

Title of project: Learning from COVID-19 related trial adaptations to inform efficient trial design - a sequential mixed methods study

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Abstract:

Background

Activities related to clinical trials (recruitment of participants, delivery of the intervention and follow up appointments) are usually undertaken in person; some of which are difficult to undertake remotely. The effects of the COVID-19 pandemic have meant that to continue, clinical trials have had to adapt the way they undertake these procedures. The aim of this study was to understand the adaptations that have been made by clinical trials units (CTUs) during the pandemic, and whether these adaptations to clinical trials have the potential to improve the efficiency of trials post-pandemic.

Methods

In December 2020, an online survey was distributed to 53 UK Clinical Research Collaboration (UKCRC) registered CTUs to identify the adaptations that have been made to trials as a result of the pandemic (work package 1, WP1). Case studies were selected for further investigation, ensuring variation in key characteristics (e.g., CTU, disease area). Staff involved in the selected case studies were interviewed to discuss the potential for the adaptation to improve the efficiency of future post-pandemic trials (WP2). The interviews were transcribed verbatim and analysed qualitatively. Findings were reviewed by a group of CTU and patient representatives at an online workshop (WP3) that focused on the potential of these adaptations to improve the efficiency in trials post-pandemic. The results of the study were written up within a freely accessible guidance document, aimed at CTUs.

Results

Forty studies, involving 86 adaptations, were reported in the survey responses from 21 CTUs (WP1). Of these, 14 trials were selected as case studies for in-depth data collection (WP2). The workshop was undertaken with 15 CTU and 3 patient representatives. Adaptations were not seen as leading to direct efficiency savings for CTUs; however, some adaptations may lead to improved recruitment and retention. A few adaptations were seen as likely to directly improve trial delivery for sites and participants beyond the pandemic, these were: a **two-stage remote-first eligibility assessment, recruitment outside the NHS via a charity, and remote consent**. Other adaptations were thought to have benefitted participants and could be used as a back-up option in future trials, and therefore may indirectly improve trial efficiency. All adaptations were perceived to be applicable in specific contexts. Providing trial participants with the flexibility to choose how to undertake a trial activity may potentially increase the representation of underserved groups in future trials. Barriers to using these adaptations include concerns around sampling biases and the validity of remotely collected outcomes.

Conclusions

Most trial adaptations were specific to certain trials and circumstances. Three adaptations were identified as potentially leading to efficiency gains. Although not their primary aim, many adaptations provided participants with increased flexibility to undertake trial procedures, but we found concerns around potential biases created by mixing trial procedure modalities. It is currently uncertain whether the potential advantages of greater flexibility in trial procedures justifies the risk of different modalities of data collection eliciting different responses from participants whilst losing the known benefits of research champions and a clinician/researcher facilitating recruitment. Future research should focus on the acceptability of the adaptations to trial participants, the effect of the adaptations on the scientific integrity of the trial and quantitative evidence of efficiency.

Introduction

Many clinical trials were suspended in the UK due to concerns around COVID-19 related social distancing and in order to allow pandemic related studies to be undertaken [1]. Social distancing resulted in some clinical services pausing their delivery, and patients (especially older adults) self-isolating for long periods. Trialists had to make pragmatic decisions to revise trials to permit them to continue while adhering to social distancing, with limited evidence or guidance regarding the best ways to achieve this. The main concerns for Clinical Trials Units (CTUs) were around maintaining recruitment of trial participants, intervention delivery, and outcome assessment, all of which have the potential to be affected by social distancing rules.

The aim of this project was to assess the adaptations CTUs made during the pandemic and to identify those adaptations that may improve the efficiency of clinical trials after the pandemic, specifically focussing on three areas– recruitment, delivery of the intervention and outcome assessment.

Methods:

Guidance document development

The guidance document was developed using three consecutive work packages (WPs). Ethical approval for this study was gained from the School of Health and Related Research, Research Ethics Committee (REC), within the University of Sheffield.

Work package 1 (WP1) – survey of UK CTUs

All UK Clinical Research Collaboration (UKCRC) registered CTUs were sent a survey to identify studies that have adapted their trial procedures in light of the pandemic. The survey was emailed to the Director of each CTU, and asked respondents to identify studies that had made one or more trial adaptations, where the adaptation(s) made were thought to have the potential to improve the efficiency of other trials post-pandemic.

Work package 2 (WP2) – in-depth qualitative interviews with selected cases

Case studies were selected from WP1, which were purposively sampled to ensure diversity of type of change made, and other key variables. Only those perceived to have the potential to increase the efficiency of future trials were selected.

An in-depth qualitative interview was undertaken with a representative from each trial to understand the challenges and benefits of each adaptation, and the impact on trial efficiency.

Work package 3 (WP3) - workshop with CTU and patient representatives

Those adaptations that were deemed from WP2 to be potentially beneficial in future trials were discussed within a workshop attended by a group of CTU and PPI representatives. The aim of the meeting was to discuss whether the identified adaptations could increase the efficiency of future trials.

Collaborations

The project involved collaboration with the individuals named in *Appendix 1*. The collaborators were involved in:

- Survey design (WP1);
- Selection of case studies for WP2, and review of documents;
- Design of the workshop (WP3);
- Review of the final guidance document.

Results:

Overview

Twenty-one CTUs responded to the survey (WP1), describing 40 studies that had made a total of 86 adaptations. From these, 14 case studies were selected and included in WP2. In the workshop (WP3), 15 CTU and three patient representatives met to discuss the findings from WP2.

Overall, there were a lack of adaptations that were thought to directly impact on efficiency at CTUs. Instead, adaptations could have a direct benefit to NHS sites, by reducing resource requirements, or they may benefit participants, by increasing flexibility. Many interviewees viewed incorporating flexibility into trial procedures as important as improving efficiency.

Below, the adaptations identified in WP2 are discussed, including their potential effect on future trials – within this, the discussions with CTU and patient representatives within the workshop (WP3) are incorporated.

Future use of the adaptations

Adaptations that benefit NHS sites and may directly improve the conduct of future trials

Three adaptations were thought to potentially improve the conduct of future trials: a **two-stage remote-first eligibility assessment** (*a two-stage eligibility assessment, where eligibility is assessed remotely prior to an in-person eligibility assessment*), **recruitment outside the NHS via a charity** (*where charities are used to identify potential participants*), and **remote consent** (*where consent is gained remotely, either via telephone or online*).

These adaptations have the potential to save NHS sites time and resources. A **two-stage remote-first eligibility assessment** may reduce trial costs by potentially saving trial sites time and resources in avoiding in-person visits for those who are not eligible for the trial; **recruitment outside the NHS** may completely avoid the need for NHS staff input into

recruitment. **Remote consent** may make it easier for patients to take part in the trial, potentially increasing recruitment rates and reducing the recruitment phase of the trial – however there is insufficient evidence that this is the case.

All three of these adaptations were only thought to be applicable to certain trials. For the **two-stage remote-first eligibility assessment** adaptation, this may include smaller studies (as this adaptation is particularly resource intensive for CTUs) and those that involve a high number of ineligible participants being initially identified (e.g., recruitment via social media platforms). CTUs may be unable to undertake this adaptation where they do not have the necessary regulatory approvals to receive identifiable data. **Remote consent** may be unsuitable for populations who have limited access to the required technologies. For all three adaptations, regulations around the governance of clinical trials of investigational medicinal products (CTIMPs) may mean that CTU staff are unable to undertake these procedures, due to the need for suitably qualified clinical staff to undertake these.

CTU representatives had concerns around the effect of these adaptations on the scientific validity of the trial. Both **recruitment outside the NHS** and **remote consent** may alter the sampling frame of the trial, therefore, it is unlikely that these adaptations will be used in future trials as the sole consent or recruitment method. The CTU, and potential trial participants, may not have access to the technology to enable **online remote consent** to be successfully implemented.

Adaptations that benefit participants and indirectly improve the conduct of future trials

Other adaptations were unlikely to directly reduce the cost of future trials (i.e., they did not directly save the trial sites or CTU time) but benefitted the trial participant through improving the flexibility by which trial procedures could be completed, and therefore may indirectly reduce trial costs. These were: **couriering of the IMP to the participant** (*where the study drug is sent to the participant, rather than having to attend a pharmacy*) and **remote collection of outcome measures** (*telephone or postal collection of PROMs, and remote collection of biological measures - blood pressures and a measure of blood glucose*).

A barrier to increasing flexibility and incorporating multiple modalities of outcome collection into the trial may be the impact on scientific integrity. Undertaking an outcome assessment adaptation alongside the ‘traditional’ data collection procedure may cause two distinct populations to be formed, for instance where participants systematically undertake the outcome assessment procedure differently at home. Specific PROMs may not be validated for remote use.

Other adaptations

Seven adaptations were thought to be either inefficient, only applicable during the pandemic, or there was insufficient information collected in WP2 to assess the potential value in future trials. These are listed in *Appendix 1*.

Conclusions:

Summary of findings

Of the 14 adaptations investigated, three were thought to have the potential to improve efficiency directly by reducing resources required at the CTU or trial site: a **two-stage**

remote-first eligibility assessment, recruiting outside the NHS via a charity, and remote consent. However, these adaptations may only be applicable to certain trials and settings. Other adaptations identified in this study may benefit participants and indirectly benefit trials through increasing the appeal of participation in the trial.

The effect of these adaptations on the scientific integrity of the trial is the most prominent barrier to implementing these adaptations. The most concerning biases are changes to the sampling frame that may occur when changes are made to recruitment processes (e.g., recruitment outside the NHS via a charity, and remote consent adaptations) and changes to outcomes if there are systematic differences in the way an outcome is collected remotely, compared to in-person. The effect of the adaptations on the scientific integrity of the trial could form the basis of future research in this area, as could the acceptability of the adaptations to trial participants and sites, whose views were not included in this study.

Implications:

The information contained within the guidance documents may be used by CTUs to learn about adaptations that were implemented during the pandemic and should allow CTUs to understand the potential challenges of undertaking these adaptations, in order to decide if a certain adaptation would work in their trial. In the guidance document, we have also identified potential avenues for future research.

Dissemination:

Two documents have been created for CTUs to refer to. A **summary document** provides overarching results from the study, including brief results of this study and guidance for future trials. A **detailed report** provides detailed information regarding the adaptations. Both will be made accessible [here](#). The results of the study will be published in an open access academic journal.

Acknowledgements

We would like to acknowledge the CTU staff who provided potential case studies to WP1 and gave their time to discuss the adaptations they had made within a qualitative interview. We would also like to thank the CTU and patient representatives for their time attending the workshop.

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Appendices

Appendix 1 – list of collaborators

Professor Cindy Cooper – Director, Sheffield Clinical Trials Research Unit

Professor Alicia O’Cathain – Professor of Health Services Research, School of Related Research, The University of Sheffield

Professor Chris Burton – Professor of Primary Medical Care, School of Related Research, The University of Sheffield

Professor Athene Lane – Co-Director, Bristol Randomised Trials Collaboration/Bristol Trials Centre

Caroline Murphy – Operational Director, King’s Clinical Trial Unit

Professor Jane Nixon – Deputy Director, Leeds CTU

Angela Cape – Research Pharmacist, King’s Clinical Trial Unit

Professor David Torgerson – Director, York Trials Unit

Appendix 2 – adaptations judged either be inefficient, only applicable during the pandemic, or there was insufficient information collected

Inefficient adaptations

- **postal consent processes** (where consent for participation in the trial is obtained through the participant sending the consent form via the postal service).

Adaptations that are only applicable to the pandemic

- **prioritisation in-person assessments** (*where the trial team contact the participant prior to a scheduled in-person visit to ascertain the safety or necessity of undertaking the assessment*);
- **prioritisation of in-person visits** (*where the need to collect trial outcomes is reviewed for the entire trial*);
- **remote delivery of the intervention by CTU staff** (*where CTU remotely deliver the trial intervention, instead of site-based NHS staff*).

Adaptations where the effect on efficiency is unknown

- **remote collection of spirometry and cough data** (*where spirometry and cough data are automatically collected by a device and sent to the study team*);
- **delivery of the trial intervention by any NHS Trust** (*where, instead of a clinician at the NHS Trust delivering the intervention to only participants based at that NHS Trust, clinicians from any NHS Trust can deliver the intervention to any participant*);
- **collection of biological measures at another facility / use of routinely collected outcome measures** (*where, instead of collecting the measure directly from the participant, another routine source is instead used*).

Conflict of interest declaration:

There are no conflicts of interest to report.