STUDY PROTOCOL

A review of new challenges and solutions to the timely and effective implementation of clinical research responses to high priority diseases of epidemic and pandemic potential: A scoping review protocol [version 1; peer review: 1 approved with reservations]

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Abstract

Background: Conducting and implementing clinical research response during pandemic and epidemic diseases outbreaks are often fraught with challenges due to their unprecedented nature. In previous research, challenges to the implementation of clinical research responses during pandemic and epidemic outbreaks were identified and solutions suggested. While the emergence of the Covid-19 pandemic has, on one hand, highlighted new and unresolved challenges, several novel solutions such as the Randomised Evaluation of Covid-19 Therapy (RECOVERY) trial were also implemented and reported in the literature. This scoping review, therefore, aims to synthesise and update solutions to the barriers affecting the implementation of clinical research responses during new, emerging or re-emerging diseases of pandemic and epidemic potential, to further inform strategies that would enhance pandemic and epidemic preparedness and response.

Methods: This scoping review will be conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis- Extension for Scoping Reviews (PRISMA-ScR). Search will be conducted in six scientific databases: Ovid MEDLINE, Ovid Global Health, OVID PsycINFO, Ovid Embase, Scopus Epistemonikos, and complemented by a grey literature search in Google Scholar. Terms related to clinical trial, high consequence infectious diseases and the PEARLES domains will be used in the search. Two reviewers will independently screen

Open Peer Review

Approval Status ?

	1
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1. **Joanna Orne-Gliemann**, University of Bordeaux, Bordeaux, France

Any reports and responses or comments on the article can be found at the end of the article.

retrieved articles in Rayyan software. Descriptive data of studies will be extracted into a pre-developed Microsoft Excel template while qualitative data related to the PEARLES solutions or barriers will be coded in NVivo. Results will be synthesised thematically and presented in a narrative style.
Conclusions: This scoping review will synthesise new and updated solutions to the PEARLES challenges encountered during the implementation of clinical research responses to high consequence epidemics and pandemics. Furthermore, it will examine how challenges and proposed solutions identified prior to the emergence of Covid-19 have been addressed and tested in real time.

Keywords
epidemics, pandemics, outbreaks, high consequence infectious diseases, clinical trials, clinical research response, facilitators, barriers

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Plain language summary

This is a scoping review of published evidence and research on the potential solutions to the political, economic, administrative, regulatory, logistic, ethical and social (PEARLES) barriers and solutions to implementation of clinical research responses to high consequences infectious disease outbreaks of epidemic or pandemic potential. This work builds on previous work and is an update on our scoping review carried out in 2018. The results will be compared with our previous scoping review to identify if earlier proposed solutions have been tested and if there are persisting or new challenges and solutions to epidemic clinical research responses identified in more recent outbreaks, including the Covid-19 pandemic.

Background and rationale

Designing and implementing clinical research responses to epidemics and pandemics continue to be challenged by the unprecedented nature of disease outbreaks. Clinical research is important for generating evidence to inform evidence-based treatments and diagnostics, and clinical and public health management to improve individual, population and outbreak outcomes[1]. A robust clinical research response requires planning, coordination, and significant technical and financial resources, which are often inexpedient during an epidemic or pandemic[1,2].

In previous research, we synthesised some of the challenges encountered while conducting clinical research in epidemic and pandemic settings, and summarised the potential solutions to address these that has been described in the literature[2]. These solutions range from establishing global coordination and collaboration between research networks, creating dedicated funding bodies and agreements for rapid disbursement of funds for clinical trials, strengthening and capacity-building for implementing trials in health systems, developing pre-approved study protocols, study-in-hibernation, pre-approved site agreements etc., to combat the delay often associated with starting a clinical research trial[2]. Unfortunately, however, these proposed solutions remained mere suggestions to be tested in real time. As of the time of synthesis in 2018, no study had evaluated any of the proposed solutions in the context of an epidemic or pandemic[2].

Since completion of the above study and now, the world has witnessed a pandemic of great magnitude. Due to the rapid spread and high mortality rate of the Covid-19 pandemic rapid evidence was required to inform the response through activating clinical trials[3]. While some lessons learned from previous emergency responses including collaborative research, open data sharing, and rapid dissemination of results appear to have been partially applied to the Covid-19 response, the pandemic has also highlighted new and remaining challenges[3–5]. Huge pressure on the research community, regulatory bodies, clinicians, and healthcare workers led to rapid authorization, conduct and dissemination of studies, many of which were underpowered and, in some cases, had to be revoked[5].

Nevertheless, the Covid-19 pandemic also gave rise to a number of innovative research solutions such as the Randomised Evaluation of Covid-19 Therapy (RECOVERY) trial in the UK and the Randomised, Embedded, Multifactorial, Adaptive Platform (REMAP) trial[6,7]. The RECOVERY trial, which drew on the collective strength of major hospitals across the United Kingdom, to recruit thousands of participants within a short time period, generated the first treatment evidence for Covid-19[8]. Similarly, the adaptive nature and integration of the REMAP trial in clinical care facilitated rapid recruitment of patients and allowed testing of multiple interventions simultaneously[7]. These collaborative, streamlined, and novel approaches to conducting clinical research helped to overcome some of the challenges associated with conducting clinical trials during a pandemic.

It is, therefore, important to synthesise evidence from the literature, on the applied or suggested solutions to the challenges of implementing clinical research responses during new, emerging and re-emerging outbreaks of epidemic and pandemic potential. As with our previous study, this scoping review will identify updated solutions to the political, economic, administrative, regulatory, logistic, ethical and social (PEARLES) challenges, to further inform strategies to enhance pandemic preparedness.

Objectives

- To identify and describe updated PEARLES challenges and solutions to implementation of clinical research responses to high consequence epidemics and pandemics.
- To identify if challenges described prior to the Covid-19 pandemic have been addressed, and proposed solutions have been tested in real-time.
- To inform recommendations for strengthening preparedness efforts for timely, effective and equitable trial responses to future outbreaks of public health significance.

Methods

This scoping review is an update on the PEARLES review conducted up to June 2018[2] and will be conducted using guidelines from the Preferred Reporting Items for Systematic Review and Meta-analysis- Extension for Scoping Reviews[9].

Population-Concept-Context framework criteria

The review question, eligibility criteria and search terms will be guided by the previous review, and the population, concept, context framework[10] as outlined in Table 1 below.

Search strategy

The search strategy was informed by a pilot search. A scoping pilot search of Ovid MEDLINE and Google Scholar was conducted in January 2023 using a modification of the

Table 1. Population-Concept-Context (PCC) framework to guide the review process.

PCC	Description
Population	Human population, such as healthcare workers, children, young people, adults, pregnant women, policymakers, clinical, behavioural and social science researchers and specialists, ethicists, regulators and other associated stakeholders involved in infectious disease preparedness and response.
Concept	Challenges identified to political, economic, administrative, regulatory, logistic, ethical and social barriers for timely implementation of clinical research* responses to high consequence epidemics and pandemics from inception to dissemination for action, and solutions developed or recommended to address these
Context	Epidemic, pandemic or disease outbreaks caused by diseases identified by WHO as priority diseases for research and development in recent years[11] including Covid-19, pandemic zoonotic influenza, mpox, MERS, SARS, Covid-19, Nipah, Ebola (EBOV, SUDV), Crimean-Congo haemorrhagic fever, Lassa fever, Marburg, Dengue, chikungunya, Zika, disease X. We will include all study designs, including reviews and opinion pieces if they describe and cite challenges and/or solutions to implementing clinical research responses to outbreaks. This includes qualitative and quantitative studies, using any study design. We will exclude pure public health studies, such as studies into uptake of vaccines, and studies describing implementation of non-infectious disease research during epidemics and pandemics that is not focused on challenges and solutions to implementation of infectious disease clinical research responses.

*Definition of clinical research: includes interventional and non-interventional research, e.g., RCTs, observational studies, non-randomized trials, such as studies into optimal supportive care and treatments, new diagnostics and vaccine trials.

PEARLES 1.0 search terms, with the addition of new priority infectious diseases such as Covid-19, to formulate and refine the search terms. Following a review of the pilot search results, the string of search terms and keywords using a combination of free terms and medical subject headings (MeSH) terms was developed (Extended data: Supplementary Tables 1–2[12].

Database search

The systematic search will be completed by an information librarian at the Bodleian library in Oxford. The search will be conducted in the following databases Ovid MEDLINE, Ovid Global Health, Ovid PsycINFO, Ovid Embase, Scopus, and Epistemonikos from 1 June 2018 to 28 February 2023., to identify new records published since the PEARLES 1.0 review was conducted. The full search terms are presented in the Extended data: Supplementary Table 1[12]. The search results will be submitted by the information specialist to the reviewers as an EndNote v 20 library (EndNote (RRID:SCR_014001)). A RIS file of the search results will also be available which can be used in an alternative open-access software such as Mendeley (Mendeley Desktop v1.19.8 [Release 25 January 2023]) (RRID:SCR_002750).

Grey literature search

The grey literature search will be conducted in Google Scholar by one reviewer, using the keywords presented in the Extended data: Supplementary Table 2[12], with publication year filtered for studies published between 2018 and 2023. The pilot search identified a high number of records relating to Covid-19, due to the unprecedented number of articles published during the pandemic. The Google Scholar search will therefore focus on retrieving records presenting PEARLES challenges and solutions identified during other (non-Covid-19) priority outbreaks. Due to Google Scholar's limitations with result ordering[13] and the possibility of duplicating studies already retrieved during the databases search, we will screen the first 200 records in the Google Scholar search. The search will be complemented by a Google search to retrieve any high-level reports not published in peer-reviewed journals, with the first 50 records screened.

Screening of articles

Full text papers will be retrieved using EndNote's automatic retrieval function, complemented by manual retrieval through university library access, of those articles not retrieved automatically. Due to the volume of records published during the Covid-19 pandemic title and abstract screening will be carried out by one reviewer, with a second reviewer checking a proportion of the excluded records. This will be followed by a full-text screening by two reviewers independently. Any disagreements will be discussed and consensus reached by a third reviewer. Articles not accessible through Oxford University online library access will be excluded due to non-accessibility. The screening process and results will be documented in a PRISMA flow chart[14].

Eligibility criteria

Inclusion criteria:

- Publications that offer insight into political, economic, administrative, regulatory and logistic, ethical, societal (PEARLES) barriers and solutions to implementation of clinical research responses during an infectious disease outbreak, epidemic or pandemic in any setting, from planning of infrastructures, regulatory, and review boards, staff and systems to the inception of the study, preparation, delivery and through to dissemination of evidence for action.

- Publications that describe the experience of (challenges and solutions) implementing and conducting clinical research responses to an infectious disease outbreak of epidemic potential as a descriptive summary, and/or in addition to clinical outcomes presented.
- Publications that describe solutions and/or challenges of delivering clinical research including trials, e.g., supportive care, therapeutic and vaccine trials during outbreaks, and how these were overcome.
- Studies focused on clinical treatment or clinical management in the response to an epidemic or pandemic, including observational and intervention clinical research studies, which also describes PEARLES barriers and solutions.
- Qualitative studies exploring how to address challenges, such as ethical, regulatory, creation of new organisations, integration into health services, training, to community-based studies to improve inclusion in trials, engagement of stakeholders, including governments, to data sharing systems, technologies etc.
- Any study design, including descriptive articles that present original data or analyses, narrative reviews, high-level reports, technical reports, opinion pieces presenting new findings published between 1 June 2018 and 28 February 2023
- Human studies
- Any language

Exclusion criteria:

- Animal and cell studies.
- Non-communicable disease and microbiology studies, not presenting information about PEARLES challenges and solutions for implementation of clinical research response studies to epidemics and pandemics.
- Pure non-infectious disease related records.
- Pure public health related studies.
- Clinical studies not related to an infectious disease outbreak, epidemic or pandemic.
- Publications that solely present clinical results/outcomes, without describing challenges or solutions to implementation of the clinical study.
- Human challenge studies.
- Publications on PEARLES issues related to delivering a public health response that does not include clinical research e.g., vaccination uptake studies.
- Articles not accessible through Endnote's automatic retrieval or a manual search through Oxford online library access.
- Articles in languages that we are unable to find an interpreter for within the timeframe will not be data extracted but instead listed with full bibliography.
- Abstracts, commentaries, editorials, letters, preprints protocols, opinion pieces that do not present new evidence that do not contribute any original study data or new findings, solutions or concepts.

Data charting and analysis

The data extraction template, created in Microsoft Excel for the previous PEARLES 1.0 scoping review, will be used to document the characteristics and data on the challenges and solutions presented of all included studies (Extended data: Supplementary Figure 1[12]). Data points to be extracted include study metadata (title, authors, journal, year of publication setting), study objectives, study design, PICOs (study population, intervention, comparator and outcome) and the PEARLES barriers and solutions identified from the results and discussion sections.

Depending on the volume of studies identified for inclusion in the review, studies may be further prioritised for data extraction at the data extraction stage. If there are a high number of studies for a specific disease and setting, these will be prioritised by relevance for the data extraction. If there are a number of studies extracted sufficiently presenting challenges and solutions to implementation of clinical research during a specific disease outbreak in the same setting and saturation is reached, further studies may not be extracted but instead presented with bibliography in a supplemental file.

In order to retain the context in which the PEARLES domain are being reported and to capture the thematic concept in detail, data will be extracted in a Microsoft Excel 2021 file for the thematic analysis (Microsoft Excel (RRID:SCR_016137)). The extracted data file will be coded by one reviewer aiming to report overlapping themes while maintaining the contextual detail of the data[15–17]. Deductive themes will be based on the PEARLES factors, while inductive subcodes are attributed to identified individual factors (e.g., coordination, ethical approval etc). A second reviewer will conduct a 'proportional check' of up to 40% of all the extracted data.

Data synthesis

Data will be summarised thematically as per the presentation of the previous scoping review[2] to enable a comparison of the results pre- and post- the Covid-19 pandemic, in line with the study objectives. The data will be presented in the same style as the previous scoping review to enable a direct comparison of the results from the previous review which was completed in June 2018. The analysis will include a comparison of the results to identify if solutions identified in 2018 has been addressed, if proposed solutions have been tested, and if there are remaining challenges. Further, identify if more recent outbreaks, including the pandemic has highlighted new challenges and solutions to address these.

Publication

The results will be published in a peer-reviewed journal and disseminated via presentations to key stakeholders including clinical research leads, research funders and other policy makers.

Ethics and consent

Ethical approval and consent were not required.

Data availability

Underlying data

No data are associated with this article.

Extended data

Open Science Framework: Extended data for 'A review of new challenges and solutions to the timely and effective implementation of clinical research responses to high priority diseases of epidemic and pandemic potential: A scoping review protocol', https://doi.org/10.17605/OSF.IO/P2H7G[12].

This project contains the following extended data:

- Supplementary Data- PEARLES 2.0 Protocol.docx

Acknowledgements

GloPID-R Research and Policy Team, Pandemic Sciences Institute, University of Oxford, Oxford, UK

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Open Peer Review

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Version 1

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Joanna Orne-Gliemann
University of Bordeaux, Bordeaux, France

The paper presents a scoping review protocol on timely and effective implementation of clinical research responses. This work will build on findings of the work published in BMC Medicine in 2020.

It would be useful to add a brief justification for this review in the abstract already, maybe explaining why known challenges may have evolved?

A few suggestions regarding the databases to be investigated: Maybe add Web of science? And Scopus? These are more interdisciplinary, and may provide insight into specific policy, reglementary issues.
What about grey literature, governmental or ministry or political documents?
Why not consider interviews with key stakeholders? Research investigators? Donors? Public authorities? Hospital directors? Patient representatives? All actors/beneficiaries of implementation activities.

The focus and main outcome of the review (as mentioned in the title) seems to be on **implementation** barriers and facilitators of clinical responses. Maybe a definition of what you mean by implementation would help, its often a black box from theory to practice. What are specificities of implementation that you wish to address? What difference to you make with “delivery” of the research? What framework for analysis?
Many contextual factors inherent to the epidemic at stake (transmission prevention), and to governmental measures of “containment”, may prevent proper implementation

I am not sure the PEARLES domains are “validated domains” to investigate implementation per se. Maybe it would be interesting to compare/contrast PEARLES with typical implementation frameworks? Such as CFIR? Allowing comparison with previous 2018 work but also allowing an add-on.

Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?
Yes

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

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public heath, Implementation research

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.