC, reference number 25–20) and local ethics committees. 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 and auditing purposes. Participation in these sessions was voluntary. Verbal consent was provided. In addition, active contribution to the sessions through statements, questions or comments was viewed as implicit consent to use and quote such information. No personal information with the exception of profession was collected. All these sessions were conducted with the approval of relevant authorities and held in compliance with all relevant local site-specific guidelines that govern the conduct of such engagement activities.

**Procedure**

The sessions were conducted face-to-face in the place of work of participants (e.g. meeting rooms in hospitals and affiliated universities), with the exception of one session that was conducted online due to COVID-19 restrictions. 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. 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

<table>
<thead>
<tr>
<th>Table 1. Overview of sessions.</th>
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<tbody>
<tr>
<td><strong>Site and session number</strong></td>
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<tr>
<td>1-The Mahidol-Oxford Tropical Medicine Research Unit (MORU), Bangkok, Thailand</td>
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<tr>
<td>2-Mahidol University, Faculty of Tropical Medicine (FTM), Bangkok, Thailand</td>
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<tr>
<td>3-MORU Health Research and Interest Group (HREIG)</td>
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<tr>
<td>4-Chiangrai Clinical Research Unit (CCRU) Chiangrai, Thailand</td>
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<tr>
<td>5-The Horton Hospital, Oxford University Hospitals (OUH) NHS Foundation Trust, Banbury, United Kingdom</td>
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<td>6-Mahosot Hospital, Vientiane, Laos</td>
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<tr>
<td>7-Chiangrai Prachanukroh Hospital, Chiangrai, Thailand</td>
</tr>
<tr>
<td>8-Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam</td>
</tr>
<tr>
<td>9-13 B.P. Koirala Institute of Health Sciences Dharan, Nepal (5 sessions in total)</td>
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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 participant identifying or demographic data (with the exception of profession) were 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 were 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 for the study 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[mation] 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 of 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). Upon further probing, we realised that these participants thought that the trial would challenge participants by infecting them with the virus.

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 “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 information gathered from these initiatives complemented other engagement strategies conducted such as discussions with site-specific investigators and local ethics committees as well as consultations with local community advisory boards and public advisory groups. 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 patients33.

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 because they 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-1923. 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. Subsequently, it has been recognized that there are distinct phases of disease with distinct pathophysiology and treatments which are effective. Lack of efficacy in late treatment did not preclude efficacy earlier, and the answer to the question remained important for those without access to vaccines, or if vaccines became less effective20.

These sessions were helpful in facilitating the refinement of COPCOV study key messages on the COPCOV trial website and participant information materials.

For example, to address the worry about being at more risk of getting COVID-19, we updated the participant information sheet and FAQ section of the COPCOV website to include “Am I at a greater risk of developing COVID-19 if I take part in the study?”

In addition to updating print information, the COPCOV team collaborated with an animation team to produce a video to summarise the safety information of chloroquine and hydroxychloroquine and to explain the difference between prevention and treatment in the context of COVID-19. In the animation, we used fire as an analogy to infections, “It is easier to prevent a fire, or put the fire out early, rather than late, when the damage is done. The same is true with infections.”

We also conducted many webinars and set up information booths at participating sites and at medical conferences (virtual) were also organised such as the American Society of Tropical Medicine and Hygiene (ASTMH).

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. In Nepal we conducted five sessions over 4 months where we noted a change in public opinion about the study which triggered the re-instigation of the study in 2021.

**Strengths, limitations and lessons learnt**

As for strength, these engagement sessions were organised prior to the study being considered or launched at the respective sites. This gave us an opportunity to refine our study materials, create new information materials, and in some instances (e.g. Ho Chi Minh City and Vientiane) contributed to the decision of whether the trial would be feasible 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.

As for limitations, in the case of a large multi-centre trial in a rapidly evolving pandemic, 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. These high-level discussions were conducted with funders, site investigators, ethics committees and key stakeholders in the relevant countries at the funding application stage, who had provided relevant input. As engagement activities may influence any phase of research, including the choice of research topics, study design and recruitment strategies, their impacts are likely to be strongest when started early in the course of a study. This is not always possible, especially in a pandemic. Due to the rapidly changing landscape of the pandemic as well as the perception of the study risk-benefit ratio, engagement with local communities and potential study participants at the earliest opportunity as illustrated by our experience was nevertheless a worthwhile exercise.

Due to the timing of the engagement sessions, there was a risk that participants felt their concerns were unanswered. The limitations of such engagement 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.

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. 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 committee. 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.

The majority of participants who attended the engagement sessions were healthcare workers or those who work in healthcare facilities. We chose to engage with this group because they are potential participants for the COPCOV study. As most were educated in medicine or allied health subjects, their concerns about testing drugs were based on good prior knowledge.

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 at the respective sites. Should all sites have had engagement staff, as recommended by GPP guidelines, the positive impact of the engagement activities would have been even greater. However, other forms of engagement took place at each site, following local guidelines in Kilifi, the local team engaged with the KEMRI Community Representatives. The specific findings of engagement other than that described in our methods are not reported here.

The CIOMS 2016 guidelines recommends that researchers and ethics committees should be cognizant of the point at which the process of community engagement becomes a stage of formative research that itself requires ethics review. Examples of community engagement processes that may require ethics review include systematic data collection that can be generalized and disseminated in forums outside of the community in which they were implemented, as well as any data generation that could create social risks for participants. Our engagement activities were not designed as a research study in their own right. We did not seek specific ethics approval but they were approved as part of the COPCOV study. We believed what we learned would be useful to the research community and we therefore described our experience in this paper. Participants were informed that the sessions would be recorded but we did not obtain written informed consent. It was not a requirement set out by our ethics committees. Participants were free to leave the sessions if they did not agree to being recorded. Each participating site performed the engagement activities as they saw most fit for their site, taking local cultural and logistic factors into account, consent mechanisms and approvals needed.

**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 the presence of dedicated engagement staff at research institutions 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).

Acknowledgements

We would like to thank all participants to the engagement sessions for their precious feedback. In addition: Nguyen Minh Nguyet, Ho Quang Chanh, Nguyen Thi Xuan Chau and Sophie Yacoub (OUCRU); Dr Manivanh Vongsouvath (LOMWRU) and Mahosot Hospital; Nidanauch Tasak, Areerat Thairrakhong, Sangnet Jaiboon, Panumas Konlam (MORU Chiangrai); Dr. Chaivutch Thanapaisal (CRPH, Thailand), Dr. Suchita Shrestha (OUCRU, Nepal).

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Cathrine Slack  
HIV AIDS Vaccines Ethics Group, University of KwaZulu-Natal, Pietermaritzburg, South Africa

Stakeholder engagement is an important component of research, as captured in leading international ethics guidelines. Efforts to share engagement approaches and critically reflect on these are important for the field. There are several ways this paper could be further strengthened, as set out below:

Abstract:
- The authors should locate the study in current ethics guidelines.
- They should describe the aims before describing the method.
- The stated aims are “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” however the methods are stated quite narrowly and could resonate better with the more broadly stated aims.
- Under the results, the stated results only address willingness, and concerns - which is a smaller subset of the stated aims.

Methods/ approvals and ethical considerations:
- CIOMS (2016) recommends that researchers and RECs should be cognizant of the point “at which the process of community engagement becomes a stage of formative research that itself requires ethics review. Examples of community engagement processes that may require ethics review include systematic data collection that can be generalized and disseminated in forums outside of the community (...)”(p.26). The engagement being described in this paper might have some key lessons for other researchers on the particular point raised in CIOMS (2016). The authors should reflect on whether the initial purpose of canvassing stakeholders was to plan for better engagement/research or whether the initial purpose of canvassing stakeholders was to develop generalizable knowledge for publication; or indeed whether the purpose(s) of canvassing stakeholders evolved over time or in response to inputs. The
The fact that CIOMS (2016) contains guidance on this issue (i.e., when those whose views are being canvassed are being involved in an engagement activity versus when those being engaged are being enrolled in a study) suggests that it is a tricky concern that researchers should remain mindful of and think carefully about. The authors should consider what they have learned on this issue, and make recommendations to help others.

Methods/ Procedure:
- The text states “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?” Describe what questions were posed to address the other aims.

Results:
- Describe whether the attendees gave permission to be quoted even in an anonymized way.

Strengths and limitations
- This section states “This was primarily due to the feasibility and practical reasons such as availability of experienced engagement staff at the respective sites” Comment on the recommendation in ethics guidelines that sites have funded and staffed engagement initiatives (e.g., GPP HIV 2011; GPP-EP 2016).

- “Due to the timing of the engagement sessions, there was a risk that participants felt their concerns were unanswered”. Describe the feedback that was given to attendees, or the sites from which they were drawn, on the findings from this project. This would be respectful of their contributions.

References:
- The authors should refer to the updated 2016 version of CIOMS.

Thank you for the opportunity to learn about this engagement activity and to comment on the manuscript.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

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 source data required
Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Research ethics, ethics of clinical trials, stakeholder engagement

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 24 Oct 2022

Carlo Perrone, Mahidol Oxford Tropical Medicine Research Unit, Thailand

Dear Dr. Slack,

On behalf of the authors I wish to thank you for your review, you raised some very relevant points that we answer as follows:

Abstract:
– The authors should locate the study in current ethics guidelines. Sentence added in abstract (Methods section)
– They should describe the aims before describing the method. Switched, aims now in background.
– The stated aims are “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” however the methods are stated quite narrowly and could resonate better with the more broadly stated aims. --> the questions were broad and centred on reasons for willingness or unwillingness to participate, as well as open questions in general. As we aimed to answer the aims through the questions above, no tailored questions for the other aims were asked.

Under the results, the stated results only address willingness, and concerns - which is a smaller subset of the stated aims. --> Made clearer in abstract, grouped results and conclusions together.

Methods/approvals and ethical considerations:
– CIOMS (2016) recommends that researchers and RECs should be cognizant of the point "at which the process of community engagement becomes a stage of formative research that itself requires ethics review. Examples of community engagement processes that may require ethics review include systematic data collection that can be generalized and disseminated in forums outside of the community (...)”(p.26). The engagement being described in this paper might have some key lessons for other researchers on the particular point raised in CIOMS (2016). The authors should reflect on whether the initial purpose of canvassing stakeholders was to plan for better
engagement/research or whether the initial purpose of canvassing stakeholders was to develop generalizable knowledge for publication; or indeed whether the purpose(s) of canvassing stakeholders evolved over time or in response to inputs. The fact that CIOMS (2016) contains guidance on this issue (i.e. when those whose views are being canvassed are being involved in an engagement activity versus when those being engaged are being enrolled in a study) suggests that it is a tricky concern that researchers should remain mindful of and think carefully about. The authors should consider what they have learned on this issue, and make recommendations to help others. -> We added “lessons learnt” to “strengths and limitations” and added a new paragraph at the end.

Methods/Procedure:
- The text states “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?” Describe what questions were posed to address the other aims. -> No additional questions were posed, see answer above.

Results:
- Describe whether the attendees gave permission to be quoted even in an anonymized way. We did not ask specific permission for participants to be quoted. -> Our protocol which included the engagement activities was approved relevant ethics committees. The ethics committees which approved our protocol (including the engagement work) did not require us to get specific written consent for engagement or use of anonymised quotes. This is described under ‘Approvals and Ethical Considerations’.

We only used quotes that were completely anonymised and could not be traced back to individuals. Quotes that were long and could potentially identify individuals through idiolect or had references to their specific job or place of work were not included. The topics discussed were not sensitive (e.g. related to their own health or revealing confidential information) but rather their opinions on a research project of which details were publicly available e.g. on our institutional and funder websites.

Strengths and limitations
- This section states “This was primarily due to the feasibility and practical reasons such as availability of experienced engagement staff at the respective sites” Comment on the recommendation in ethics guidelines that sites have funded and staffed engagement initiatives (e.g. GPP HIV 2011; GPP-EP 2016). -> Good point, added a comment in “strengths, limitations and lessons learnt” paragraph and in “Conclusions”.

- “Due to the timing of the engagement sessions, there was a risk that participants felt their concerns were unanswered”. Describe the feedback that was given to attendees, or the sites from which they were drawn, on the findings from this project. This would be respectful of their contributions. -> We agree. We will provide a lay report to all participating sites that includes the results of the COPCOV study and engagement activities after the completion of the COPCOV study.
Reviewer Report 18 January 2022

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Shelley Lees
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Thank you to authors who have addressed all of my comments on the paper. The paper has now addressed the wider debates about GPP in the introduction and made it clearer that this is a research study. The authors have also expanded the strengths and limitations. The paper now stands as a contribution to the literature on the important role of GPP in clinical trials during a pandemic.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

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
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?**

No
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.

Author Response 17 Nov 2021
Carlo Perrone, Mahidol Oxford Tropical Medicine Research Unit, Thailand

We thank the reviewer for her valued comments. Here is a point by point response to reviewer.

Comment: 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.

Response: We have now included a section discussing the literature in GPP and added relevant references.

Comment: 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.

Response: We are reporting the outcomes of engagement rather than research. We have added a few sentence in the Methods (Approvals and ethical considerations) to make it clearer. All participants provided verbal consent. We have also added a sentence to explain this.
Comment: 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.
Response: We have added a few sentences in the Discussion section (Implications on the COPCOV study). Additionally we have provided specific examples of how this engagement exercise impacted our trial.

Comment: 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".
Response: This was an error. We have now included this in the Results section “Concerns about safety and risk-benefit balance”

Comment: 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.
Response: We have now expanded this section.

Comment: 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.
Response: We have added a sentence in the Limitation section

**Competing Interests:** No competing interests were disclosed.