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Epidemics 41 (2022) 100626

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

The role of public involvement in the design of the first SARS-CoV-2 human challenge study during an evolving pandemic

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ARTICLE INFO

Keywords:
Ethics
Human challenge study
Public involvement
SARS-CoV-2

ABSTRACT

High quality health care research must involve patients and the public. This ensures research is important, relevant and acceptable to those it is designed to benefit. The world's first human challenge study with SARS-CoV-2 undertook detailed public involvement to inform study design despite the urgency to review and establish the study. The work was integral to the UK Research Ethics Committee review and approval of the study. Discussion with individuals from ethnic minorities within the UK population supported decision-making around the study exclusion criteria. Public review of study materials for consent processes led to the addition of new information, comparisons and visual aids to help volunteers consider the practicalities and risks involved in participating. A discussion exploring the acceptability of a human challenge study with SARS-CoV-2 taking place in the UK, given the current context of the pandemic, identified overall support for the study. Public concern for the wellbeing of trial participants, as a consequence of isolation, was identified. We outline our approach to public involvement and its impact on study design.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a complex clinical viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Research into the pathology of infection has progressed at pace, but with high rates of carrying infection without symptoms and transmission (particularly in younger people), a human challenge model offers valuable insights into early host-viral interactions that cannot easily be explained from field studies. A challenge model also provides a platform to test novel diagnostics, antiviral treatments, and vaccines in a rapid and cost-effective way, enable prioritisation of effective interventions.

The intentional controlled infection of volunteers during a challenge study is ethically complex. Recognising the potential societal benefits of the challenge infection model, the World Health Organization (WHO) convened working groups early during the COVID-19 pandemic to

Abbreviations: WHO, World Health Organisation; COVID-19, Coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; PIS, Participant Information Sheet; BAME, Black, Asian and minority ethnic.

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https://doi.org/10.1016/j.epidem.2022.100626
Received 31 January 2022; Received in revised form 11 August 2022; Accepted 31 August 2022
Available online 1 September 2022

consider necessary ethical and practical frameworks that should underpin the model (Jamrozik et al., 2021).

Implementing these frameworks was a core part of the development of the first SARS-CoV-2 challenge study (Rapeport et al., 2021), which has been demonstrated to be safe in carefully selected healthy volunteers and has provided novel insights into the early infection dynamics of SARS-CoV-2 infection (Killingley et al., 2022). One of the criteria set out by the WHO was the necessity of public consultation and engagement to inform the study (Jamrozik et al., 2021).

We have previously reported outcomes from a broad public consultation (comprising of surveys and focus groups) regarding the perceived relevance, value and acceptability of a SARS-CoV-2 challenge study (Barker et al., 2022; Gbesemete et al., 2020), which identified a high level of public acceptance before the study protocol was developed. In this paper we describe the insights provided during the public involvement sessions which shaped the study design, consent process and study participant information , and also supported the UK Research Ethics Committee's review of the study (Davies, 2021). The National Institute for Health Research defines public involvement research as research that is done 'with' or 'by' the public, not 'to', 'about' or 'for' them (National Institute for Health Research, 2021).

2. Methods

2.1. Design

This work involved online public involvement discussion groups.

Online group discussions were chosen as an approach to gain a variety of views and experiences from people of different genders, ethnicities and ages, and to capture group dynamics. Three groups were held, each covering a particular topic or theme (Table 1). The three topics were based on issues that had arisen in the public consultation and in discussions within the research team. They were (1) inclusion and exclusion criteria, with a focus on whether people from UK ethnic minority groups should be eligible given the possibility of higher risks of adverse events; (1) study materials, to ensure that they were appropriate to support informed consent; (3) emerging context, to assess whether acceptability may have changed with the approval of two vaccines and emergence of variants (late 2020).

Discussion guides were designed to stimulate discussion on the relevant topic focus (Supplementary). Discussants were invited based on their relevant background and experience (see Section 2.2).

At least 24 hours in advance of the online discussion groups, discussants were sent relevant pre-reading. Discussions were conducted on Zoom Pro. Each session was led by experienced public involvement facilitator(s). Member(s) of the team made detailed notes. Discussion groups were recorded (with discussants consent) to check accuracy of the notes and, where needed, pick up information that was not fully captured during the session. In sessions 1 and 3 discussants were split into breakout rooms for small group discussions (8–9 discussants per room). Discussants were reimbursed for their time (£25 per hour, plus a £5 contribution to Wi-Fi/data for accessing a virtual meeting in accordance with the National Institute for Health Research payment guidance (National Institute for Health Research, 2020)) and invited to complete an anonymous feedback form after the session.

The Principal Investigator (CC) attended sessions 1 and 3 to provide a study overview and answer questions. An individual from hVIVO Services Ltd. involved in development of the Participant Information Sheet (PIS) attended session 2.

For the session on participant exclusion criteria, all facilitators self-identified as from an ethnic minority. A psychologist attended the session to provide support in case any discussants found the session distressing, in recognition that ethnic minority groups were being disproportionally affected by the pandemic and there was potential for discussions to cause upset or anxiety.

Table 1
Description of each public involvement session.

Session	Date	Purpose
1. Participant exclusion criteria	22/10/2020	To explore options regarding the possible exclusion of ethnic minorities from the study (to mitigate risk to study volunteers).
2. Study materials	27/10/2020	To have the study consent processes reviewed by a public audience, to determine if they deemed them appropriate to support informed consent.
3. Emerging context	04/02/2021	To explore whether public opinion of the acceptability of a human challenge study with SARS-Cov-2 taking place in the UK had changed in light of recent developments (approval of two vaccines and rollout of vaccine programme; emergence of new variants).

2.2. Sampling

Discussants (aged 18 and over) were invited through email via established public contributor and community networks at Imperial College London and the University of Southampton to the following three public involvement discussions. Details of group compositions by age, gender and ethnicity are reported in Table 2.

1. Participant exclusion criteria
   Session 1 was attended by 32 members of the public who self-identified as from an ethnic minority.
2. Study materials
   Session 2 was attended by seven members of the public who were potentially eligible (in age and health status) to volunteer in a human challenge study: four individuals had previous experience of participating in a human challenge study; two individuals were familiar with PIS content through their public involvement activities, but had not previously participated in research studies, and one individual had no existing experience of research (either participation or public involvement).
3. Emerging context
   Session 3 was attended by 27 people who had participated in the broad public consultation (Barker et al., 2022) or public involvement session 1

2.3. Analysis

Insight reports were produced for each session from the discussion notes. Key findings were themed and reported. Key insights from the sessions were collated and shared with the SARS-CoV-2 human challenge study team in reports which detailed recommendations and the insights that supported these recommendations.

2.4. Ethics approval

Public involvement activities do not typically require ethical approval (Health Research Authority, 2022); however, given the nature of the study (as a world first), we considered it important to share the insights gathered from the public involvement work with the wider research community and, as such, gained ethics approval by Imperial College London Research Ethics Committee (ICREC reference: 20IC6319). Discussants' attendance at each session was taken as consent, and discussants were asked for their permission to record.

2.4.1. Confidentiality and data security

Identifiable data were entered directly by discussants into an online Qualtrics form. The results were downloaded to the Department of Infectious Disease Epidemiology's secure servers, Imperial College London and only accessed by MP, HJ, PP.

Discussants were given the option of renaming themselves in sessions upon joining. Recordings of the sessions were deleted after discussion

Table 2
Discussants' characteristics.

	Discussion group		
	Participant exclusion criteria n = 32	Study materials n = 7	Emerging context n = 27[a]
Age			
18–24	16	4	12
25–34	8	1	5
35–44	3	0	3
45–54	1	2	1
55–64	0	0	2
65 +	0	0	3
Prefer not to say	1	0	0
Did not answer	3	0	1
Gender			
Male	11	2	10
Female	18	5	16
Prefer not to say	0	0	1
Did not answer	3	0	0
Ethnicity		(Information not collected)	
White		–	
English/Welsh/ Scottish/Northern Irish/British	0	–	12
Irish	0	–	1
Other White background	0	–	3
Mixed/Multiple Ethnicity			
White and Black African	3	–	0
White and Black Caribbean	0	–	0
White and Asian	1	–	0
Other Mixed/ Multiple background	1	–	1
Asian/Asian British			
Indian	4	–	1
Pakistani	4	–	2
Bangladeshi	2	–	2
Other Asian background	3	–	0
Black/African/ Caribbean/Black British			
African	6	–	1
Caribbean	1	–	1
Other			
Arab	2	–	0
Kurdish	2	–	0
Any other ethnic group	0	–	2
Prefer not to say	0	–	1
Did not answer	3	–	0

[a] Six individuals who attended the emerging context session also attended the participant exclusion criteria session.

notes were checked for accuracy. No identifiable information (name, age, gender or ethnicity) was linked or stored with discussants opinions or views.

Contact details provided by those who signed up to a mailing list to receive email updates and invites to future activities relating to the broad public consultation have been retained. Additional identifiable data has been deleted.

3. Results and discussion

3.1. Participant exclusion criteria

At the time of study design, large UK data sets reported an increased risk of poor outcomes after contracting COVID-19 for ethnic minorities (Williamson et al., 2020), with the highest hazard ratios identified for people of Bangladeshi or African ethnicities. There was also evidence that healthcare staff from ethnic minorities were disproportionately affected (British Medical Association, 2022). Some of this increased risk from COVID-19 could be explained by factors including socio-economic status and underlying health conditions (such as diabetes), but even after adjusting the data, there was still a disparity compared to people of white ethnicity (Public Health England, 2020).

One of the core principles of establishing a SARS-CoV-2 challenge model was to reduce as much risk as possible to study participants. However, this needed to be considered in the context of making the model relevant to as much of the population as possible and addressing health inequalities in publicly-funded research. Public involvement was essential to support the decision-making regarding the possible exclusion of ethnic minorities from the study to mitigate risk to study volunteers.

Discussants at this session did not have a consensus opinion on whether it was ethical to include ethnic minorities in the study. Some voiced the opinion that it was more important to be inclusive (an example was given that if vaccines are only tested in white ethnicities, they might not be as effective in ethnic minority groups), while others strongly disagreed based upon the increased risk for some becoming seriously unwell as a result of taking part in the study. Most discussants emphasised that, whatever the decision, transparency and clear communication was critical to justify it, and, if ethnic minorities were able to volunteer, the increased risk needed to be fully explained. Some suggested a staged approach; expanding the study to be more inclusive once early safety had been demonstrated.

Regarding being asked about ethnicity, most discussants were happy (and expected) to be asked this during study screening. However, some raised issues with the options used on forms to describe ethnicity. Individuals with mixed-heritage noted their only option was often "other" because they did not identify with any of the categories provided. There was consensus regarding dislike of Black, Asian and minority ethnic "BAME" as an umbrella term because it is too broad and conflates different ethnic minority groups together. Given that the risks of a poor outcome were markedly different in various ethnicities, discussants made the point that grouping everyone together isn't accurate or useful.

The views of discussants attending the session informed the study team's decision-making during the protocol design. Although at higher risk of serious outcomes, it was decided that people from ethnic minorities should not be excluded from the study. To help mitigate some of the extra risk to volunteers from ethnic minorities, a risk-assessment tool (QCOVID™ (Clift et al., 2020)) was used and a cut-off score applied for all potential study volunteers (ethnicity being one of the variables included in the risk calculation). The protocol set out that once the study had been shown to be safe in the initial small cohort of volunteers, the cut-off score from the risk assessment tool could be removed, in agreement with the staged approach favoured by some of the session discussants.

3.2. Study materials

Rigorous informed consent was one of the key criteria for ethical acceptability of COVID-19 human challenge studies outlined by the WHO. Consent processes should be such that there is 'virtually no doubt that participants comprehensively understand the potential risks of participation' (Jamrozik et al., 2021). Ensuring a group of people reviewed the consent processes, to determine if they were appropriate, was deemed essential to support informed consent.

To support constructive discussion, discussants were asked to consider how easy the PIS was to understand, whether it contained all the information they would like to know, if the language was appropriate, and if the style and format aided understanding.

Overall, all discussants considered that whilst the PIS was long, this was appropriate due to the nature of the study. The individual with no previous experience of research did find the PIS intimidating initially

due to the length, but agreed all the information was necessary. Discussants who had previously taken part in human challenge studies considered the PIS to be comparable or better than material they had received for similar studies.

The section in the PIS explaining the risk of participation was seen by discussants as a fundamental part of making an informed decision. The wider public consultation work also identified the importance of a clear explanation of risk (Barker et al., 2022). Discussants reviewing the PIS felt that more of the document should be dedicated to explaining risk, with the data presented in different ways. Following this feedback, the study team included comparisons and visual aids to help make the risks easier to relate to, for example, comparing the risk of hospitalisation to that of having a car accident and using an analogy about the capacity of a football stadium to contextualise the risk of becoming seriously ill or dying.

Discussants deemed it important to address several additional items in the PIS, including questions about the practicalities of quarantine. These items, along with the action taken to address them, are documented in Table 3. The study team decided to provide some Supporting information through the inclusion of a separate document rather than making the PIS longer.

A generic video, designed to be shared with potential volunteers for similar human challenge studies with respiratory infections (influenza and respiratory syncytial virus), was shared with discussants and feedback sought. Discussants felt that the animation and voiceover were too general and impersonal to be helpful to potential participants for the SARS-CoV-2 human challenge study. If a video was to be used, discussants expressed a preference for the Principal Investigator and study team to be part of the video, and for visuals to be included showing the actual facility in which participants would be staying.

Discussants were consulted on other aspects of the consent process. The appropriateness of a test to determine that a participant fully understood what was involved in taking part was discussed. Those who had taken part in human challenge studies previously described feeling pressure whilst being tested to confirm their understanding, but all discussants agreed a test was important given the gravity of the decision people were making. A quiz to determine understanding was included as part of the final study consent process.

Concern for the mental wellbeing of participants was identified in our broad public consultation work (Barker et al., 2022) and was also raised by discussants at this public involvement session. The group wanted to know what support and counselling would be provided to participants. Discussants shared their own experiences of self-isolation at home throughout the pandemic and how it had longer-term consequences on their wellbeing beyond the self-isolation period. This led to the study team including an additional assessment at the end of the study isolation period to evaluate individual's anxiety and wellbeing, as well as ensuring regular informal contact between the medical staff and the volunteers during the quarantine period to minimise the volunteers' feeling of isolation and to check on their general welfare.

3.3. Emerging context

Our broad public consultation indicated that, at the time of the first consultation (October 2020), there was a high degree of agreement that a human challenge study with coronavirus should take place in the UK (Barker et al., 2022). In February 2021, the UK COVID-19 vaccination programme was ongoing, with two vaccines licensed for use, and the Alpha variant (lineage B.1.1.7) was reported by Public Health England as a 'Variant of Concern' and had become the dominant circulating strain. In light of these developments, it was considered appropriate to undertake further public involvement discussions about the acceptability of a human challenge study with SARS-CoV-2 taking place in the UK. We wanted to understand if, and how, public views had changed.

One discussant described that their views had changed significantly since the vaccine rollout, and they could no longer see justification for

Table 3
Feedback gained during study material session and the action taken to address it.

Feedback item	Detail	Action taken
Document navigation	There was consensus that the PIS needed a contents page and good cross-referencing (i.e. see section 'X' for more information). It was highlighted that headings were not always appropriate to describe the text that followed.	A contents page was added to the PIS.
Covid-19 information	Not everyone was aware that 'coronavirus' was the family of virus and 'COVID-19' was the disease. There was confusion for some people in how this had been explained. There was a request for clarity.	Clarification was added.
Study design diagram and description	The study design diagram was noted to be extremely helpful but too small. It was suggested that the different stages of the study could be differentiated by different colours (e.g clinic quarantine and post quarantine study follow up). It was requested that brief information could be provided on the procedures.	Study design diagram was made larger and clearer. Details of procedures were laid out in bullet points in the main body of text.
Information about quarantine	There was confusion about whether quarantine was mandatory or if participants were free to leave if and when they liked. Clarification around self-isolation if a participant leaves early was missing. There was agreement that a paragraph should be included in a different section of the PIS, that explained why staying in quarantine is important.	General clarifications were added to provide clarity about quarantine guidance and help avoid confusion. The paragraph explaining the importance of quarantine was moved to the main section on quarantine. (The study was not run with a legally enforced quarantine, but instead by co-operation of well-informed volunteers.)
Quarantine specifics	Discussants requested information about what a typical day participating in the study looked like be included.	This was not added to the PIS so as not to increase the length further. A typical day description was included as a separate document.
	While it was deemed clear that participants can't have visitors, it wasn't explicitly stated that the participants couldn't interact with each other and that participants would be completely isolated for the period.	Text was added, explicitly stating that participants cannot interact with each other, and they will be in isolation for the quarantine period (with the exception of the frequent interactions with the research clinical unit staff).
	Discussants requested information about what participants should/can bring with them.	Information on what facilities are provided within rooms and what items participants are able to bring with them, to make their stay as comfortable as possible, was included in the participant video.
	Good Wi-Fi was considered especially important, particularly for participants who wish to continue working remotely.	A statement about Wi-Fi availability was incorporated into the participant video.
	Discussants requested information about accessibility to windows. Discussants who had participated in other studies	Details about the view and room windows was included in the participant video.

(continued on next page)

Table 3 (*continued*)

Feedback item	Detail	Action taken
	which included quarantine described the challenges of isolation in a room with no window.	

the study, particularly as COVID-19 cases were high at the time, which meant field studies could easily be undertaken. On the contrary, others remained supportive of a human challenge study taking place, considering that the need for fewer participants in human challenge studies gave an advantage over field studies. Discussants also felt that vaccines were not the only solution to address the pandemic and that further information about the virus, which could be provided by a human challenge study, was needed. This included understanding why some people do not get infected or remain asymptomatic, and for how long people are infectious. Additional considerations and concerns raised during this discussion echoed those identified during the October 2020 broad public consultation reported elsewhere (Barker et al., 2022) and public involvement sessions 1 (participant exclusion criteria) and 2 (study materials).

Overall, discussants indicated support for a human challenge study with SARS-CoV-2 taking place in the UK at the time. An anonymous post-session online poll (completed by 22/27 discussants) revealed that 82 %, of those who responded, said that they "Agree" or "Strongly agree" that a human challenge study with SARS-CoV-2 should take place in the UK. Two people stated "Neither agree nor disagree", one "Disagree" and one "Don't know/Undecided".

4. Strengths and limitations

The short timescales for carrying out these activities meant that the members of the public involved were identified from our existing public involvement networks. Individuals who support public involvement activities are typically committed to health research and are often middle class (Ocloo and Matthews, 2016). Despite this, the insights largely mirrored the results of the broad public consultation (Barker et al., 2022), which had a wider diversity and number of respondents, supporting an ability to apply a level of generalisation to the findings. As the broad public consultation and the public involvement sessions were all conducted virtually, the voices of individuals who are digitally excluded are not included.

Although session 3 (emerging context), held in February 2021, largely echoed insights gained in October 2020 relating to the acceptability of a human challenge study, we recognise that the context in which this work was carried out is important in understanding and interpreting the results. Opinions regarding the overall acceptability of the study may have changed since this work was completed, as the circumstances of the pandemic and the knowledge of the virus have changed.

5. Conclusions

In this paper, we document the public involvement undertaken during the urgent design and ethical review of the world's first human challenge study with SARS-CoV-2. The involvement activities informed changes in study design including:

- Supporting decision-making around the study exclusion criteria by exploring opinions of the balance between minimising risk to potential volunteers from groups experiencing more severe outcomes from SARS-CoV-2 and making the study as inclusive as possible.
- Addition of new information, comparisons and visual aids to study documentation to help volunteers understand the practicalities of, and contextualise the risks involved in, participating in the study.
- Inclusion of an additional anxiety and wellbeing assessment at the end of study isolation, to protect volunteers and mitigate public concerns for the mental wellbeing of participants.

Key to the team's ability to identify and involve individuals, including those with relevant experience, within short timescales was the utilisation of public involvement facilitators and their existing networks. This prevented any delay to establishing the research. Public involvement facilitators were also able to design inclusive group discussions and facilitate these to elicit views from discussants.

An important aspect of the public involvement activities was having a relevant member of the study team in attendance. This ensured that someone with sufficient knowledge was on hand to provide an overview and answer questions, allowing discussants to engage fully in the conversations. It also demonstrated to discussants that the study team valued their opinions and the public involvement was not tokenistic. This maximised research transparency, identified as important in our broad public consultation (Barker et al., 2022). It ensured that the study team heard the public insights directly and were able to influence and improve study design accordingly. It also supported the study team to respond to community concerns, a goal of the public engagement outlined by WHO (Jamrozik et al., 2021).

We have demonstrated how detailed and meaningful public involvement can be rapidly carried out, informing and adding value to the design and review of an urgent pandemic study. Insight gained from the public involvement activities were submitted to the UK Research Ethics Committee. A covering letter included a summary of the broad public consultation (Barker et al., 2022) and public involvement activities, and a Supplementary table summarised the insights gained, and the actions taken. A member of the study team also provided a verbal description at the Research Ethics Committee. The public involvement activities were integral to the review and approval of the study (National Institute for Health Research, 2021).

CRediT authorship contribution statement

Maria Piggin: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Emma Smith:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **Peter Mankone:** Writing – review & editing. **Leah Ndegwa:** Writing – review & editing. **Diane Gbesemete**: Conceptualization, Investigation, Writing – review & editing. **Philippa Pristerà:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Michael-Bahrami-Hessari:** Investigation, Writing – review & editing. **Halle Johnson:** Investigation, Writing – review & editing. **Andrew P Catchpole:** Investigation, Writing – review & editing. **Peter JM Openshaw:** Writing – review & editing, Supervision, Visualization. **Christopher Chiu:** Investigation, Writing – review & editing, Supervision, Visualization, Funding acquisition. **Robert C Read**: Writing – review & editing. **Helen Ward:** Writing – review & editing, Supervision, Visualization. **Caroline Barker:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing.

Funding

The UK Vaccine Taskforce of the Department of Business, Energy and Industrial Strategy of Her Majesty's Government provided a grant to fund this public involvement work. The funders played no role in the design, delivery or analysis of this work.

Data availability

No data was used for the research described in the article.

Acknowledgements

The authors would like to thank the members of the public who shared their time and perspectives with us. Thank you to Katherine Baker, Carmel McGrath, William Barney Jones, Fola Afolabi, Kinda Ibrahim and Nadia Zaman who supported the administration, facilitation and/or note taking of the discussions. National Institute for Health Research (NIHR) Imperial Biomedical Research Centre Patient Experience Research Centre, NIHR Southampton Biomedical Research Centre, NIHR Southampton Clinical Research Facility and NIHR Applied Research Collaboration Wessex receive infrastructure funding from the NIHR. This work was also supported by the Human Infection Challenge Network for Vaccine Development (HIC-Vac) funded by the GCRF Networks in Vaccines Research and Development which was co-funded by the MRC and BBSRC (this UK funded award is part of the EDCTP2 programme supported by the European Union). The authors gratefully acknowledge support from the Royal Free London NHS Foundation Trust, and hVIVO Services Ltd (particularly input from Danny Smith and Johnny Janes).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.epidem.2022.100626.

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