The University Of Sheffield.

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

RESEARCH PROTOCOL
(Version 2.0 Dated 26/11/2020)

Final Protocol

Sheffield Clinical Trials Research Unit (CTRU)

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

Contents

Abbreviations

COVID-19 – Coronavirus disease 19

CTU – Clinical Trials Unit

IMP – Investigational medicinal product

NHS – National Health Service

NIHR – National Institute for Health Research

PPI – Patient and Public Involvement

PRioRiTY – Prioritising recruitment and retention in randomised trials

ScHARR- School of Health and Related Research

UKCRC – United Kingdom Clinical Research Collaboration

WP – Work package

General information

Sponsor Details:

The University of Sheffield

Principle investigator:

Robin Chatters
Trial Manager/Proposal Development Assistant
Sheffield Clinical Trials Research Unit
School of Health and Related Research
The University of Sheffield.
Contact: r.chatters@sheffield.ac.uk / 01142222969

Co-applicants:

Professor Cindy Cooper
Professor of Health Services Research and Clinical Trials
Sheffield Clinical Trials Research Unit, The University of Sheffield

Professor Chris Burton
Professor of Primary Medical Care
School of Health and Related Research, The University of Sheffield.

Professor Alicia O'Cathain
Professor of Health Services Research
School of Health and Related Research, The University of Sheffield.

Professor Athene Lane
Professor of Trials Research
Bristol Trials Centre, University of Bristol.

Caroline Murphy
Operational Director
King's Clinical Trial Unit, King's College London.

Angela Cape
Research Pharmacist
King's Clinical Trial Unit, King's College London.

Professor David Torgerson
Director of York Trials Unit
York Trials Unit, The University of York

Professor Jane Nixon
Deputy Director
Leeds Clinical Trials Unit, The University of Leeds

Protocol amendments since version

Not applicable

1. Lay person summary

Many routine health care appointments, which were once undertaken face-to-face, are now being undertaken remotely (i.e. over the telephone or via video call) due to the social distancing rules put in place during the COVID-19 pandemic. These face-to-face appointments have, in the past, been used to recruit patients to clinical trials, or collect their follow-up data during a clinical trial. Therefore many clinical trials have had to adapt their procedures in order to carry on during the pandemic.
The aim of this project is to find out how clinical trials have adapted to the pandemic, specifically focussing on the recruitment and follow-up of trial participants. The overall aim is to identify adaptations that have the potential to improve the efficiency of future clinical trials.
In order to do this we will send a survey to all clinical trials units (departments that assist medical professionals in undertaking clinical trials) in the UK in order to identify studies that have made adaptations to their recruitment or follow-up procedures due to COVID-19, and that have the potential to improve the efficiency of clinical trials. We will then select five to eight case studies to collect detailed information about, which we will collect by interviewing the staff who were involved in the study. We will ask them about the adaptation they made to the study and the lessons they have learnt. The data collected from the interviews will then be presented to a selection of researchers and patients at a workshop, where the trial adaptations will be discussed and a guidance document, which will suggest ways in which trials can be made to be more efficient, will be put together.

2. Introduction

Many clinical trials have been 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 has resulted in some clinical services pausing their delivery, and patients (especially older adults) self-isolating for long periods. In order to restart, trialists are having 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) are around maintaining recruitment of trial participants, and outcome assessment, both of which have the potential to be affected by social distancing rules. Another concern is intervention delivery, e.g., adapting face-to-face interventions so they can be undertaken remotely. However, considerations related

to intervention delivery are mainly the responsibility of clinical judgement rather than trial efficiency, and are therefore unlikely to be led by the CTU.

Prior to the pandemic the use of remote techniques has generally been restricted to a minority of trials, either where the trial is not based around routine clinical care appointments, so recruitment [2–5] and outcome assessment [5] are undertaken remotely, or where the intervention can be delivered remotely or is technological in nature [6]. The vast majority of NIHR funded trials are rooted within routine care practices and therefore rely on in-person contact.

The need for such trials to attempt to reduce in-person contact presents a rare opportunity to study novel adaptations in trials. It seems likely that post-pandemic healthcare will change and remote contact may become the new normal - clinical trials will need to adapt. Therefore, guidance is needed in order to assist CTUs and to inform the efficient design of trials post pandemic.

Recommendations regarding how to adapt such trials during the pandemic have been made, which include the use of electronic consent [4,7,8], undertaking visits away from main hospitals [9], virtual safety monitoring [7,10–12] and delivering investigational medicinal products (IMPs) directly to the patients home [10,11,13]. For many of these, there is a lack of evidence to support their use in practice. For example, delivery of IMPs to patient's homes is not suitable for all agents, and electronic consent procedures may not be suitable for vulnerable or socially isolated groups. In addition, there may be innovations occurring within CTUs that are unreported.

The aim of this project is to assess the adaptations CTUs are making to incorporate social distancing procedures and identify those adaptations that may improve the efficiency of clinical trials after the pandemic. The focus is on adaptations to CTU procedures rather than adaptations made in research sites, specifically focussing on two areas – recruitment and outcome assessment (including safety monitoring).

This investigates research priorities identified by the Prioritising recruitment and retention in randomised trials (PRioRiTY) study [14] and Clinical Trials Transformation Initiative [15] regarding optimisation of the recruitment process and the use of technology in the consent process.

3. Aims and objectives

Aim

To identify adaptations made by CTUs to clinical trials during the COVID-19 pandemic that have the potential to improve the efficiency of clinical trials post-pandemic.

Objectives

1. Identify adaptations clinical trials units (CTUs) have made to clinical trial recruitment and outcome assessment procedures in order to allow clinical trials to continue during the COVID-19 pandemic, by undertaking a survey of registered CTUs (work package 1);

2. Share the responses to the survey with the UKCRC (UK Clinical Research Collaboration), in order to facilitate further research in this area.

3. Select case studies from work package 1 that have the potential to improve the efficiency of trials post-pandemic and qualitatively interview CTU staff involved in these selected studies to identify the lessons learnt from making such adaptations (work package 2);

4. Undertake a workshop with key stakeholders in order to produce guidance for CTUs to aid increasing the efficiency of trials (work package 3).

4. Study design

A sequential mixed methods study in 3 work packages (WPs):

WP1 - A survey of registered CTUs within the UK to identify potential case studies for WP2 - identification of the work undertaken and range of approaches taken by CTUs to adapt trial procedures to the new social distancing measures;
WP2 – Selection of five to eight case studies of trials that have made substantial changes because of the pandemic, and where the adaptations have the possibility of improving the efficiency of trials post pandemic. Case studies will be further investigated via qualitative interviews with staff based at the CTU who were involved in designing or implementing the adaptation, aiming to understand the adaptations in more detail and identify lessons learned;

WP3 – A workshop with investigators and patient representatives, to refine guidance for CTUs regarding promising remote recruitment and outcome assessment techniques that may increase the efficiency of trials in the future.

Work package 1

Overview
All UK CTUs will be surveyed to identify studies that have adapted their trial procedures in light of the pandemic. The survey will aim to collect information regarding the adaptations made and lessons learnt. CTUs will be asked to identify studies that are potentially good case studies for WP2, using the following criteria:

- An adaptation has been made to the recruitment process or outcome assessment/follow-up procedures;
- The study is multi-centre, involves randomisation and is being managed with extensive input from the CTU;
- The adaptation made is thought to be sustainable beyond the trial and has the potential to improve the efficiency of other trials post-pandemic.

Identification of participants
Initially, the survey will be sent to a member of each CTU's management team (e.g. the Director, Assistant Director, CTU manager, Operational Lead, Lead Data Manager or similar). More than one individual at each CTU may be approached if a response is not obtained from the CTU, or if more information is required from the CTU. The individuals that are contacted will be able to suggested others at their CTU to complete the survey, if it is felt they are better placed to complete it.

The preferred approach is that the CTUs will initially be contacted directly by the UK clinical research collaboration (UKCRC), who will send an email to all CTUs.

However, if this is not possible, a list of UKCRC registered CTUs will be obtained from the UKCRC website (https://cdn.ymaws.com/www.ukcrc-ctu.org.uk/resource/resmgr/registration_ids/2019-20_reg_ids_nov19.pdf). Contact details of the Director of the CTU, or Assistant Director, will be obtained from the CTU's website.

Additional individuals at the CTU may be identified from either the CTU's webpage or by the UKCRC.

The initial email will be accompanied by information about the project and a link to the electronic survey.

A reminder email will be sent to the participant if the survey has not been completed, or if they have not responded to the email to say they are no interested in the study. The reminder will be sent around 1 week after the initial email.

Survey

The first page of the survey will describe the aims of this project. The survey will ask respondents to identify potential case studies that meet the above criteria described in the *overview* section. The initial email to respondents will ask if someone else in their CTU would be more suited to completing the questionnaire. If the participant suggests that someone else may be better placed to complete the survey, the survey will be sent via email to that person.

Basic information regarding the case study will be collected, including the name of the study and nature of the adaptation made. Respondents will have the option of ticking a box to state they are happy to be contacted to discuss the adaptations they have identified (either an informal telephone discussion to collect more information about the adaptation to ascertain if it should be selected as a case study, or alternatively, if selected as a case study and participant for WP2, a qualitative interview). The survey will allow respondents to submit four potential case studies – if they have selected more they will be directed to contact one of the study team, who will collect the additional case studies via the telephone or email.

The survey will be delivered using Google Forms. Data will be analysed and will involve descriptive statistics and qualitatively summarising open-ended responses (e.g. the nature of the adaptation) [16].

Work package 2

Sampling

The results of the survey will be used to select five to eight case studies, depending on the diversity of adaptations. This number of case studies has been specified in order for the workload to be manageable within the project timeframe, but also for enough case studies to be sampled in order for diversity to be achieved. Each case study (or trial) will be run by a different CTU. They will be purposively sampled to

ensure diversity of type of change made. Only those perceived to be successful and to have the potential to increase the efficiency of trials in the future will be selected. Maximum diversity will be attended to by selecting different disease areas, adaptations made and setting of the research. Case studies will be selected by the project management group (see *section 5, oversight*), who will selected case studies based on the following criteria:

1. The adaptation has improved, or is likely to improve, the recruitment rate, diversity of trial participants, or the efficiency (time and/or cost) of recruitment;
2. The adaptation has improved, or is likely to improve, the retention of participants, completeness of data within the trial, or the efficiency (time and/or cost) of follow-up or outcome assessment;
3. The adaptation meets one of the criteria described in 1) or 2) above, and the adaptation has been used frequently across multiple trials.

If a number of trials have undertaken similar adaptations, then multiple studies may be grouped under a 'theme', and each 'theme' will be become a case study. If this is the case, fewer individuals from each trial may be interviewed in order to keep the workload to a manageable level.

Potential participants for this work package will be identified from staff that are involved in the case study/trial, and have been involved in designing and/or implementing the adaptation. Potential participants will be identified through one of the following mechanisms:

1) Potential participants will be selected from individuals who have either complete the WP1 survey, or have been suggested as contacts by respondents to the survey;
2) Extra contacts may be gained from asking the CTU respondents to the WP1 questionnaire to suggest individuals who may be well placed to participate in a qualitative interview about the adaptation made, if such individuals haven't already been suggested;
3) The websites of case studies (trials) may be reviewed in order to identify participants for WP2, if suitable participants have not already been suggested by the CTU contact themselves.

Recruitment

Individuals will be emailed a copy of the patient information sheet (PIS) and consent form, with a reminder email 1 week after the initial email if no response, and a

telephone call or email 1 week further on if still no response. If the participant agrees to participate, a convenient time and date for the interview will be scheduled. Consent to participate in the qualitative study will be gained via a consent form, which will be completed by the participant prior to the interview, and sent back, via email or post, to the researcher. The participant will sign the consent form using an electronic, or wet ink, signature. The form will then be countersigned by the researcher, and a copy of the completed consent form emailed or posted back to the participant.

Data collection

Semi-structured interviews will be carried out with 10 to 16 individuals based at the participating CTUs who were involved in setting up and/or implementing the adaptation, typically with two staff involved in each case study (e.g. Chief Investigator, Trial Manager, Data Manager). Staff will be selected depending on the nature of the adaptation made, and who is best placed to discuss it in detail. Prior to the interview, the researcher will reconfirm that the participant consents to participate and will talk the participant through pertinent aspects of the participant information sheet. Interviews will be undertaken by telephone or video call and will be semi structured, with a topic guide which will evolve throughout the study both from the survey and from early case studies. The topic guide will be tested first on members of the project team in order to check face validity and the flow of the interview. Interviews will last around 30 to 45 minutes.
The qualitative interviews are expected to cover:

- Details of the adaptations that were made;
- Specific circumstances influencing the need for the adaptation;
- How the adaptations were implemented in practice, including challenges;
- The effect of the adaptations on the role of the CTU, the conduct of the trial, trial participants and research sites;
- Lessons learned;
- Costs and benefits of making adaptation;
- Reasons why the adaptation is considered to have the potential to make future trials more efficient.

All interviews will be digitally recorded (with consent) on an encrypted dictaphone and transcribed for in-depth analysis. Transcripts will be anonymised prior to analysis.

Analysis

Data will be analysed using inductive thematic analysis within NVivo software. A research assistant will undertake data analysis (familiarisation, coding and identification of themes). RC will oversee analysis, by reading all transcripts and checking that the coding structure and themes identified match the contents of the transcripts, and that any important themes have not been missed. Themes and sub-themes will be discussed by the project management group (see *section 7, oversight* section). Data saturation will not be considered; rather we will look to achieve "information power", as conceived by Malterud et al, where the size of the study is determined by the amount of information the sample holds [17]. Emphasis will be on collecting detailed data from experienced participants.

Work package 3

Results from WP1 and 2 will be presented to a selection of CTU staff and investigators involved in trials that have made adaptations identified via the initial survey. Individuals will be invited by email. Invitation emails will also be sent to patient and public involvement (PPI) members of the trials included in WP2 (see *section 5*, *public and patient involvement*), with agreement sought from the PPI representative by the trial team in which the individual is involved to pass on their contact details to this study.

Around 15 to 20 individuals will be invited to a workshop held either via video conference, or in person at a central location. Individuals will be selected in order to ensure variability in disease area of the trial, nature of adaptation made, geographical location, involvement in WP1 or WP2 of this study, and speciality (i.e. clinician, health economist, statistician, trial manager).

Invitees will be sent an email inviting them to the workshop, with a reminder email sent 1 one afterwards in the event of no response.

The workshop will aim to inform the development of the guideline document, which will identify adaptations that can be made to improve efficiency. Attendees will be asked to inform the development of the guidelines by assessing, a) which adaptions from WP1 and 2 have the potential to increase efficiency, b) the generalisability of these adaptations, b) the challenges and feasibility of implementing them, c) ethical

implications, d) costs and benefits. Attendees will also be asked to identify any other 'major' adaptations that have the potential to improve the efficiency of trials and were not included in WP2, and to advise on the format of the guidance document.

The workshop will commence with a presentation of the results of WP1 and WP2. Attendees will also be provided with a written version of the results, which will contain draft recommendations which will be refined over the course of the workshop. Discussion of the results and their generalisability will be guided by the workshop facilitators. Attendees will be split into small groups in order to discuss individual adaptations, before feeding back to the entire group. Further discussion of the implications of the adaptations, significant adaptations that have not been covered, and a discussion of how the guidance document should look, will then be facilitated.

The workshop will be audio recorded in order to enable the workshop discussions to feed into the guidance. Formal consent will not be taken, but participants will be told prior to attending the event that the meeting will be audio recorded. No transcript will be made because the workshop will not generate research data. It's aim is to aid interpretation of the findings

Once written, the guidance document will be reviewed by the project management group.

5. Patient and Public Involvement

Individuals who are already acting in a PPI capacity for trials that have been included as a case study in WP2 will be invited to attend the workshop (WP3). Such individuals will be provided with training specific to this study prior to the workshop (consisting of an introductory meeting, prior to the workshop, to provide an overview of this study, the aims of the study, and an overview of the workshop). Those who attend the workshop will be provided with a £150 voucher to reimburse their time, and will be provided with travel expenses (if the workshop is undertaken in person). Vouchers will also be provided for attendance at the introductory meeting (£50).

6. Participant withdrawals

Participants will be able to withdraw their data from the survey (WP1) at any point up to the end of the study, as long as they are not selected as a case study in WP2.

Individuals taking part in WP2 will be able to withdraw at any point prior to the end of the qualitative interview. After this point, the data will be incorporated into the analysis and will not be withdrawn.

7. Oversight

The principal investigator, co-applicants and key staff involved in the project at Sheffield CTU (e.g. research assistant, trial support officer) will meet regularly over the course of the project to input into the running of the study.

8. Publication

The guidance produced from the WP3 will be published within a journal and will also be made available on the Sheffield CTU website.

The results of WP1 and WP2 may also be published separately within a journal. Confidentiality will be ensured by anonymising participant's identities within the report. Due to the likelihood of individuals being identifiable from the name of the trial they work on and disease area, this information will not be used in reports and the direct quotations included within them.

9. Data storage and sharing

Data storage

Data collected from WP1 will be stored on the Google Forms platform and also downloaded onto the University filestore (X drive).

Transcripts produced from WP2 will be pseudo-anonymised, with both unedited and pseudo-anomyised versions stored on the University filestore (X drive).

All files will be stored within folders with restricted access rights. Only those who have the need to access the data (i.e. PI, research assistant and trial support officer based in Sheffield CTU) will have access to these folders.

Data retention

Unedited survey responses and interview transcripts will be retained for 3 years after the end of the project.

Anonymised survey responses and pseudo-anonymised interview transcripts will be retained for 5 years after the end of the project.

Data sharing

Whole transcripts from WP2 will not be shared with other researchers, due to the risk of identification from the qualitative transcripts.

Data collected from the surveys in WP1 will be shared with the UKCRC (including contact details or the respondents). The UKCRC are also interested in undertaking research in this topic area – consent for this sharing of data will be sought within the survey itself. The UKCRC will also be requested to delete the personal information of respondents within the same time frame as discussed above in *data retention* (i.e. after 3 years).

10. Finance

Research funding has been obtained from National Institute of Health Research CTU support funding stream.

11. Ethics approval

Ethical approval will be sought from the School of Health and Related Research (ScHARR) ethics committee.

Ethical approval will not be sought from an NHS research ethics committee, which means that individuals with only NHS contracts (who are not contracted to a University) will not be able to participate in this study.

12. Timetable

Month	1	2	3	4	5	6	7	8	9	10	11	12
	Oct-20	Nov-20	Dec-20	Jan-21	Feb-21	Mar-21	Apr-21	May-21	Jun-21	Jul-21	Aug-21	Sep-21
Develop survey (WP1) & qualitative documents (WP2)	■	■										
COLLABORATOR MEETING: agree survey contents & qualitative design		■										
Develop university ethics submission & HRA submission		■										
Submit ethical approval - WP1 and WP2		■										
Gain ethical approval			■									
Distribute survey			■									
Send survey reminders & follow up responses via phone				■								
Analyse surveys				■	■							
COLLABORATOR MEETING: confirm case studies & finalise qualitative study documentation						■						
Seek amendment for qualitative documents, if required						■	■					
Undertake qualitative interviews (WP3)							■	■				
Analyse qualitative interviews (WP3)									■			
COLLABORATOR MEETING: discuss qualitative results & design workshop										■		
Workshop (WP3)											■	
Write-up guidance and report (WP3)											■	
COLLABORATOR MEETING: review guidelines											■	■
Disseminate												■

13. References

1. Thornton J. Clinical trials suspended in UK to prioritise covid-19 studies and free up staff. BMJ. 2020;
2. Akers L, Gordon JS. Using facebook for large-scale online randomized clinical trial recruitment: Effective advertising strategies. J Med Internet Res. Journal of Medical Internet Research; 2018;20:e290.
3. Rothwell E, Wong B, Rose NC, Anderson R, Fedor B, Stark LA, et al. A randomized controlled trial of an electronic informed consent process. J Empir Res Hum Res Ethics. SAGE Publications Inc.; 2014;9:1–7.
4. Meehan A, Bundorf MK, Klimke R, Stults CD, Chan AS, Pun T, et al. Online Consent Enables a Randomized, Controlled Trial Testing a Patient-Centered Online Decision-Aid for Medicare Beneficiaries to Meet Recruitment Goal in Short Time Frame. J Patient Exp [Internet]. SAGE Publications; 2020 [cited 2020 May 4];7:12–5. Available from: http://journals.sagepub.com/doi/10.1177/2374373519827029
5. Mountain GA, Hind D, Gossage-Worrall R, Walters SJ, Duncan R, Newbould L, et al. “Putting Life in Years” (PLINY) telephone friendship groups research study: Pilot randomised controlled trial. Trials. 2014;
6. Rollman BL, Belnap BH, Mazumdar S, Abebe KZ, Karp JF, Lenze EJ, et al. Telephone-Delivered Stepped Collaborative Care for Treating Anxiety in Primary Care: A Randomized Controlled Trial. J Gen Intern Med. Springer New York LLC; 2017;32:245–55.
7. Nicol GE, Karp JF, Reiersen AM, Zorumski CF, Lenze EJ. “What Were You Before the War?” Repurposing Psychiatry During the COVID-19 Pandemic. J Clin Psychiatry. 2020;
8. Rai AT, Frei D. A rationale and framework for seeking remote electronic or phone consent approval in endovascular stroke trials - special relevance in the COVID-19 environment and beyond. J Neurointerv Surg [Internet]. British Medical Journal Publishing Group; 2020 [cited 2020 May 13]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32381522
9. McDermott MM, Newman AB. Preserving Clinical Trial Integrity during the Coronavirus Pandemic. JAMA - J. Am. Med. Assoc. American Medical Association; 2020.
10. Tarantino P, Trapani D, Curigliano G. Conducting phase 1 cancer clinical trials during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–related disease pandemic. Eur. J. Cancer. 2020.

11. Managing clinical trials during Coronavirus (COVID-19) [Internet]. [cited 2020 May 11]. Available from: ttps://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19
12. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency [Internet]. 2020. Available from: https://www.fda.gov/media/136238/download
13. Tan AC, Ashley DM, Khasraw M. Adapting to a pandemic - conducting oncology trials during the SARS-CoV-2 pandemic. Clin Cancer Res. 2020;
14. Hennessy M, Hunter A, Healy P, Galvin S, Houghton C. Improving trial recruitment processes: How qualitative methodologies can be used to address the top 10 research priorities identified within the PRioRiTy study. Trials. BioMed Central Ltd.; 2018;19:1–5.
15. Lentz J, Kennett M, Perlmutter J, Forrest A. Paving the way to a more effective informed consent process: Recommendations from the Clinical Trials Transformation Initiative. Contemp Clin Trials. 2016;
16. O'Cathain A, Thomas KJ. "Any other comments?" Open questions on questionnaires - A bane or a bonus to research? BMC Med. Res. Methodol. 2004.
17. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qual Health Res. 2016;