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Factors that impact on recruitment to vaccine trials during a pandemic or epidemic: a qualitative evidence synthesis (Protocol)

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[Qualitative Protocol]

Factors that impact on recruitment to vaccine trials during a pandemic or epidemic: a qualitative evidence synthesis

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (qualitative). The objectives are as follows:

This is a protocol for a Cochrane Review (qualitative). The review aims to explore the factors associated with a person's decision to take part in a pandemic or epidemic vaccine trial.

BACKGROUND

Description of the topic

In March 2020, the World Health Organization (WHO) declared a COVID-19 pandemic (WHO 2020). COVID-19 is a multi-system disease caused by severe acute coronavirus-2 (SARS-CoV-2) (Li 2020). Amid uncertainties about the spread and severity of the disease and the effectiveness of available interventions, vaccine development was prioritised for managing and controlling the pandemic (Sethi 2020). Consequently, the demand for rapid vaccine development and testing resulted in a large number of vaccine trials (Darzi 2021; Janiaud 2021). However, there is a lack of information on factors influencing recruitment to vaccine trials (Detoc 2019).

Recruitment rates for clinical trial participation, more generally, are variable across countries and trials (Darzi 2021; Davis 2020). Recruitment to randomised trials is challenging, and poor recruitment can result in the need for additional time or funding, reduced confidence in results or early closure (Kaur 2012; Swan 2009; Treweek 2018). Evidence indicates that around half of all trials fail to recruit the prespecified target number of participants (Bower 2007; McDonald 2006; Sully 2013). Failure to recruit is one of the primary reasons for discontinuation in clinical drug trials (Walters 2017).

Recruitment to vaccine trials can be particularly challenging (Cattapan 2019; Harrington 2017). Unlike treatment trials, vaccine trials typically involve healthy volunteers who may have concerns about the risks associated with enrolling in a vaccine trial (Harrington 2017). Potential participants may also have other concerns, and weigh benefits and harms differently (Borobia 2021; Detoc 2017; Gouglas 2018).This can result in recruitment difficulties and subsequent trial discontinuation (Detoc 2019; Petkova 2020). Older people, who are disproportionately affected by COVID-19, are less likely to participate in a vaccine trial (Flores 2021). Vaccine safety and efficacy must be established before public use, and this requires high-quality evidence from well designed and conducted vaccine trials (Detoc 2019). Evidence suggests that vaccine hesitancy and doubts about vaccine safety may influence the recruitment of participants to vaccine trials (Larson 2016; Wilson 2021).

Furthermore, due to the urgent nature of vaccine development in a pandemic or epidemic, potential participants might be concerned about the rapidity of vaccine development and perceive that steps in the scientific process have been shortened, which may erode public confidence in participating in trials (Dyer 2020; Langford 2020). Limited timelines for recruitment increase recruitment pressures (Wilson 2021), and this can create a tension if potential trial participants do not have sufficient time and information to guide their decision on whether to join a trial (Cattapan 2019).

How the intervention might work and how the health condition might affect people

Vaccine trials depend primarily on the willingness of a diverse group of healthy volunteers to take part in large-scale trials. Hence, it is important to identify factors influencing people's decision to take part, including during a pandemic or epidemic, and support transparency of information and decision-making to optimise informed choice (Carlsen 2016; O'Callaghan 2020).

Support from the public for trials overall, and even more so during a pandemic or epidemic, is evident (Elliot 2019; Gobat 2018). Factors such as trust in health professionals, trust and confidence in the government, and knowledge of the disease have been identified as influencing factors (Finset 2020; Gobat 2019; Jaklevic 2020). It has been suggested that people may use an instinctive decision-making style related to decisions around trial recruitment during a pandemic or epidemic (Gobat 2018). A decision to take part in a clinical trial can be influenced by several factors, including: how trial information is communicated; personal factors, such as how other people can influence the decision; and the potential benefit and harm of taking part (Houghton 2020). Specific factors associated with people taking part in vaccine trials can include older age (Hodgson 2021), having heard about vaccine trials through multiple sources, and financial incentives (Cattapan 2019; Detoc 2019; Gobat 2018). Taking part in a vaccine trial in a pandemic or epidemic is also influenced by factors such as concerns about the disease prevalence and spread, confidence in the vaccine safety and the impact of restrictive measures during a pandemic or epidemic (Langford 2020). These can influence people's willingness to consider taking part in trials as their concerns for self and family and the negative psychological effects of quarantine and stress can impact on the decision-making process (Brooks 2020; Wang 2020).

Understanding factors that influence people's decisions to participate in trials is likely to help shape future communication between trialists and potential participants. However, this communication does not simply aim to convince the individual to take part in a pandemic or epidemic vaccine trial. It has the further objective of supporting the individual's informed choice about participation. In an informed decision-making situation, the person may choose to take part in a vaccine trial or, equally, choose not to.

Why is it important to do this review?

Previous reviews about recruitment to trials have considered barriers from the participant's perspective (Prescott 1999), and from the perspective of recruiting clinicians (Fletcher 2012; Prescott 1999). Other reviews have focused on recruitment to trials for specific therapeutic indications (e.g. oncology; Fayter 2007) or specific vulnerable populations (Glover 2015). In a recent qualitative evidence synthesis, Houghton 2020 reviewed the barriers to and facilitators of recruitment to clinical trials across different healthcare settings from the perspective of both trial participants and decliners. Whilst this body of work offers valuable insight into potential factors associated with trial recruitment, such as perceived risk, treatment preference and trial burden, it falls short of providing specific insights for decision making for taking part in vaccine trials in a pandemic or epidemic.

To gain a comprehensive understanding of the factors associated with recruitment to vaccine trials during a pandemic or epidemic requires exploration of the barriers and facilitators that guide decision-making among potential trial participants.

Qualitative research explores how people perceive and experience the world in which they live. Through synthesising qualitative studies exploring people's attitudes, views and decisions about pandemic or epidemic vaccine trial participation, we can identify factors that trialists should consider when developing strategies to inform and support public decision-making processes about recruitment to pandemic or epidemic vaccine trials. The findings

from this review will inform current and future COVID-19 vaccine trials and, more broadly, inform vaccine trials conducted in similar circumstances in the future.

OBJECTIVES

This is a protocol for a Cochrane Review (qualitative). The review aims to explore the factors associated with a person's decision to take part in a pandemic or epidemic vaccine trial.

METHODS

Criteria for considering studies for this review

Types of studies

We will include primary studies that use recognised methods of qualitative data collection and data analysis, including: ethnography, phenomenology, case studies, grounded theory studies and qualitative process evaluations. We will include studies that use qualitative methods for data collection (e.g. focus group discussions, individual interviews, observation, diaries, document analysis, open-ended survey questions) and qualitative methods for data analysis (e.g. thematic analysis, framework analysis, grounded theory). For mixed-method studies, we will include them if it is possible to extract the data collected and analysed using qualitative methods. Studies will be eligible regardless of whether they were conducted alongside studies of the effectiveness of interventions to improve vaccination uptake in a pandemic or epidemic. We will include both published and unpublished studies and studies published in any language.

We will exclude studies that collect data using qualitative methods but do not analyse them using qualitative analysis methods (e.g. open-ended survey questions where the response data are analysed using descriptive statistics only). We will not exclude studies based on our assessment of methodological limitations, because these may contribute insights into particular contexts or circumstances as well as to the overall phenomenon. We will use the information about methodological limitations to assess our confidence in the review findings.

Topic of interest

We will include studies with a primary focus on people's experiences of, and attitudes to, participating in a vaccine trial during a pandemic or epidemic. Eligible studies will report the views and experiences of adults (≥ 18 years). This includes adults who have been invited to participate in trials as well as adults who have not received an invitation.

By 'vaccine trials in a pandemic or epidemic' we refer to prophylactic or therapeutic vaccine trials related to the disease that caused the pandemic or epidemic, and in which the trial is being conducted in response to, and during, the pandemic or epidemic. We will include studies conducted in any setting that is experiencing a pandemic or epidemic. We consider an epidemic to be a large disease outbreak within a region and a pandemic as an epidemic that spreads over multiple regions or continents. We consider a prophylactic or therapeutic vaccine as one that builds immunity in an individual and is intended to prevent disease spread, prevent development of symptoms and reduce severity of disease.

Search methods for identification of studies

Electronic searches

The Cochrane (EPOC) Effective Practice and Organisation of Care Information Specialist will develop the search strategies in consultation with the review authors.

We will search the following electronic databases.

- MEDLINE, Ovid
- CINAHL (Cumulative Index to Nursing and Allied Health Literature), EbscoHost
- Scopus
- PsycINFO
- Epistemonikos
- ORRCA (Online Resource for Research in Clinical triAls)

We will develop search strategies for each database. We will not apply any limits on language or publication date. Where appropriate, we will include a methodological filter for qualitative studies. See Appendix 1 for the MEDLINE search strategy, which we will adapt for other databases. We will provide all strategies used in the final review.

Grey literature

In addition to searching the databases outlined, we will conduct a grey literature search of theses via Ethos, the DART-Europe E-theses portal and ProQuest Dissertations & Theses Abstract & Index.

Searching other resources

We will review the reference lists of all included studies and key references (i.e. relevant systematic reviews) (Horsley 2011). We will conduct a cited reference search for all included studies in Web of Science Core Collection, Clarivate Analytics and Google Scholar.

We will search the Cochrane COVID-19 Study Register for any qualitative study relating to COVID-19 vaccine trials, because that is an ongoing pandemic at the time the searches will be conducted. The Cochrane COVID-19 Study Register includes pre-print material.

We will check the reference lists of studies included in linked intervention reviews to identify any qualitative studies associated with these studies. We will also contact researchers with expertise relevant to the review topic to request studies that might meet our inclusion criteria. We will select the included studies that exactly match the eligibility criteria.

Selection of studies

Two review authors will independently assess each title and abstract of the identified records to evaluate eligibility. We will use Covidence software for title and abstract screening. We will exclude references (at title and abstract screening) that do not meet the eligibility criteria. After that, we will retrieve the full text of all the papers identified as potentially relevant by either or both review authors. Two review authors will then assess these papers independently. We will resolve disagreements by discussion or, when required, by involving a third review author. Where appropriate, we will contact the study authors for further information. Where review authors are also authors of any of the studies identified in the searches, they will not assess these studies for inclusion.

Language translation

For titles and abstracts published in a language beyond the proficiencies of the team, we will carry out an initial translation through open source software (Google Translate). If this translation indicates possible inclusion, or if the translation is insufficient to decide, we will retrieve the paper's full text. We will then ask Cochrane networks or other networks proficient in that language to assist us in assessing the full text of the paper for inclusion. We will consider asking the original authors to assist in the provision of translation of the full text of the paper. If this cannot be achieved for a paper in a particular language, the paper will be listed under 'Studies awaiting classification' to ensure transparency in the review process. We will use professional translation services if needed.

Sampling of studies

Qualitative evidence synthesis aims for conceptual richness and contextual comparisons, and large amounts of study data can impair the quality of the analysis. Depending on the number of studies eligible for inclusion, we may need to sample the studies for more meaningful analysis.

To allow for the broadest possible variation within the included studies, we will use maximum variation purposive sampling to select from the eligible studies (Ames 2017; Suri 2011). Potential sources of variation may include the characteristics of the participants such as age and gender, the type of vaccine and associated disease it aims to prevent, the year in which the trial was conducted and the country income level. We will also assess the data richness of eligible studies, for instance by using the approach used by Ames 2019. Once we have determined suitable variables, we will create a sampling frame and map all eligible studies onto the frame. We will then review the studies within each cell of the frame and decide how many studies to include in the review. We will also purposely seek additional studies that address characteristics not previously identified as important, but that are identified during the initial analysis.

We will include a PRISMA flow diagram to show the results of our search and of screening and selecting studies for inclusion. Where the same study (i.e. using the same sample and methods) has been presented in different reports, we will collate these reports so that each study (rather than each report) is the unit of interest in our review. We will include all unique data from all related study reports. We will include a table listing studies that we excluded from our review at the full-text stage and the main reasons for exclusion.

Data extraction

We will use Qualitative Data Analysis Software (QSR) NVivo Version 2020/R1 to manage data extraction and synthesis (Nvivo 2020). We will extract information about the first author, publication date, study language, country, setting, type of pandemic or epidemic, type of vaccine, participants' age, gender, socioeconomic status, ethnicity and any other information relevant for any planned subgroup analyses. We will extract information about how the study was designed and conducted. Finally, we will extract all data relevant to the review's objective, including descriptions of themes and categories as well as illustrative quotes. PM, CH, LB, EM and MD will individually extract pertinent information about design, setting and methods, and the data from all the sampled studies. We will pilot test the data extraction form and process initially, and review authors will agree on any revisions.

Assessing the methodological limitations of included studies

At least two review authors (from PM, LB, MD, CH, EM) will independently assess methodological limitations for each study using a quality assessment tool for qualitative studies used in previous Cochrane Reviews (Ames 2017; Ames 2019; Houghton 2020). Where any of the review authors are also authors of included studies, they will not be involved in assessing the study's methodological limitations. We will resolve disagreements by discussion or, when required, by involving a third review author.

We will assess methodological limitations according to the following domains.

- Are the settings and context described adequately?
- Is the sampling strategy described, and is this appropriate?
- Is the data collection strategy described and justified?
- Is the data analysis described, and is this appropriate?
- Are the claims made/findings supported by sufficient evidence?
- Is there evidence of reflexivity?
- Does the study demonstrate sensitivity to ethical concerns?
- Any other concerns?

We will report our assessments in a Methodological Limitations table, using a 'yes/no/can't tell' rating. We will use these assessments to support our GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research) assessment of our confidence in the review findings (Lewin 2018).

Data management, analysis and synthesis

We will use the 'best-fit framework approach' to identify a 'lens' to analyse and synthesise the evidence from our included studies (Booth 2015). The best-fit framework synthesis method requires identification and subsequent modification of an existing model from a similar, yet different, phenomenon of interest (Carroll 2013). Our choice of the best-fit method acknowledges that the context-specific nature of vaccine trials in a pandemic or epidemic may require further thematic synthesis, either external to or within the proposed framework.

The best-fit a priori framework synthesis involves four stages:

1. identify a pre-existing conceptual model or framework;
2. include all relevant qualitative studies satisfying criteria;
3. map data from included studies onto framework;
4. use a thematic synthesis approach to generate completely new themes to supplement the framework's themes.

We will determine our final choice of framework after familiarising ourselves with the data in the included studies. We are currently considering using a thematic framework based on themes from the previously published Cochrane qualitative evidence synthesis that has explored what influences people's decision to take part in trials in general (Houghton 2020). This framework includes three themes with a further six subthemes, described below.

- Trial influences on decision to participate
  - Communication of trial information
  - Significant trial components
- Personal influences on the decision to participate
  - Influence of other people
  - Weighing up the risks and benefits
- The impact of potential outcomes on the decision to participate
  - Personal benefits of trial participation
  - Making a difference: benefits for others

We will code the evidence from the included studies against the proposed framework. We will create new or revised themes using thematic synthesis on any evidence that cannot be coded against the framework. We will then produce a new framework combining existing framework and new themes supported by the evidence.

We will manage this process using QSR NVIVO V2020/R1. This will enable four review team members to work effectively and transparently on the synthesis. We will use the attributes function in NVivo to generate 'queries', which will facilitate potential subgroup analysis, such as age, geographical location, or income setting.

Developing implications for practice

When we have finished preparing the review findings, we will examine each finding, identify factors that could influence recruitment for pandemic or epidemic vaccine trials and develop prompts for future trialists. We will present these prompts in the implications for practice section. These prompts are not intended to be recommendations, but will be phrased as questions to help trialists consider the implications of the review findings within their context. We will send these implications for practice to a selection of stakeholders from different countries and COVID-19 vaccine trialists to gather their feedback about the relevance of these prompts and how they are phrased and presented.

Assessing our confidence in the review findings

At least five review authors (PM, LB, MD, EM, CH) will use the GRADE-CERQual approach to assess our confidence in each finding (Lewin 2018). GRADE-CERQual assesses confidence in the evidence based on the following four key components.

1. Methodological limitations of included studies: the extent to which there are concerns about the primary study's design or conduct that contributed evidence to an individual review finding.
2. Coherence of the review finding: an assessment of how clear and cogent the fit is between the data from the primary studies and a review finding that synthesises those data. By cogent, we mean well-supported or compelling.
3. Adequacy of the data contributing to a review finding: an overall determination of the degree of richness and quantity of data supporting a review finding.
4. Relevance of the included studies to the review question: the extent to which the body of evidence from the primary studies supporting a review finding applies to the context (perspective or population, phenomenon of interest, setting) specified in the review question.

After assessing each of the four components, we will judge the overall confidence in the evidence supporting the review finding. We will judge confidence as high, moderate, low, or very low. The final assessment will be based on consensus among the review authors. All findings start as high confidence and will then be graded down if there are important concerns regarding any GRADE-CERQual components.

Summary of qualitative findings table and evidence profile

We will present summaries of the findings and our assessments of confidence in these findings in a summary of qualitative findings table. We will present detailed descriptions of our confidence assessment in an evidence profile.

Integrating the review findings with other Cochrane Reviews

We will integrate our key review findings with the Cochrane Review by Houghton 2020, which explores factors influencing people's decisions to participate in healthcare trials. We are particularly interested in the extent to which our findings reflect or differ from the Houghton 2020 review, as well as comparing our confidence in the evidence in the context of pandemic or epidemic vaccine trials.

We will also explore how we can integrate the findings from both qualitative reviews with those of a related Cochrane Review of the effectiveness of recruitment interventions (Treweek 2018), to explore how the interventions assessed in the review could be better designed or implemented in the context of pandemic or epidemic vaccine trials. We will consider using the proposed framework from Houghton 2020 as an integration tool to compare the findings across the two qualitative evidence syntheses and the intervention review. We will consider several possible approaches, including a logic model approach (Ames 2020), or a matrix approach (Harden 2018), depending on the nature of our findings.

Review author reflexivity

Author reflexivity considers any influences or biases that may impact the review process (Flemming 2021). The core review team includes researchers with and without a healthcare background. All review authors are researchers within health care. Some are focusing on trial methodology, and others on qualitative research in trials (PM, LB, MD, PM, LB). All review authors have training and expertise in qualitative research and qualitative evidence synthesis. Most were involved in a previous Cochrane qualitative evidence synthesis reporting on the factors that influence people's decision whether to take part in a trial (Houghton 2020).

The review team have varying views on vaccine development and vaccination programmes. This variety will minimise the risk of one perspective dominating the review. These views have arisen from different personal and professional experiences, such as, but not exclusive to: practicing as an infectious diseases doctor in a pandemic (XHC); conducting research in the areas of pandemic vaccine trials (RC), infectious diseases (XHC), recruitment to trials (CH, MD, PM, LB, DD), public health and health services research (AB, CG, EM); and as the recipient of vaccinations due to a chronic health condition (AB). All authors believe that trial participation, both in the context of a pandemic or epidemic and otherwise, should be voluntary. Moreover, all authors believe in the importance of easy access to evidence-based information about the potential benefits and harms of trial participation, including information about potential side effects and uncertainties.

Central to reflexivity is remaining open to any viewpoints that may influence decision-making. This will be achieved through regular team meetings at each stage of the review process where the team will critically discuss personal views and experiences of vaccine development and vaccination programmes. In addition, the lead author (PM) will maintain a reflexive journal to capture key discussions and decisions reached at team meetings.

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Paul Miller, Cochrane Information Specialist, for his work on topic refinement and support in developing the search strategy.

When preparing this protocol, we used EPOC's Protocol and Review Template for Qualitative Evidence Synthesis (Glenton 2020).

This review is part of a larger study being undertaken by the VACCELERATE consortium.

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APPENDICES

Appendix 1. Draft for MEDLINE Search strategy

1	patient selection/

(Continued)

2	patient participation/
3	motivation/
4	exp volunteers/
5	or/1-4
6	exp vaccines/
7	exp immunization/
8	or/6-7
9	5 and 8
10	((participat* or recruit* or enrol* or non-particip* or nonparticip* or selection) adj6 (epidemic* or pandemic*)).ti,ab,kf.
11	((participat* or recruit* or enrol* or non-particip* or nonparticip* or selection) adj6 (vaccin* trial* or vaccin* research or vaccin* clinical trial* or vaccin* clinical stud* or vaccin* clinical research or vaccin* stud* or immuni*)).ti,ab,kf.
12	((barrier? or motivat* or facilitat* or decision? or decline? or refuse? or refusal or experience? or attitude?) adj6 (trial* or research or study or studies) adj6 (vaccin* or immuni* or pandemic* or epidemic*)).ti,ab,kf.
13	or/9-12
14	((participat* or recruit* or enrol* or non-particip* or nonparticip* or selection) and vaccin* and (trial* or research or study or studies)).ti.
15	((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab. or interviews as topic/ or focus groups/ or narration/ or qualitative research/
16	px.fs.
17	15 or 16
18	13 and 17
19	14 or 18

CONTRIBUTIONS OF AUTHORS

The protocol was drafted by PM, LB, MD, CH. All the review team reviewed several drafts of the protocol and offered comments and suggestions (PM, LB, MD, EM, CG, DD, AB, SS, RC, XHC, CH). The search strategy was developed by Paul Miller and reviewed by an Information Specialist in Cochrane Norway.

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