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

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1. 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 take precedence [1]. Social distancing resulted in some clinical services pausing their delivery, and patients (especially older adults) self-isolating for long periods. To restart, trialists had to make pragmatic decisions to revise trials to permit them to continue whilst adhering to social distancing guidelines, 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.

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 [2–4] 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 patient's 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. There may be innovations occurring within CTUs that are unreported.

The aim of this project was to assess the adaptations that CTUs make to incorporate social distancing procedures, and identify those adaptations that may improve the efficiency of clinical trials after the pandemic. We specifically focussed on three main areas of interest – recruitment, delivery of the intervention and outcome assessment (including safety monitoring). We will focus on intervention "logistics" (i.e., delivery of IMP or methods of delivering a behavioural intervention), rather then changes to the active content of the intervention itself.

This report provides a detailed description of the study, including a comprehensive description of the methods (with the qualitative aspects adhering to the COnsolidated criteria for REporting Qualitative research (COREQ) checklist [14]), and detailed results, including quotations.

An abridged 'summary report' of this study can be downloaded from here.

2. Methods

This study comprised of three consecutive work packages (WPs). Below, we describe these work packages.

The reporting of the qualitative element of this study

2.1. Work package 1 (WP1: survey)

2.1.1.Aims

To identify studies, with involvement from UK CTUs, that have made adaptations in order to continue the trial during the pandemic.

2.1.2.Data collection

All CTUs in the UK were sent a survey (see *appendix 1*) on 14/12/2020 by the UK Clinical Research Collaboration (UKCRC), with a reminder sent on 19/01/2021. The survey was sent to the Director of each CTU, who was asked to complete the survey or identify a colleague within their CTU to complete it. Respondents could supply up to four case studies using the online survey. The individual completing the survey selected potential case studies from their CTU based on the following criteria:

- A randomised trial with major involvement from the CTU;
- An adaptation has been made to either the recruitment, intervention delivery, or follow-up procedures in order for the trial to adapt to the impact of COVID-19;
- In the opinion of the individual completing the survey, the adaptation is transferable to other trials and has the potential to improve the efficiency of trials post-pandemic.

2.2. Work package 2 (WP2: selection of case studies and in-depth qualitative interview with case study representatives)

2.2.1.Aims

To select case studies and collect in-depth information about the selected case studies by undertaking qualitative interviews with study representatives, in order to understand how the adaptation was undertaken, the challenges and benefits of doing so, and the impact on trial efficiency.

2.2.2.Selection of case studies

Following the second reminder in WP1, and after a few days of no further responses being received, case studies were selected. Case studies were selected purposefully, using the following criteria:

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

Priority was given to those studies that had made adaptations to all three of the main areas of interest (recruitment/consent, follow-up, and intervention delivery).

In selecting case studies, variation was ensured in the following characteristics:

- CTU from which case study originated;
- Trial type (drug/behavioural/physical/surgical);
- Disease area;
- Population age eligibility criteria;
- Target sample size;
- Treatment/preventative;
- Adaptation made.

The case studies were initially selected by RC, with the final selection being approved by the project steering group, which comprised of the main study team, plus the study collaborators.

2.2.3. In-depth interviews with case study representatives

Recruitment

Interviewees were identified from the survey responses. Where one or more individual was named as a potential contact on the survey, the individual thought to be most involved in the adaptation was approached – often this was the trial manager. Individuals were emailed a copy of the patient information sheet (PIS) and consent form, with a reminder email one week after the initial email if no response, and a telephone call or email one week further if still no response. If the participant agreed to participate, a convenient time and date for the interview was scheduled.

Consent to participate in the qualitative study was gained via a consent form, which was completed by the participant prior to the interview, and sent back, via email or post, to the researcher. The participant signed the consent form using an electronic (typed, or image of their signature inserted into the form) signature. The form was then countersigned by the researcher, and a copy of the completed consent form emailed or posted back to the participant.

Data collection

Semi-structured interviews were carried out with individuals based at the participating CTUs who were involved in implementing the adaptation – this was usually the trial manager or research fellow who coordinated the study. A semi-structured topic guidance was used to guide the interviews, which was tested within the first interview (this interview was included in the final analysis). Interviews were carried out by RC (a male Research Associate with a BSc and previous experience of qualitative interviewing) and KS (a female Research Assistant with an MSc and previous experience of qualitative interviewing). Repeat interviews were not carried out, and transcripts were not returned to the participant for comment or correction. There were no other individuals present at the interviews. Interviews lasted from 27 to 146 minutes.

The qualitative interviews covered:

- Details of the adaptation(s) 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;
- Whether the adaptation is considered to have the potential to make future trials more efficient.

All interviews were undertaken via Google Meet, with the audio from the interview recorded (with consent) using in-built functionality within the Google Meet platform and transcribed for in-depth analysis. As COVID-19 social distancing rules at the time meant that CTU staff were encouraged not to travel to the office, both the interviewers and the interviewees were at home when the interview was undertaken. Transcripts were anonymised prior to analysis.

Relationships with participants

A relationship between two of the participants and KS (one participant) and RC (one participant) was already developed, due to the interviewees being based at the same CTU as the interviewers. There was no relationship already formed between any of the other participants and the interviewers. However, all interviewers were likely to have some knowledge of the interviewers and their goals.

Analysis

Data was analysed using inductive thematic analysis within NVivo software using a phenomenological orientation. Analysis was undertaken by RC (familiarisation, coding and identification of themes). The coding tree was split into two main themes – those related to individual adaptations, and those that cut across multiple adaptations. Within the former, there were codes for each general adaptation (e.g., remote consent), with sub-themes regarding discrete methods of undertaking these (e.g., telephone, or online), and then a third level of codes regarding the process of undertaking that implementation, the benefits, challenges, considerations for the future, and potential impact on efficiency. Data saturation was not considered; rather we looked to achieve 'information power', as conceived by Malterud et al, where the size of the study was determined by the amount of information the sample holds [15]. Emphasis was placed on collecting detailed data from experienced participants. Participants did not provide feedback on the findings; however, non-participants did feedback on the themes within the workshop (WP3).

2.3. Work package 3 (WP3: workshop with CTU and patient representatives)

2.3.1.Aims

To seek the views of CTU representatives and patient representatives into the findings from work package 2, including their views on the potential effect of the adaptations on efficiency.

2.3.2.Selection of workshop attendees

Potential workshop attendees were identified via the following approaches:

- Respondents to WP1, that were not approached to, or could not participate in, WP2;
- CTU staff who may be interested in trial adaptations (e.g., trial managers, directors) were identified via CTU websites and by study co-applicants;
- Public and patient involvement (PPI) representatives were approached who were already acting as PPI representatives for trials included in WP2. In addition, PPI representatives contributing to trials run from Sheffield CTU were approached.

The workshop consisted of RC providing an overview of the findings from the study for those adaptations that were found to either directly or indirectly improve clinical trials. Those adaptations that were deemed to only be pandemic specific, or where the impact was unknown, were not discussed within the workshop.

After the findings were presented, the workshop attendees were split into small breakout groups, where the findings of the study were discussed, including their general reflections on the findings, challenges and benefits, and contexts in which the adaptation may or may not work in the future. A group discussion was then held to feedback on the discussions had within the breakout rooms.

3. Results

3.1. Introduction

This report is split into three main sections:

- a description of the studies included in WP1 and WP2, and the adaptations that were made (*section 3.2*);
- a description of cross-cutting themes identified across the adaptations identified in WP2 (*section 3.3*);
- an in-depth description of each adaptation including a brief literature review, the challenges, benefits and future use of each adaptation (from WP2), and a reflection on the future use of the adaptations gained from the workshop (WP3). Each section regarding future use has a section regarding the interviewee's views on future use, and then a box which contains the author's view on the future use of the adaptation.

An overview of the adaptations, and the potential for them to improve future efficiency, can be found in a separate summary document.

3.2. Overview

3.2.1. Work package 1 – survey of CTUs

Response rate

Twenty-one CTUs responded to the survey, providing information about 40 studies that made a total of 86 adaptations during the pandemic.

Conditions and interventions

The studies were varied with regards to the population being studied, including individuals with conditions such as brain tumours, urinary incontinence, Parkinson's and autism. One study aimed to treat COVID-19, such that this study was already set-up to function within a pandemic (*Study D*) – this study was excluded from the analysis, due to the adaptations to the trial being planned from the start.

The interventions varied, with 20 studies testing drugs (one of which testing both a drug and a device), eight testing surgical interventions, eight testing psychological or physical interventions, one testing a complex intervention investigating the use of medical appointments to help patients make sense of their condition, and one testing technology to monitor blood glucose. One study was a prospective cohort and did not involve an intervention.

Size of design of studies

The target sample size of the studies varied from 21 to 7646 (mean 1031). Four studies were pilot or feasibility studies (mean target sample size 78, range 21 to 100), whilst 32 studies were fully powered trials (mean target sample size 1012, range 72 to 6000). In addition, *Study D* was an adaptive platform trial with a sample size of 3000. There were two non-randomised studies, which involved observation only (*Study L*), and qualitative only data collection.

Overview of adaptations

Basic information was collected in WP1 regarding the adaptations made. The adaptations made to the trials included adaptations to:

- the recruitment or consent process (29 adaptations across 23 studies),

- follow-up processes (20 adaptations across 14 studies),
- the delivery of the investigational medicinal product (IMP) to the participant (6 adaptations across 6 studies).
- the delivery of the intervention (non-IMP studies) to the participant (9 adaptations across 9 studies)

3.2.2. Work package 2 (WP2) – qualitative interviews with case study representatives

Twenty-five individuals were invited to participate in WP2. Eleven did not participate: a response was not obtained from four, one was not interested in participating due to a lack of time, five interviews were not undertaken due to the study having not yet commenced or implementing the adaptation, and one individual responded too late to be included in the study. Representatives from 14 studies, that had made adaptations to their trials in order to continue during the pandemic, were interviewed between 5th March 2021 and 25th May 2021. All interviews were undertaken with one interviewee, except for one study (*Study E*), which was undertaken with two study representatives within the same interview. All 14 interviewees were involved in the management of the trial, either being a trial manager (n=11), senior trial manager or research fellow (n=3), or research assistant (n=1).

The adaptations made fell broadly into four categories, where adaptations made to: screening or recruitment processes (pre-consent); consent processes; follow-up processes; or intervention delivery (including IMP distribution) processes.

There was variation in the extent to which the adaptations were used. At the point of being interviewed, some adaptations had only recently been implemented and had therefore not been used extensively. Other adaptations had been implemented some time before the interview but had not been extensively used due to low levels of recruitment to the trial. Other adaptations had been used extensively.

3.2.3. Attendance at the workshop

Eighteen individuals attended the workshop, consisting of:

- The study lead (Robin Chatters, RC);
- Three study co-applicants (Cindy Cooper – Sheffield CTRU, Caroline Murphy – King's College London, Alicia O'Cathain – School of Health and Related Research, The University of Sheffield);
- Eleven CTU representatives – trial managers (n=3), heads of research/directors (n=2), senior trial managers/research fellows (n=3), medical statisticians (n=2), data manager (n=1);
- Patient representatives (n=3).

3.3. General themes across all adaptations (from WP2)

Prior to describing the adaptations (see *Section 3.4*), two main themes are described that spanned the numerous adaptations. These relate to the development of the adaptations, and the important features and components of the adaptations.

3.3.1. Development of the adaptations

There were three themes related to the development of the adaptation – the different starting points at which the adaptations were made, input sought from stakeholders, and the level of risk inherent to the trial.

Different starting points

An important contextual factor was how much of the trial was undertaken remotely at the point of the pandemic starting, as this affected the amount of work the trial team had to undertake in order to adapt to the new social distancing requirements of the pandemic.

Three trials (*Study B, Study K, Study J*) were already mostly undertaken online; the pandemic provided the motivation to create a wholly online, remotely conducted, clinical trial. The trial team adapted already implemented remote trial procedures to this new situation, or only had to adapt specific elements of the trial (e.g., consent only).

> *Everything else in our trial is remote so basically the only thing that wasn't remote was consent. Now we are a fully remote trial.* Study J

Other studies were more traditional in their nature, relying on in-person contacts for recruitment, and requiring participants to attend the hospital for intervention delivery and follow-up. This meant that staff had to quickly adapt multiple trial processes from scratch, which took significant CTU staff resources to complete.

Input from stakeholders or individuals outside the trial team

The prompt to make adaptations came from different sources, sometimes the trial teams, sometimes the trial site(s) or trial sponsor, and less often individuals outside the trial team.

Different stakeholders had contributed to its development in different ways. Not all trial sites wanted to be involved in, or were asked to be involved in, developing an adaptation – this was due to time pressures at both the CTU and the trial sites themselves. However, when site input was sought, either by sending an email to all sites, or specific sites, the input from sites was invariably seen by the interviewees as useful. Not all sites or sponsors agreed with ideas for adaptations and indeed could strongly prefer alternative adaptations.

A key stakeholder in the development of adaptations were PPI representatives. They helped shape adaptations, identified innovative adaptations, or test adaptions. This was especially true in Study G, where PPI representatives helped shape the mechanism by which data related to a respiratory function outcome was remotely collected.

> *[we sought PPI input] mainly in the development of the app, because we had a big debate on whether we were going to use text to motivate them and show them through how they were completing their assessments, or, using a medal to sort of show, a gold was good blow which is like a grade A, and a bronze was a C. We put up these mock-ups of the protocol, of the app together and showed that to a couple of patients. It was unanimous that everybody didn't like the medals.* Study G

However, PPI representatives were not always involved in the development of the adaptation due to time pressures felt by trial teams to produce an adaptation quickly.

Regulatory bodies were another important stakeholder (e.g., Medicines and Healthcare products Regulatory Agency, MHRA). Regulatory bodies seemed open to the adaptations, with the interviewees reporting minimal problems seeking the necessary approvals. A couple of the interviewees expressed surprised at the ease at which their adaptations were approved, seemingly because the trial teams were utilising 'new' adaptations that they had not attempted before. This was true for *Study J*, where

a consent procedure that did not involve the participant signing a consent form, and instead the form being signed by a witness based at the NHS site, was assumed to potentially cause ethical issues, but this was not questioned by the ethics committee.

> *I think that I would just keep an open mind about remote processes of consent and really look into them and don't rule them out. I was a little bit sceptical that we would get buy in from the sponsor. And I really thought it may get pushed back from the REC… it didn't happen.* Study J

Those making the adaptations sometimes sought input from outside the trial stakeholders, which involved asking other trial managers at their CTU about their experiences of a certain procedure, or gaining information from internet sources, including journal articles and webinars from the UK Trial Manager Network (UKTMN).

Risk level of the trial

CTUs routinely classify the risk level of a trial, usually either 'low' or 'high'. This level of risk determines how the trial procedures are conducted. The interviewees stated that the level of risk involved in the trial affected the development and implementation of the adaptation. This commonly affected adaptations to the consent process, where the low-risk nature of the trial afforded more flexibility in the adaptation in terms of who undertook the consent process, how the participant's identity was confirmed, and how the participant's signatures were gained. Higher risk studies were thought to require input from clinically qualified individuals, which an interviewee thought CTUs may struggle to provide.

> *It was quite a simple concept in some way that both the trial staff felt comfortable talking about it to the participants but also the participants felt comfortable talking about it to the trial staff. If it was a lot higher risk I think they would have, on both sides, wanted it to be somebody clinically qualified that they had that discussion with.* Study B

The level of risk also affected the couriering of drugs, which was often simpler for low-risk drugs than the couriering of higher risk controlled drugs. Logistical challenges were common - controlled drugs had to be returned to the pharmacy, and some drugs required temperature controls when in transit. Even for those drugs that were not controlled, monitoring was required to ensure the participant had received the drug.

3.3.2.Important components or features of the adaptations

There were five important features of the adaptations common across many of the adaptations: the mechanisms by which the adaptations functioned, flexibility, access to technology, relationships with participants, and the effect of the pandemic.

General adaptation mechanisms

The adaptations functioned by four mechanisms – centralisation, decentralisation, removal or addition of trial procedures. These categories are not mutually exclusive, with some adaptations involving multiple mechanisms.

A common adaptation was the centralisation of trial processes, the aim of which was to circumvent the need for NHS staff to undertake the trial procedures at a time when NHS staff time was limited. Tasks were centralised so that the CTU would undertake trial procedures in most cases, although in a

few cases these tasks were undertaken by charities. One study (*Study M*) involved the decentralisation of study processes, where interventionists from any NHS Trust, not just trial sites, could deliver the trial intervention, enabling participants to be recruited from any NHS Trust.

Trial processes were also added to or removed. There were two ways of adding to a process – either by adding a new process alongside an already existing one (e.g., allowing participant to provide outcome data via the telephone, as well as at routine clinical appointments), or by adding a new step to an already existing process (e.g., an extra screening step).

Only one adaptation involved the removal of trial procedures in order to streamline the trial and to avoid unnecessary workload (*Study F*), where the need for the participant to provide written consent to provide screening measures was removed.

Another mechanism by which the adaptations functioned was through delivery of trial procedures remotely, rather than in-person. Such remote trial procedures were undertaken centrally, either at each trial site, CTU, or remotely at the participant's homes. This could either involve CTU staff or trial site staff undertaking the intervention or couriering the study drug, recruiting participants to the trial, or undertaking outcome assessments remotely. Some adaptations involved the participant undertaking remote follow-up procedures usually undertaken by a member of site staff (e.g., blood pressure and spirometry measurement).

Flexibility

Flexibility was required from trial participants and CTUs in order to ensure the trials could continue during the pandemic.

Adaptations were often undertaken alongside the 'old' technique of undertaking the trial procedure, such that there was often a choice to make regarding how to collect the outcome. The way in which this decision was made differed between adaptations. In some adaptations participants *had* to be flexible, as criteria were set by the trial team to determine the participant's pathway (i.e., whether a particular procedure is undertaken remotely, or in-person). For example, in *Study C*, participants were telephoned one week prior to their appointment to ascertain if they should be seen in person or if a telephone follow-up should be conducted.

In other adaptations, flexibility was framed as 'patient choice'. These adaptations aimed to increase the ability for the trial participant to undertake trial procedures flexibly, with the participant deciding how the trial procedure would be conducted. In some cases, interviewees valued this flexibility to such an extent that they wanted to use the adaptation in future trials, even when the adaptation was not seen as increasing efficiency for the CTU or trial sites.

Interviewees described indirect benefits to increasing flexibility. Trial sites were thought to benefit, with flexibility potentially making the trial look more feasible to potential research sites. The second was that increasing flexibility was thought to make it easier for participants to take part in the trial, thus improving recruitment rates.

> *This is a huge selling point for us particularly because R&D's are quite reluctant to take on new studies at the moment, quite rightly they're under a lot of pressure. And it's a huge selling point for us to say we have this full flexibility and it's fully remote if you want it to be. And it certainly is a benefit to the trial to have that.* Study J

For CTUs, flexibility was mainly required in terms of the researcher's role, or time. Many adaptations required the CTU staff to take on activities usually reserved for the trial site. This necessitated a change in the CTU staff's role, and in some cases, in depth training on the new way of working. Many adaptations also required the staff to work flexibly to fit in with the trial participant's needs – this commonly occurred when staff were remotely collecting outcome measures and participants were unavailable during usual work hours.

Access to technology

Access to technology was not only an issue for trial participants, but also for CTUs.

Many adaptations were based on the participant utilising digital technologies, whether that be a computer, tablet or mobile phone. Interviewees were aware of the potential difficulties of participants utilising such technology; in two studies interviewees described how participants had dropped out of the trial due to issues around using technologies.

> *I think there might be a few that drop out, because the technology fear side of things. Study G*

Trial teams reacted to this challenge in different ways. Some trial teams chose not to undertake remote procedures that required the use of digital technologies. Other trial teams were aware of the potential for technology to reduce the likelihood that participants would take part but accepted this risk. Alternatively, some trial teams altered the adaptation to try to make improvements for those with poor access to technology, e.g., by providing a choice of consent procedures using digital or paper format. Training was provided to participants to try to support them, either prior to them using the technology (i.e., training to prevent issues occurring), or in an ongoing manner in case of any issues (i.e., reactive support).

The CTU's access to technology also impacted the adaptations that could be implemented. In a few cases, the exact method of implementing the adaptation was guided by the technology the CTU already had access to at the start of the pandemic. If they did not have the relevant software, then they did not make adaptations.

> *At the time, we did not have software which was capable of delivering e-consent, and we now have redcap, we didn't have at that time.* Study A

Relationships with trial participants

Maintaining a good relationship with trial participants was an important aspect of the adaptations. This shaped the adaptations that were made, with trial teams keeping this need at the forefront of their mind when designing the adaptations.

Maintaining a good relationship was especially important in the trials that involved participants with chronic conditions – e.g., trials involving participants living with motor neuron disease (MND), or parents of children with autism. In some cases, the decision of whether to implement a centralised remote adaptation was down to the perceived importance of the relationship between the participant and the trial team. In some cases, keeping close relationships with participants could outweigh the importance of efficiency.

> *I'd say, for this participant group, with an intervention that's quite hands-on, and time-consuming, that local relationship, to me, seems more important than streamlining, or doing everything centrally where you've got total control over it.* Study M

Interviewees highlighted that shifting procedures from the trial site to CTUs may have a negative effect on the relationship between trial site staff and the participant. Even when research procedures were undertaken remotely by individuals outside the participant's clinical care team, relationships with participants could be formed. However, this was more challenging when participants could not be visited in-person. Forming these relationships sometimes took longer when undertaken remotely.

Negative and positive contextual issues related to the pandemic

The adaptations made should be understood within the context of the pandemic, in that, there were certain restrictions to the adaptations which could be made. There were three main restrictions cited by the interviewees – the pandemic prevented participants from leaving their house unless necessary, thus limiting the use of the postal service; CTU staff worked from home, limiting the identifiable information that could be sent to staff's homes; and to enable the study to continue, CTUs often had to develop the adaptations quickly, which limited the amount of input sought into developing the new processes.

> *I think off the top of my head the amendment was implemented on the 2nd April and the lockdown was the 23rd March. I think, off the top of my head so within a week we had a basis of all these processes put in place for them to be able to continue.* Study E

Some aspects of the pandemic were seen more positively. Early in the pandemic, UK research regulators (e.g., MHRA, Health Research Authority (HRA), Research Ethics Committees (RECs)) streamlined their approval processes so that HRA or REC approvals were not required for certain amendments, and instead, the Sponsor could approve these. Guidance was published by multiple regulatory bodies, on such topics as gaining informed consent remotely, and protocol deviations, which reassured trial teams. The MHRA and HRA provided guidance regarding trial practices during the pandemic, one of which was around protocol deviations.

> *We obviously monitor the MHRA HRA guidelines during this time, and, you know, reassured us that obviously, there'll be more protocol deviations and which is just ensuring it's documented accordingly and adapting if needed*. Study I

3.4. Overview, challenges, and benefits of each adaptation

The adaptations are described briefly in *Table 1*. In this section, each of the adaptations are described in detail, along with a brief overview of the literature, and the challenges and benefits associated with them articulated. Then the potential for using the adaptation in the future is summarised from the perspectives of the interviewees and the perspectives of workshop participants. Finally, the report authors make a final assessment to the potential to use the adaptation in the future. It should be noted that only those adaptations that were deemed to be potentially relevant for future trials from WP2 were discussed within the workshop (WP3).

The seven adaptations for which detailed information was collected during WP2 were:

- Two-stage remote-first eligibility assessment– see *section 3.4.1*
- Recruitment outside the NHS via a charity– see *section 3.4.2*
- Remote consent – see *section 3.4.3*
- Remote delivery of the intervention by CTU staff – see *section 3.4.4*
- Delivery of trial intervention by any interventionist at any NHS Trust – see *section 3.4.5*

- Couriering the IMP to the participant's home – see *section 3.4.6*
- Remote follow-up, including remote collection of biological measures, remote collection of patient reported outcome measures (PROMs), prioritisation of trial outcomes or in-person visits, and collection of outcomes from a routine source – see *section 3.4.7*

3.4.1. Two-stage remote-first eligibility assessment

(i) Description of the adaptation

Two studies made adaptations to how the screening process was undertaken. In both adaptations, screening of participants to ascertain their eligibility to participate in the trial was undertaken via telephone at an earlier time-point to that at which it was previously undertaken. Measures that could not be collected remotely were collected in-person at a later time-point.

In one of these trials (*Study B*), a second adaptation was also implemented (recruitment from outside the NHS via a charity (see *section 3.4.2*)). This second adaptation resulted in participants being invited to participate in the trial who were potentially ineligible, so this extra screening step was implemented.

(ii) Evidence base from a literature search

Evidence could not be located regarding the use of a split remote-first eligibility assessments.

(iii) Challenges and benefits

Challenges

The addition of an extra remotely conducted screening step caused a couple of challenges. Firstly, one interviewee reflected it was challenging to explain the recruitment process to the participant because recruitment involved multiple steps. Secondly, the use of multiple steps meant that the screening and recruitment processes sometimes took longer to complete.

Interviewees were concerned that participants may have struggled to discuss sensitive topics over the telephone. It was therefore important to ensure participants were aware of the questions that would be asked during the screening telephone call, so that they could prepare accordingly.

> *When we carry out the pre-screening telephone call we are having to talk about menopause and periods and so, we were trying to make sure that the participant was aware. So, for example when someone said that you know I can take that call when I'm at work I would then, because we're always in contact via email, we'd say you know, are you somewhere that you could talk privately.* Study C

One interviewee stated that the scientific integrity of the trial might be affected by moving the collection of baseline screening measures to an earlier time-point and further away from randomisation.

Benefits

Time and resources were saved by screening out patients early, so they did not have to attend for an in-person visit. This saved site staff time and prevented them from having to book limited clinic space. Centralisation of screening at the CTU allowing expedited completion of these activities and enabled conversations regarding informed consent to be started at an earlier time-point, thus providing potential participants more time to consider participating in the trial. This final benefit was especially

relevant to *Study A*, where, prior to this adaptation being made, the recruitment process was described as rushed due to limited opportunities for in-person visits.

> *We've had a particular site where they had an issue with the fact that we were potentially putting patients in an emergency type recruitment situation at the pre surgical visit when in fact they weren't an emergency patient… you've only got one clinic visit so therefore you must consent now. I think that left pressure and even that was happening potentially even before COVID.* Study A

One of the studies undertook the screening call centrally (*Study B*), whereas in the other two, the research sites undertook this (*Study A* and *Study C*). Both approaches were thought to have their benefits, with participants having thought to have benefitted from talking to an investigator where this was undertaken by trial sites, and if the CTU undertook this, it permitted clinical staff more time to discuss things in a later appointment.

> *I think that helped having the central staff being able to do that first so that when the physio saw them, everybody got more out of that physio appointment*. Study B

(iv) Potential for use of the adaptation in the future

Based on the interviewees views, a separate screening telephone call undertaken prior to informed consent was a potentially efficient trial adaptation for specific trial types, by decreasing the number of participants having to attend the site for a full eligibility assessment. However, moving screening assessments to an earlier time-point may affect the scientific validity of the study.

During the workshop, CTU representatives felt that this adaptation may only save time or resources in specific trial types, and generally may be unlikely to be cost saving for many trials. It was suggested that in most scenarios, it is possible that this adaptation may lead to an increased workload for NHS sites or CTUs, due to an extra appointment being required. However, this adaptation may only be of benefit to specific trial types, including those studies where a high proportion of participants may be ineligible (e.g., trials recruiting participants via social media), and those trials where the individuals undertaking recruitment have limited time to undertake recruitment activities (e.g., trials in primary care). CTU representatives also suggested that it may be difficult for CTUs to undertake this adaptation if they do not have the necessary approvals to receive and hold identifiable patient data. This adaptation may be unsuitable for CTIMPs (where a clinically qualified individual is required to confirm eligibility). If a CTU were to undertake screening activities, the measures collected to assess eligibility would need to be non-clinical.

During the workshop, PPI representatives suggested that it was important to that some form of face-to-face contact is retained. They felt that facial expressions and body language are important during these processes, which remote screening (especially telephone) may preclude.

CONCLUSIONS: two-stage remote-first eligibility assessment

- May benefit trial sites and participants and decrease costs in specific trial types/settings, through reducing the need for all participants to attend an in-person eligibility visit.
- Only likely to increase efficiency if a high number of potential participants are ineligible and can be screened out prior to an in-person visit (e.g., studies recruiting from social media platforms).
- CTUs may be unable to undertake this adaptation due to potential data governance issues, or the screening measures being undertaken requiring clinical knowledge to collect or interpret.
- May only be applicable to smaller trials.
- Moving baseline or screening assessments to an earlier time point prior to randomisation may affect the scientific integrity of the trial.

3.4.2. Recruitment outside the NHS via a charity

(i) Description of the adaptation

Two studies (*Study B* and *Study K*) recruited participants from outside the NHS via a charity, which either sent information about the trial to participants on their mailing list, or published the trial on their website, allowing participants to self-select. Participants in both trials were directed to complete an online screening form to ascertain their eligibility.

(ii) Evidence base from a literature search

There is a lack of information in the literature regarding **recruitment outside the NHS** via charities. Recruitment via social media platforms is extensively discussed, with commonly reported disadvantages being the risk of misinformation [16] and sampling biases (overrepresentation of younger individuals) [17]. When compared to in-person recruitment, one systematic review found that online approaches were more time and cost effective, but in-person recruitment resulted in a better recruitment rate [18].

(iii) Challenges and benefits

The main benefit of this adaptation was that it enabled many participants to be contacted at once, at a time when NHS sites were struggling to find the capacity to undertake research procedures. Interviewees stated that this approach often yielded a low response rate, and participants required following up in order for a response to be obtained – either via email or telephone. *Study K* looked at ways of improving the response rate to an email invitation, including changing the subject line and incorporating NHS site logos.

> W*e did look at subject line, words to include or not to include, …trying to see like how we could send it, you know with the survey invitation, sort of getting sites to send it from their NHS emails because it's a bit more legitimate; and localising and including logos can always help as well.* Study K

Another problem was that CTUs had to trust that the charity would follow instructions and trial procedures. Initially it was planned that participants would be purposefully invited, but the charity invited all individuals on their database, increasing the work of the CTU in identifying eligible

participants.

> B*ecause it was a feasibility study, we wanted a range of expanded disability status scale (EDSS) scores as part of the eligibility. But when it actually came to sending it out, we sent it out to everybody within that area rather than people that had a clinically confirmed score over a range.* Study B

(iv) Potential for use of the adaptation in the future

Interviewees felt that recruitment outside the NHS via a charity has the potential to improve the efficiency of future trials, through being able to contact participants quicker than traditional in-person recruitment techniques. However, this adaptation is unlikely to be used a stand-alone recruitment technique, due to the impact it may having of the sampling frame. A range of recruitment techniques was viewed as the most beneficial approach – incorporating both non-NHS and NHS recruitment techniques – to increase the size and the diversity of the sample.

> *I think it's great to still have NHS site involvement and if we could we definitely would and If things change then we definitely would get them back on, we would like them back on board. Because again you access different groups of people you'll get the people that won't be online necessarily from NHS sites, so you get different age groups, different populations, depending on which site you go for.* Study K

CTU representatives present at the workshop agreed that this adaptation may be used as an adjunct to 'traditional' recruitment techniques (i.e., recruitment via the NHS). However, due to concerns around the effect this adaptation may have on the sampling frame, it may not be useful if used solely to recruit participants. This adaptation was thought to only be beneficial if there is large enough charity to have an extensive list of participants with the condition of interest.

The challenges of this adaptation included the potential for charities to require training in recruitment processes, which would have a resource requirement from both CTUs and the charities. Charities may not have the relevant information or skills to be able to identify individuals who are too vulnerable to be put forward for the research. Charities may also have limited resources to undertake research, and therefore, relevant costs may need to be included in the grant.

CONCLUSIONS – recruitment outside the NHS via a charity

- May benefit trial sites and participants and decrease the cost of trials, by bypassing the need for NHS staff to identify, approach and recruit participants.
- May impact on the external validity (sampling frame) of the trial if, where participants without the disease in question, or those that do not receive treatment from the NHS, are recruited to the trial.
- Likely only to be used in the future as an adjunct to 'traditional' NHS focussed recruitment pathways.
- Only likely to be applicable to certain studies. Bypassing NHS sites may only be practical for low-risk studies.
- Recruitment via social media is well represented in the literature, but not recruitment via charities. However, both techniques may have similar challenges, including biased sampling [17], and better recruitment rates in-person [18].

PPI representatives at the workshop felt that the relationship between the participant and recruiting individual were important – these may not exist prior to recruitment if a charity is being used. However, charities may have more time to support individuals with their condition or the recruitment process, therefore benefitting participants.

3.4.3. Remote consent

(i) Description of the adaptation

Eight trials made adaptations to the consent process.

There were two elements to this adaptation – the mechanism by which the participant was informed about the trial (i.e., the 'informed' component of informed consent) and the mechanism by which consent was recorded.

The adaptations either informed participants about the trial via post, online, telephone or email. Consent was recorded via all these mediums, plus also via audio in *Study M*.

Flexibility was an important aspect of this adaptation. In three studies (*Study M, Study G, Study J*), participants and/or trial staff were given a choice of mediums by which informed consent could be gained. The choice of which consent procedure to use was dependant on the participant's preference, or the site's perception of which consent procedure would best suit them.

The physical signing of the consent form differed between studies. Forms were signed in a manner that was commensurate with the medium in which they were to be returned by the participant, e.g., electronically for consent forms sent via email. However, there were exceptions in two studies (*Study J* and *Study M*) where the participant did not have to complete the consent form; instead, an independent witness (either known to the participant, or based at the NHS Trust) signed the consent form on the participant's behalf.

In one trial, the adaptation to the consent process consisted of the removal of the need to complete a consent form – a paper consent form was required to collect screening measures, including bloods, whereas the process was adapted so just verbal consent was required.

(ii) Evidence base from a literature search

Remote consent procedures are generally well accepted across four recent systematic reviews [19–22]. Barriers identified include participant's access to technology (particularly thought to be an issue in older adults) [19,21,22], and participants preferring traditional paper consent techniques, potentially due to issues around trust and data security [21,22]. These reviews presented guidance for future studies, including the clinician or researcher being present to answer questions [20–22], seeking patient input into the consent materials [20], and using interactive features to aid comprehension [22]. Previous studies have found that 'research champions' are important to the recruitment and consent process [23,24].

(iii) Challenges and benefits

Challenges

The challenges of this adaptation can be split into those that related to the trial participant, the 'quality' of the informed consent, and those that affected the CTU and research sites.

Trial participant

The main challenges that faced participants were those of digital literacy, and the onus of undertaking consent activities being switched to the participant.

As many of these adaptations were undertaken via digital technology, participants sometimes found the use of these technologies challenging. Support was required in some instances to assist participants in completing the consent form. The use of remote consent technologies were thought to create a biased sample.

One interviewee reflected that, in comparison to in-person techniques of gaining consent, the onus with remote techniques was on the participant to undertake and complete the consent process. In this study (*Study L*), the participant had to post the consent form back. In multiple studies, reminders were required to illicit a response from participants.

Quality of informed consent

The 'quality' of informed consent was discussed by some interviewees. Consent was more challenging to undertake remotely, mainly due to non-verbal cues being missed.

> *I think that there are some participants that I would feel much better if I had them in a room in front of me and I can see their body language and I can see if they've understood what I've said and if they look like they feel a little bit unsure or you know you can tell it better face to face. You pick up on cues can't you better so I guess that could be a drawback as well*. Study J

Sensitive conversations over the telephone were challenging. Remote consent was particularly challenging in studies involving chronic illnesses where the relationship between the participant and their clinical team was important. Remotely forming a bond between the researcher and participant took more time than it would face-to-face and was particularly an issue when the CTU were undertaking consent activities instead of the NHS site.

> *I think the most difficult thing for them was for any brand-new participant where you couldn't actually meet them and I think face to face is key in a group like this. When it can't happen it's a little bit more difficult, so I think for them it just ended up extending the time so that they had that ability to be able to get across their personality to them and the interest in the trial.* Study E.

CTU

The challenges that faced CTUs were mainly technical in nature and were related to the development or implementation of the adaptation. Setting up the remote consent procedures took CTUs significant time and resources. In some cases, multiple options for gaining consent were considered, and within each option there were numerous choices to make regarding how to implement the new process.

As CTU staff were working from home there were also issues with sending participant completed forms to CTU staff's homes due to data governance concerns.

Research site

The most prominent challenge that affected sites was the variable success, or uptake, of these remote consent procedures. Across the adaptations, this presented in different ways. Interviewees noticed

variation in the success of remote consent within a site (e.g., between Consultants), or across sites. In one trial, some sites were not aware of the new processes, or in another, sites were not keen on the new process, potentially due to the complexity of the new procedures.

The adaptations had a varied impact on trial sites' workload – this was dependent on whether the CTU or the trial site was undertaking the consent activities. Some of the adaptations relied on the trial site to undertake activities (e.g., sites sent out consent packs to participants in *Study L*), some were undertaken so that just the CTU were involved in consent procedures (e.g., *Study B*), whereas others involved a mix of both (e.g., in *Study M*, the CTU had to create the consent form in Qualtrics, and then send this out to participants).

Benefits

The benefits of this adaptation can be categorised into those that were COVID specific, those that benefitted the participant and those that benefitted the trial site.

COVID specific benefits

The benefits of the telephone consent procedure undertaken in the *Study L* was discussed in terms of the pandemic, with remote consent being better than not being able to recruit to the trial, or missing participants.

> *I guess it's just kind of recruiting all potential participants onto the study. Because obviously all the changes at the site, everything being done remotely and just that minimal kind of research nurse contact. The benefit is obviously we get more participants consented into the study. I would say probably that's the main benefit.* Study L

Benefits to the participant

Time was the main benefit to the participant. Telephone consent was thought to enable participants more time to discuss the trial (compared to consent being taken at an in-person visit). In one trial where consent was originally taken quite close to a surgical intervention (*Study A*), remote consent provided potential participants more time to decide whether to take part in the trial.

Benefits to the trial site

Remote consent procedures meant that the site did not have to book their limited clinic space. It was also easier for sites to arrange telephone follow-ups when research nurses worked part-time.

(iv) Potential for use of the adaptation in the future

The use of remote informed consent procedures was generally seen by the interviewees as an adaptation that has the potential to improve the efficiency of clinical trials. The efficiency savings were not related directly to the process of gaining consent, as many adaptations were more time consuming than seeking consent at a routine in-person appointment. However, efficiency savings were mainly regarding the improved flexibility for participants that remote consent allows. Several interviewees thought this may improve recruitment rates, but as the adaptation only had recently been made in these studies, such an effect had not been observed in the trials.

One consent adaptation, where consent was gained via a postal consent process (*Study L*), was clearly not seen as having the potential to improve efficiency. This adaptation was not seen as efficient when compared to other remote consent methods, due to the time taken to administer and follow-up participants.

> *I would say my gut says 'no' [it is not efficient], just because I feel like we're moving towards doing everything electronically now and especially during COVID. I can't see like postal consent being a viable option in the future when everything is going remotely. With all the paperwork and the extra time it takes, I just think that's not efficient in itself.* Study L

The appropriateness of using remote consent was thought to be context specific. Populations where remote consent may work particularly well are those where a close relationship is not required between the researcher and participant, which may be those studies that do not involve chronic, long-term, conditions.

There were conflicting views regarding whether this adaptation improved or worsened the 'quality' of informed consent. Some interviewees reflected that remote consent adaptations caused a reduction in quality, due to the participant not being in the room with the researchers.

Other interviewees described that remote consent allowed the participant more time with the researcher, and more time to consider their involvement. What we can conclude from this is the benefits or challenges of remote consent are study specific.

Remote consent was seen by workshop attendees as an adaptation that may benefit clinical trials and is already being used across many trials in the CTU's portfolio. However, it was noted that the trial Sponsor may not support the use of remote consent – different Sponsors may have varying approaches.

A distinction between remote consent (i.e., where mediums other than an online form are used to record consent, e.g., consent over the telephone) and online consent, was made. Remote consent may be simpler to implement for CTUs, due to being less technologically advanced. Additionally, the technology required for online consent may result in some participants being unable to participate in the trial, therefore having the potential to shift the sampling frame. Due to this potential for bias, the group discussed that remote consent could be used alongside traditional consent procedures. Remote consent may be of particular benefit to those individuals who are more unwell or vulnerable.

Workshop attendees believed that detailed guidance is required in order to help CTUs implement remote consent.

Patient representatives at the workshop reflected on the idea that the potential for the participant's family or friends to be present during the consent process may have both positive (ability to provide the participant with support and be involved in the conversation) and negative (lack of confidentiality, and potential for friends of family to coerce the participant into involvement in the trial) effects.

CONCLUSIONS – remote consent

- May benefit trial sites and participants and decrease the cost of trials, by making it more likely for participants to engage in, and complete, the consent process, therefore increasing recruitment rates and reducing the recruitment phase of trials, thus reducing their cost. However, there is insufficient evidence to confirm this association.
- The interviewees (WP2) felt that remote consent required increased resources at the CTU. However, in this study, as only CTU staff were interviewed, this may reflect a biased representation of the resources required, as the increased workload required from one individual at the CTU may be more cost-effective than multiple individuals at sites having to undertake this activity.
- There is a potential for the sampling frame to shift if consent is solely undertaken remotely –remote consent could therefore be combined with traditional methods of obtaining consent.
- Remote consent may be particularly beneficial for individuals who are particularly unwell or vulnerable.
- The ability of individuals other than the participant to be present at consent may have a positive (ability for others to help participant decide whether to participate) or negative (potential for coercion) effect on the process.
- Remote consent is generally well accepted across four recent systematic reviews [19–22]. However, participants may prefer paper techniques due to concern around trust and data security.
- One remote consent adaptation identified in this study did not necessitate the participant to sign the form, and instead a witness at the trial site signed the form on the participant's behalf. As far as we are aware, this procedure has not been previously described in the literature.
- Previous literature suggests research champions [23,24], and clinicians/researchers being present during consent [20–22], are important enablers to consent and recruitment– centralising consent activities may inhibit the ability of these individuals to assist with recruitment.

3.4.4. Remote delivery of the intervention by CTU staff

(i) Description of the adaptation

In one study (*Study K*), CTU staff were trained in the facilitation of the intervention, and delivery of the intervention was centralised, rather than being facilitated by Nurses at research sites. A bank of freelance Nurses were recruited to assist with intervention facilitation.

(ii) Evidence base from a literature search

There is evidence across a diverse range of populations regarding the **remote delivery of interventions**, however, no evidence could be located specifically regarding CTU staff assisting with this.

(iii) Challenges and benefits

Interviewees considered the benefits of this adaptation to be limited. The main benefit was that a smaller centralised team delivering the intervention allowed for more controlled delivery of the intervention and direct feedback to the study team.

There were two main challenges: those relating to the scientific integrity of the trial, and those relating to the resources required at the CTU. Central facilitation meant that the trial was unable to answer the research questions set out from the start – the interviewee did not explicitly state which secondary outcomes may be affected, but this may have been research questions around whether the intervention could be implemented across the NHS, with NHS Nurses at various sites across the UK trained to facilitate it.

The CTU administering the intervention instead of trial sites effected the delivery of the intervention. The range of facilitators were reduced, which may have increased the effect individual facilitators had on the delivery of the intervention. Clearly, this adaptation increased the CTU's workload.

> *In term of us yeah as a central team, it's definitely upped the amount that we have to do*. Study K

(iv) Potential for use of the adaptation in the future

Interviewees generally felt this adaptation was necessary during the pandemic to allow the trial to continue, and may not be relevant outside of this context. This adaptation was therefore not discussed within the workshop.

CONCLUSIONS – Remote delivery of the intervention by CTU staff

- The benefits of this adaptation were unique to the context of the COVID-19 pandemic, and it is unlikely that this adaptation could be used widely after the pandemic, due to the effect on the generalisability of the intervention.

3.4.5. Delivery of trial intervention by an interventionist at any NHS Trust

(i) Description of the adaptation

One study (*Study M*) allowed therapists from any location (either trial sites, or other NHS Trusts who were not a trial site) to deliver the complex intervention. This, coupled with the remote consent adaptations implemented in *Study M*, meant that participants could be recruited from anywhere, not just from the trial sites.

(ii) Evidence base from a literature search

Evidence could not be located in the literature regarding the **delivery of the trial intervention by an interventionist at any NHS Trust**.

(iii) Challenges and benefits

The major benefit was an increase in the pool of potential participants, which was thought to have a major benefit on recruitment. However, seeking excess treatment costs was challenging, due to therapists from other NHS Trusts being involved in the participant's care. As the *Study M* Sponsor is a Higher Education Institution (HEI), this was rectified, as the Sponsor was able to collect all excess treatment costs and distribute these accordingly, but this was thought not to be possible for NHS Sponsors under the current system.

> *The excess treatment cost funds go to the sponsor and then the sponsor can allocate those funds as required. [our Sponsor is a] Higher Education Institution; had it been [an NHS*

> *Sponsor], then we wouldn't have got the excess treatment costs because it would have fallen into that threshold issue but because they're an HEI, there's no threshold, so they get all the money.* Study M

Other challenges included research sites having concerns around who would have responsibility for the clinical care of participants in the case that medical concerns were raised during intervention or follow-up procedures. The transfer of data between NHS sites to confirm eligibility was also challenging.

(iv) Potential for use of the adaptation in the future

This adaptation was seen by the interviewee as having the potential to improve the efficiency of clinical trials and was thought to improve the representation of underserved groups.

> *If you can recruit from anywhere, you potentially increase the access of underserved groups*. Study M

However, at the point of being interviewed, the adaptation had not been used extensively, with only one site set-up to receive external referrals. Therefore, the impact of this adaptation is unknown – as a result, this adaptation was not discussed within the workshop.

CONCLUSIONS: Delivery of the trial intervention by any NHS Trust

- At the point of being interviewed, the adaptation had not be used extensively, with only one site set-up to receive external referrals. Therefore, the impact of this adaptation is unknown.
- Issues with the payment of excess treatment costs mean that it is unlikely that this adaptation could be used as standard.

3.4.6. Couriering the IMP to the participant's home

(i) Description of the adaptation

Four studies couriered study medications to participants, rather than the participant having to attend a central location to collect it. The couriering of the IMP was either organised by the CTU (1 study, *Study C*), or by the research site (3 studies – *Study F, Study A, Study I*), with the exact method of couriering often varying between sites.

In two of the studies, pharmacies were already couriering medications to participants, which formed a starting point for the development of this adaptation. The CTU therefore undertook a process of reviewing and approving the site's courier processes.

> *We issued out kind of guidance of saying, if you need to courier medication, please keep us informed of your logistics and we can get that approved.* Study I

Return of the IMP was an important aspect of this adaptation. One study was testing a controlled drug, which meant that strict rules were in place regarding the return of unused IMP. In this study, the IMP could be posted back, or alternatively, taken to a local pharmacy – the policy differed between sites.

> *At the end of study, we have to ask them to send post back, the tab the IMP to the research team, or give it to their local pharmacy. It depends on each trust or the site what they want to do. I mean, everybody's got their own different policy.* Study F

(ii) Evidence base from a literature search

Couriering of the IMP to the participant's home has been discussed by several review articles since the start of the pandemic, however there are a lack of discussion of the challenges of benefits of doing so, with these articles stating that couriering of the IMP to the participant is an option [25–27].

(iii) Challenges and benefits

Benefits

The major benefit was the time saved by participants in not having to attend in person to collect their medication, especially those that lived far away from the trial site. This was seen as having the ability to potentially increase the desirability of the trial to potential participants.

Challenges

Challenges mainly involved the time or resources involved in implementing or undertaking this adaptation, logistical issues, or the effect on adherence data.

Significant resources were required by both the research site and CTU in implementing this adaptation. CTUs were required to monitor and ensure the safe delivery of the IMP to the participant (either by receiving automated notifications from the courier, or by directly contacting the participant to ascertain receipt of the IMP). Trial sites often had to develop new standard operating procedures (SOPs) and, in some cases, had to organise the courier. Studies varied with regards to whether there were budgetary issues - the couriering of IMPs can be expensive, and this was not catered for in the trials budget for one trial, although for two trials, the site travel budget was repurposed for this activity.

> *This is the main thing with this adaptation as a consideration of cost as the biggest effect on our trial, and not something we had budgeted for. We need to be aware of that and try and minimise our costs as much as possible.* Study A

Logistical issues included specific implementation issues in one study - wet signatures of trial participants were required by some sites, so participants had to remain at home in the morning of the day of delivery. The need for temperature controls was a potential pitfall, where the efficiency of this adaptation could be decreased. There were also issues when the site pharmacy closed before the courier picked up the IMP.

Not all the studies necessitated that unused drugs or packaging should be returned, which therefore influenced the measurement of adherence data, which as a result, was collected remotely. Interviewees reflected that this could have affected the validity of the data, with participants having to be trusted that they are reporting adherence correctly.

(iv) Potential for use of the adaptation in the future

Couriering of the IMP was seen by the interviewees as an adaptation that could be used in future studies, but focus was mainly on the benefit to the participant, and the benefits this may have to recruitment, rather than improved efficiency.

> *But although it's less efficient it does make your study more appealing for participants to take part. So you have to balance that out. I guess it depends on how difficult your study is to recruit to and whether that's a factor that you have to think about*. Study C

When asked whether they would courier IMPs to participants in the future, one interviewee stated the future focus was to only offer the courier to those participants who were too unwell or unable to attend the site – this appeared to be due to budgetary concerns.

> *Having a courier for patients that are too unwell to travel to clinic visits, that will definitely continue after COVID; patients that, you know, that are, you know, we could potentially have patients that are quite far away.* Study A

Within the workshop, the safety implications of delivering drugs remotely to participants was a main concern. The combination of this adaptation with others (e.g., remote follow-up), may mean that the participant is not being seen in-person for long periods of time – there is a risk that the participant is not receiving or taking the drugs, which may be missed by the trial team if the participant is not being contacted.

There were also concerns around the validity of this adaptation. In a pragmatic trial, couriering the IMP to the participant may not reflect the method by which the IMP would be delivered in the 'real-world' – therefore, the results of the trial may not reflect those that may be found in practice.

Situations where the intervention and control drugs are being sent from two different facilitates may cause bias between the two arms, e.g., where the time lag between randomisation and receipt of the IMP is different between the two arms.

PPI representatives in attendance at the workshop were generally happy with this adaptation. It was recommended that participants should be able to choose a time-slot for delivery of their IMP, rather than having to remain at home waiting for the courier to attend. There were concerns around intercept of the drugs by those who are not prescribed them. A possible solution could be allowing local pharmacies to prescribe the IMP, rather than the participant having to attend a hospital pharmacy, which may involve more travelling.

CONCLUSIONS: Couriering the IMP to the participant's home

- May impact indirectly on trial efficiency, through making the trial more attractive to potential participants and avoiding the need to attend in-person to receive the IMP.
- Concerns around the effect of this adaptation on the scientific integrity of the trial may mean this adaptation is not relevant to all IMP trials – concerns including external validity (where, in a 'real-world' setting, the drug would usually be collected by the participant in-person) and potential between arm bias (if there are differences in the couriering of the drug between the trial arms).
- However, couriering of the IMP is may be onerous for trial sites, and/or CTUs to implement. Therefore, it is unlikely to directly reduce trial costs.

3.4.7. Follow-up

(i) Description of the adaptation

To avoid missing data, four distinct adaptations to follow-up processes were implemented, with some studies undertaking one of these adaptations, and others undertaking multiple. The four adaptations are separately described below.

Remote collection of PROMs

PROMs were collected via telephone in the four studies that undertook this adaptation (*Study A, Study N, Study H and Study F*), via post in one study (*Study C*), via various methods in one study (video, telephone, online - *Study M*), and via post or telephone in another (*Study E*). Outcomes were either collected by site staff (*Study I, Study A*), CTU staff (*Study N*, *Study M*), or either the site or CTU staff (*Study F*). CTU staff often required training to collect the PROMs.

Remote collection of biological outcomes

The remote collection of biological measures was undertaken in three studies, where the following outcomes were collected remotely – a measure of blood glucose control (HbA1c - *Study N*), blood pressure (*Study F, Study C*), hand photographs (*Study C*) and spirometry and cough sensor data (*Study G*). In two studies (*Study F* and *Study C*), blood pressures were collected to maintain the safety of participants at a time when they could not attend in person to have these collected. In *Study C,* blood pressures were only monitored if the investigator felt there was a clinical requirement to monitor the participant's safety. It worthy to note that the remote collection of spirometry and cough data in *Study G* study had not yet been implemented at the point of the interview being undertaken.

For the majority of these measures, the participant collected the outcome by themselves at home; this was then collected by telephone by the study team. The exception to this was the collection of a measure of blood glucose control (*Study N*), where the sample was sent to a central laboratory for analysis, and the spirometry and cough sensor data (*Study G*), where data was automatically sent electronically to the study team.

Collection of outcomes from a routine source

In two studies (*Study G*, *Study N*) participants did not have to attend the site for biological measures (i.e., blood tests), and instead could attend a local GP surgery to have these collected.

> *So it'd be exactly the same as it would have been if they'd gone to the site. The site will order the bloods, they'll be taken by the GP following their usual trust policies to do so, and then the patients will obviously go in to the GP, but they'll still be, their bloods will be taken and they will be processed by the site.* Study G

Prioritisation of trial outcomes or in-person visits

One trial prioritised trial outcomes across the trial (*Study I*), and another trial (*Study C*) assessed the safety of collecting trial outcomes in-person prior to each follow-up visit.

> W*e would say 1 week before each of these visits the investigator's going to call you to carry out a safety assessment to check that it's safe to go ahead with that visit remotely or whether you need to be seen face to face in the clinic.* Study C

(ii) Evidence base from a literature search

High response rates were identified for **online data collection of PROMs** when compared to email, telephone or mail follow-up across two studies [28,29], and high response rates when tested alone [30,31]. **Online data collection** was also deemed to be the most acceptable to participants across two studies [31,32]. Reminders are important when undertaking online questionnaires [33]. Providing participants a choice of return methods (online or paper) resulted in a higher response rate than online only in one study [34].

Other studies have assessed the accuracy of **remote data collection**. Computer assisted data collection was as accurate as paper surveys [35,36]. However, in two other studies, there were differences in responses to the questionnaires when comparing telephone vs mail, or paper to electronic versions [37,38]. In one systematic review aiming to review modes of collection of subjective outcomes, the mode of administration (in person or remote) was significantly associated with bias, but not changes to precision [39].

The **remote collection of blood pressures** has been discussed as being acceptable for patients receiving clinical care (e.g. outside of a research setting), in populations such as pregnant or recently pregnant women, and individuals with heart failure [40–42]. However, there is a lack of evidence regarding it's acceptability within clinical trials and older adults. The remote collection of measures of blood glucose control are not referred to in the literature.

The author could not locate literature specifically regarding the **remote collection of spirometry and cough data**. However, the **remote collection of biological measures** has mostly focussed on the use of wearable technologies, specifically "BYOD" (bring your own data), where a participant uses their own smart phone or other device to collect data. In one literature review, 81% of studies found the use of these technologies to be positive [43]. The main benefit of this technology was regular monitoring outside the clinical environment, which may more accurately represent the participant's health status compared to traditional data collection, with increased data collection frequency allowing a better understanding of disease variability [44]. However, the challenges cited included lack of scientific evidence to support their use, data security and the lack of optimisable features for the study question [43,44].

(iii) Challenges and benefits

Challenges

The challenges of remote data collection can be split into those that affected the scientific integrity of the trial, those that affected the participant's experience, and those that affected the resources required at either the trial site or the CTU.

Scientific integrity

Missing or inaccurate data, and blinding, were the main concern around the trial's scientific integrity, although the use of the spirometry device that automatically uploaded data negated this issue in *Study G*. Data was missed due to the nature of the pandemic and in-person visits being viewed as infeasible or unsafe. When it was feasible to collect data remotely, the main cause of missing data was participants not answering their telephone, so study teams attempted to contact participants several times to collect their data and minimise data loss.

> *With the CRFs I think it all went well cause even after 3 times if somebody would not pick up and we would send an email explaining and they would come back saying 'oh so sorry I thought it was just like yeah somebody trying to sell me something'.* Study N

The accuracy of the data was also a concern, with trials having to 'trust' the data that participants were providing. There was also a risk of missing side effects when participants were not being seen in person. Blinding of trial staff was affected in one study where CTU staff collected outcomes from participants.

Participant experience

The main challenge of collecting PROMs over the telephone were the complications of asking participants sensitive questions over the telephone.

> *If you're sitting with your children, that's a very difficult question to answer. And the chances are, they won't answer honestly. So we've flagged throughout the trial, and we've put a big emphasis on asking the patient if they're alone and if they'd like to just step into another room.* Study A

For those studies where the CTU undertook data collection, there was a need to inform the participant that those collecting data were not clinically qualified, so could not answer any clinical queries.

CTU or trial site resources

As many of the adaptations involving shifting tasks from trial sites to CTUs, there was a clear increase in resources required by the CTU. Some adaptations seemed more onerous than others from the CTU's point of view – this was especially true for larger trials, for example *Study N*, where the CTU had to arrange remote follow-up for 300 participants over multiple time-points.

> *I think the main challenge is the time and burden for CTU because it's, well I basically did the self-test kits and the majority of CRFs. But it does take a lot of time, cause each CRF over the phone is like 15 to 20 minutes for the 6 month follow up and up to 40 minutes for the 12 month, and we had 300 patients - it was quite labour intensive.* Study N

Despite trial sites having less ownership of follow-up processes, there were still roles for trial sites in this process, which included prompting participants for missing data, and reviewing particularly anomalous data for safety concerns.

Benefits

The benefit of remote follow-up was mainly the flexibility it allowed the participant and research sites by avoiding the need for the participant to attend a central location for follow-up, or for the site staff to travel to the participant's home to undertake follow-up. This reduced the costs to the site or participant and saved them time. This, in turn, was thought to have the potential to improve recruitment rates.

> *Everybody's got the feeling the recruitment is going to be much easier… everybody agrees that is, they are all positive and good changes to their study. And they said, maybe we should have it when we designed this study.* Study F

The benefit of a few adaptations were viewed either partly – or entirely - in terms of the pandemic.

The remote collection of a measure of blood glucose control allowed *Study N* to continue, and the remote collection of blood pressures allowed *Study F* to continue with less protocol violations due to data previously being missed due to the pandemic. Follow-up by telephone was particularly seen as a 'needs must' adaptation during the pandemic across many of the trials that implemented this adaptation. The prioritisation of outcomes (*Study I*), or assessment of whether a study visit should be undertaken in-person (*Study C*), is likely to only be useful during a pandemic.

Specific mediums of data collection were associated with specific benefits. Follow-up by telephone was thought to avoid discriminating against older adults with limited access to technology and was particularly flexible; postal data collection was thought to be the least intrusive and most flexible for the participant; whilst online (video) data collection limited missing data and benefitted participants during an extended period of self-isolation.

In *Study G*, the automation of the data collection process, and centralisation of data collection was seen to be of benefit to the trial. Although most studies reduced the data they were collecting, the use of the automated spirometry system allowed more data to be collected, with additional secondary measures being added to the study as a result. The use of automated cough sensors was thought to be efficient due to the sites training participants directly, rather than training Nurses to then train participants, which improved the consistency of the training.

> *It probably would have been quite inefficient because the company were going to train me to do it, and then I were going to be training each of the sites at the SIV. Whereas now, it'll be me or, and another member of staff, will be trained to do the calls with the patients directly. It is a bit more consistent in that it's only going to be like one or two people that are going to be training all of the patients to do that, rather than thirty-five plus.* Study G

(iv) Potential for use of the adaptations in the future

Views of the interviewees (WP2)

Collection of outcomes from a routine source

The collection of outcomes from a routine source, rather than collecting these specifically for the trial, was seen by the interviewees as having obvious benefits, that included a reduction in travel time for the participant, and reduced resources required at the trial sites. However, there was limited discussion of the potential for missing data around the collection of blood results from routine sources, and it may be that in practice, this adaptation may only have been used in the pandemic as it is better than not collecting data at all. This adaptation was therefore not discussed within the workshop.

Remote collection of biological measures: remote spirometry and cough data

A second adaptation that has clear benefits is the remote collection of spirometry and cough data – interviewees believed that this adaptation reduced the burden on both the research sites, CTUs and participants. The remote collection of spirometry and cough data is clearly only appropriate for certain trials; the cost of implementing such a system may be prohibitive.

However, this adaptation had not be implemented at the point of the interview being undertaken, so it is unknown if participants will find this method of data collection satisfactory. Therefore, this adaptation was not discussed within the workshop.

Prioritisation of trial outcomes or in-person visits

Interviewees stated that these adaptations are only likely to be applicable during the pandemic, due to the loss of data that would result from the prioritisation of outcomes. Assessment of the safety of follow-ups is only likely to be applicable during the pandemic. Therefore, these adaptations were not discussed within the workshop.

Remote collection of PROMs and biological measures (blood pressures and blood glucose (HbA1c)

Interviewees stated that the remote collection of these outcomes was thought to improve the participant's experience of the trial, through increasing flexibility, but not necessarily improve the efficiency of undertaking the trial. The remote collection of many outcomes was problematic due to a low response rates and the level of resources required at the CTU.

The collection of PROMs by CTUs via telephone was labour intensive – both the process of collecting the data, and the time needed to train CTU staff to collect such data. It may only have been possible during the pandemic due to CTU's staff other workloads decreasing.

> *During the pandemic most of my roles and responsibilities sort of declined because the trial was put on hold, there weren't any new recruits, so I had more time to do the things I did last year so the CRFs and the self-test kits.* Study N

When asked if the adaptations will be used after the pandemic, some interviewees stated the adaptation would be replaced by other options or would be used as a backup. This was the case for all adaptations involving the remote collection of PROMs, with interviewees either stating that they would revert to online data collection methods in the future (*Study E and Study H*), will be used as a back-up (*Study N*) or will not be required as face-to-face appointments are likely to recommence (*Study A*). This was also the case for the remote collection of biological measures (e.g., the measurement of blood glucose control in *Study N*). Generally, interviewees believed these adaptations could be used for those participants that live far away from the study site.

> S*ending the self-test kits worked well but by no means 100%, and we would have got more HbA1c [a measure of blood glucose control] if we could continue the way we were doing… I think we will continue with it just as a back-up option. But it might be a real opportunity for remote patients for specific research. Study N*

In the workshop (WP3), the three adaptations that were deemed to have the potential to improve the future trial efficiencies were discussed – the remote collection of PROMs, and remote collection of biological measures (blood pressures and blood glucose (HbA1c).

Views of the workshop attendees (WP3)

Workshop attendees discussed that the main concern around these adaptations was the effect they may have on the scientific integrity of the trial. Outcomes with some form of interpretation or subjectivity involved (i.e., blood pressure) may be particularly prone to bias, potentially where the participant could select the lowest measure to report to the trial team. There may be systematic changes to the way in which the outcomes are collected between the home and clinical environment; this may be a particular issue for the remote measurement of blood pressure, where, although this may increase the validity of this measure in respect to how it reflects the participant's *actual* blood

pressure, it may create bias if other participants (or the same participant) are having their blood pressures measured in the clinical setting.

The validity of the remote collection of PROMs was also cited by workshop attendees as an issue, with certain PROMs not validated for use over certain mediums. The use of postal data collection was thought to be particularly problematic for rapidly changing outcomes – e.g., those in an emergency setting. The remote measurement of blood glucose was thought to have less of an effect on scientific integrity; however, accurate devices may be expensive.

A second risk to the scientific integrity of the trial was thought to be compliance, or missing data. Compliance may depend on the patient group – those individuals who are less engaged with their treatment may provide different results to others. There may be high levels of missing data when PROMs are collected remotely – this was deemed to be dependent on the modality of data collection used, with telephone collection of PROMs possibly leading to lower levels of missing data compared to other modalities (online/post). However, telephone data collection may be challenging for longer questionnaires, and may require CTU staff to work out of hours in order to contact participants. Postal data collection was associated with high levels of missing data and may require significant CTU resources to administer reminders to participants. Generational differences may exist in the acceptance of different methods of data collection; younger generations were thought to prefer text messages, whilst older generations were thought to prefer data collection via the telephone.

Patient representatives felt that questions may be misinterpreted via the post – therefore, telephone data collection may be preferential for more complex outcome measures. Over the telephone, repetitive outcome measures (e.g., the researcher repeating the same answer options after each question) was viewed as irritating, potentially decreasing the likelihood the participant will complete future follow-ups.

There is a need to ensure that remote biological tests are not too burdensome for participants. It is likely, for some outcome measures (e.g., blood glucose in diabetes), participants are already familiar with the process of collecting this outcome. However, there still may be barriers – for example the participant accessing a post box in order to return the sample for analysis.

CONCLUSIONS: Remote collection of PROMs

- May indirectly reduce the cost of the trial by making the study more appealing for potential participants through increases to flexibility.
- May be more labour intensive than traditional data collection techniques (i.e., collecting outcomes at a routine visit). However, may make the trial more attractive to participants, and therefore make it more likely for them to participate.
- Telephone data collection may be preferable over postal data collection and may be associated with lower levels of missing data. However, data collection via telephone may not be preferential for repetitive, long or complex questionnaires, and such data collection may be more onerous for the CTU compared to postal data collection.
- In the literature, online data collection is often reported as more accurate and acceptable, compared to other techniques of data collection. However, this method is not represented in our sample of studies.

CONCLUSIONS: Remote collection of biological measures: remotely collected blood pressures and blood glucose (Hb1Ac)

- May indirectly reduce the cost of the trial by making the study more appealing for potential participants through increases to flexibility.
- Remotely collecting blood pressures and blood glucose were labour intensive for CTUs, and alone is unlikely to reduce trial costs, unless this adaptation removes the need for the participant to attend the site for an extra follow-up visit.
- There are issues with the validity of collecting blood pressures remotely – participants may select the reading to feed back to the trial team, in which case, mixing methods of data collection (e.g., in person and remote) may cause bias.
- Even 'simple' outcomes that the participant is used to collecting may cause the participant difficulties, e.g., when having to access a post box to send samples for analysis.
- Compliance may differ within populations, potentially with regards to how engaged individuals are with their therapy.

CONCLUSIONS: Remote collection of biological measures: remote spirometry and cough data

- The remote collection of spirometry and cough data is clearly only appropriate for certain trials; the cost of implementing such a system may be prohibitive. It was largely unused within the one study that used this adaptation, therefore, the impact on trial efficiency is unknown.
- In the literature, 'BYOD' (bring your own data) is discussed in detail, with benefits thought to include a more accurate representation of the participant's health status.

CONCLUSIONS: Collection of measures from a routine source

- There was limited discussion of the potential for missing data around the collection of blood results from routine sources, and it may be that in practice, this adaptation may only used in the pandemic as it is better than not collecting data at all.

CONCLUSIONS: Prioritisation of trial outcomes or in-person visits

- Limited discussion of the impact of these adaptations on missing data
- Likely to only be applicable during the pandemic

It was noted that adaptations that relied on the participant to undertake a certain activity (e.g. remote

collection of blood glucose), although largely thought to benefit inclusivity, may make it more difficult for those with chaotic lifestyles to participate in the trial.

4. Discussion

General findings

Of the 14 cases investigated there were three adaptations that were thought to have the potential to improve the efficiency of clinical trials after the pandemic. These functioned by directly reducing the resources required at NHS trial sites, and were: a **two-stage remote-first eligibility assessment**, **recruiting outside the NHS via a charity**, and **remote consent**. Other adaptations (**remote collection of outcome measures** and **couriering the IMP to the participant**) may benefit participants and indirectly benefit trials through increasing the appeal of participation in the trial. The identified adaptations may only be applicable to certain trials and settings, each having their own specific challenges and benefits, which are outlined.

There are barriers to the implementation of these adaptations. Due to concerns around the effect of these adaptations on the scientific validity of trials (e.g., changes to the sampling frame for recruitment adaptations, and outcome assessment bias), the majority of adaptations were perceived to only be useful in future trials as an adjunct to more traditional methods. However, even using certain adaptations as an adjunct may cause bias, for example, if there are systematic differences in the way an outcome is collected remotely, compared to in-person. Additionally, CTUs may struggle to undertake these adaptations due to limited infrastructure (e.g., computer systems for online consent, and limited staff capacity to undertake centralised trial tasks), a lack of clinical expertise to collect clinical measures, and an absence of regulatory approvals that allows the storage of identifiable data.

When adapting clinical trials, researchers may consider asking trial sites and PPI representatives their opinions of the adaptation, including the feasibility of undertaking the new procedure, and the effect on the representation of key participant groups. As these adaptations often involved the responsibility for undertaking research procedures being switched from NHS or research staff to the participant, researchers may consider costing in reminders and support for participants.

Comparison to existing literature

This investigation of the adaptations made to clinical trials to allow them to continue during the pandemic broadly mirrors those of other surveys of CTUs or investigators that have found that clinical trials had to rapidly adapt during the pandemic, also identifying similar adaptations [45,46]. However, other studies have found that many trials had to pause recruitment activities, but then adapted follow-up and intervention delivery processes in order to allow these to continue [46]. The cessation of trial recruitment was not identified in our study, possibly due to CTUs being asked to identified studies that had made adaptations to the recruitment process.

The remote collection of informed consent was found to potentially impact on the efficiency of trials in this study, and is widely supported in the literature [19–22], so could be incorporated into future studies. However, there is evidence to suggest that participants may prefer paper consent due to concerns around trust and data security – participants may need to be reassured regarding this [21,22]. The centralisation of research procedures, and the remote delivery of consent, may negatively affect consent rates by limiting the use of Research Champions, and the presence of clinicians during consent, both of which have been found to be important in previous studies [20–22,24]. Previous

literature provides some recommendations not identified in this study - including the clinician or researcher being present to answer questions [20–22] and using interactive features to aid comprehension [22]. These may have not been identified in this study due to the nature of the pandemic (a researcher could not be present during recruitment due to social distancing rules), and the speed at which adaptations needed to be made meaning that there was not time to add interactive features. In this study, we may have identified a new mechanism of undertaking remote consent, not identified in a recent review of such procedures [47], where the participant does not sign the consent form, and instead a witness based at the trial site signs it on their behalf. However, it is unclear whether this adaptation would be ethically appropriate, and approved by RECs, post pandemic.

Other adaptations were less well evidenced in the literature but were found in our study to potentially have an indirect impact on trial efficiency. Future studies may consider online data collection; although this adaptation was not represented in this study, it is well evidenced in the literature and is reported as being acceptable to participants and accurate [31,32]. The speed at which CTUs had to adapt their trials may have meant that there was not time to develop these intricate data collection processes. There was a general view expressed in this study, and some literature, that allowing participants to choose the medium by which they undertake trial procedures is beneficial. However, previous studies have found that different modalities of undertaking data collection may result in differences in responses [37,38].

Many of the other adaptations identified in this study were not represented in the literature, including splitting the eligibility assessment and recruitment outside the NHS via a charity.

Strengths and limitations

A strength of this study is that all CTUs in the UK were surveyed in order to obtain details of studies that had made adaptations in order to continue during the pandemic. The survey had a good response rate, with 23 of 53 CTUs (43%) reporting adaptations which they considered could be case studies. We interviewed a proportion of staff from those studies (n=14), purposefully sampling for important variables (e.g., target sample size, CTU location). Detailed qualitative interviews were undertaken with representatives from the selected studies, gaining comprehensive information about the adaptation that was made.

There are several limitations to this study. Firstly, the selection of 14 out of 40 studies may have resulted in novel or particularly effectual adaptations being missed. However, the studies were selected purposefully, ensuring variation in key characteristics. Some adaptations were seemingly underrepresented in this study, including online data collection. This may be because of the speed at which CTUs had to adapt their processes, with the set-up of an online system being particularly onerous. Secondly, some case studies involved adaptations that had not been implemented or had been seldom used at the point of the interview taking place, and therefore the effect of the adaptation was unknown at this point. Thirdly, only CTU representatives were interviewed, therefore representing a biased view of the adaptations made, and excluding the views of trial sites and participants. Lastly, the contextual factors of undertaking research during the pandemic cannot be ignored – the motivation for trial participants, CTU staff, and other stakeholders (regulatory bodies, sponsors) to enable research to continue during the pandemic may have been a major enabling factor

that allowed the adaptations to function. Such motivation may be unachievable outside of the pandemic. In addition, there were limitations to running trials during the pandemic which meant that the trial teams were restricted to undertaking adaptations in a certain way – for example, consent forms could not be sent to a CTU staff member's house.

Implications & future research

Implications

Clinical trials have previously been slow to implement new technologies, possibly due to concerns around confidentiality, poor infrastructure, and data accuracy [48]. However, prior to the pandemic, many clinical trials had already adapted their trials so that they were partially, or completely, undertaken remotely [49,50]. In this study, we have identified adaptations that may be used in specific trials or populations, which may lead to benefits for the NHS sites and/or trial participants. Many of these adaptations are already in use in trials, including remote consent and follow-up procedures, and will continue to be used after the pandemic. With the information gained from this study, clinical trialists can learn about adaptations that can be implemented in specific circumstances and potentially increase trial efficiencies, including specific challenges and benefits associated with them.

Allowing trial participants' the flexibility to undertake trial procedures in their preferred manner was a key component of the adaptations identified in this study, with many interviewees prioritising this over general benefits to the efficiency of trials. Researchers should therefore consider trying to allow participants such flexibility. However, concerns around the bias which these adaptations may cause and a lack of technology within CTUs to implement these adaptations may result in CTUs cautiously implementing these novel trial procedures.

Many of the adaptations included in this study involved the central delivery of study procedures. This has the potential to improve trial efficiency, by removing the need for multiple individuals at multiple sites to undertake a procedure, allowing for a more controlled delivery of the process and saving time and resources. Interviewees stated that many of these adaptations involved significant increases in work for the CTU, which were not costed into the grant, and were therefore hard to resource. However, in future trials, CTU resources could be incorporated into the cost of the trial, therefore reducing this barrier.

There are considerations to take into account when transferring tasks from an NHS site to a CTU. The link between clinical staff and trial participants may be lost – in some conditions, especially those that are chronic or life limiting, this relationship may be a key motivator for the participant to be involved in the trial. In addition, remotely conducting conversations regarding sensitive subjects may be challenging for participants, and CTU staff may not be suitably trained to undertake the activity, or may not have a suitable relationship with the participants. This shift also undermines the infrastructure and strategic developments to support research from within the NHS.

Future research

Focus of future research

Below, we provide implications for future research:

- The acceptability of these adaptations to trial participants and trial sites is unknown. Future research could concentrate on the adaptations with an unknown impact including delivery of interventions by interventionists at any NHS Trust and the remote collection of spirometry and

cough data. The remote collection of follow-up data could be investigated, especially postal and telephone modalities, and the remote collection of blood pressures.

- The impact of the adaptations on key variables could be explored, including, but not limited to, the impact on the representativeness of the trial sample of the population of interest (for recruitment adaptations), data validity and completeness, and participant retention (for follow-up adaptations). A specific example of where research is required is regarding remotely collected blood pressures, and whether these differ from those taken in the clinic.

Design of future research

Studies within a trial (SWATs) could be used to quantitatively evaluate the effect of the adaptations on key trial variables – including recruitment and retention rates [51]. However, such SWATs may be logistically challenging to undertake as they would involve running two or more complex trial processes consecutively, and randomising participants to each. It may be difficult to undertake a SWAT in procedures that are undertaken prior to the participant consenting to participate in the trial (e.g., recruitment, consent, and eligibility procedures), as the participant would also need to consent to take part in the SWAT. For these adaptations, the experience of trial teams of implementing these adaptations could be reported and shared within journal articles– this may include a comparison of the sample within the trial with the population of interest, to assess changes to the sampling frame that such adaptations may cause. Detailed information regarding the intricacies of how the adaptation was undertaken should be published to allow other trial teams to replicate the adaptation.

There are other benefits that are more challenging to quantify that should be investigated, including benefits to the quality of informed consent and the general experience of participating in research. Such benefits could be investigated within qualitative studies. Ideally, trials would undertake a 'novel' adaptation alongside the traditional technique, with interviews undertaken with participants and their responses compared.

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Appendices

Appendix 1 – Work package 1 (WP1) survey

To view the survey, please follow this link:
https://www.sheffield.ac.uk/scharr/research/centres/ctru/learning-covid-19-efficient-trial-adaptations.

Appendix 2 – Case studies from work package 2 (WP2)

In this section, one study has been selected from each adaptation, and a detailed description of the case study provided. Where more than one study undertook an adaptation, case study have been selected based on 1) the perceived generalisability of the case studies to UK CTU's portfolio of work, 2) the level of detail provided by the interviewee in the their interview regarding the intricacies of the adaptation. Please note, that in order to preserve the anonymity of trial teams, limited information can be provided regarding the nature of the study, e.g., the population or disease area.

Recruitment outside the NHS via a charity– study B

In study B, a charity maintained a list of registered individuals in the local area that were in contact with the charity. An email or letter, including an information sheet, was sent to the individual. The information sheet directed the participants to visit a website if they were interested in participating in the trial. The website required the participant to log into it – this involved the participant setting up an account, where they entered some basic details about themselves, including a basic confirmation of the eligibility criteria, and contact details. The system automatically sent an email to the study team at the CTU, telling them that someone had registered for the study. Upon receipt of this email, a member of the CTU team telephoned the participant to undertake a detailed eligibility assessment.

This was a feasibility study, and therefore, a diverse range of individuals were desired. The charity was provided with instructions to purposefully approach individuals with a wide range of disability levels. Unfortunately, the charity approached all individuals within the local area. The trial team had to undertake an extra screening step due to this.

Split remote-first screening assessment – study C

This study already had a pre-screening telephone call incorporated into the trial processes. If people passed this screening call they would then be booked into a face to face screening visit. In this adaptation, the in-person screening visit was split into those assessments that could be undertaken over the telephone, and those that remained in-person. The trial investigator (who was medically trained) undertook the phone call. Medical history was taken during the new screening call, along with demographics, concomitant medications, which therefore saved time during the in-person visit. Each telephone assessment took 30 to 40 minutes, and included the investigator describing the study, as informed consent would be taken at the following in-person appointment. The pre-screening call had to be undertaken 10 weeks prior to baseline, and the face to face visit 6 weeks prior to baseline.

Remote consent – study J

This study was a low-risk trial in pregnant women. Remote consent via means other than via the internet (telephone email) was selected as it was deemed there was too much development time in creating an online platform for consent. In addition, postal consent was deemed to be too slow. Researchers at the NHS sites contacted potentially eligible participants, with the PIS and consent form emailed to them. Sometime was allowed for the participant to digest the information – the participant was then contacted to ascertain if they were interested in participating in the trial via one of two mediums – telephone, or video call. When obtaining informed consent, the participant's identity had to be confirmed through the standard local NHS protocol at that site – this may have consisted of

confirming the participant's full name, date of birth, and/or address. If the participant was happy to provide consent to participate in the trial, she could print the consent form at home, sign it, capture the signed consent form using either a scanner or camera, before sending the form via email to the trial team. If the participant did not have a printer, or had limited access to the relevant technology, another option was for the research site to print the consent form and for a witness (an individual who works at the site and is GCP trained) to sign the consent form on behalf of the participant. The role of the witness was to ensure the decision to take part in the trial was fully informed all questions had been answered. The form was then also countersigned by the individual who was taking consent.

Remote delivery of the IMP – Study A

This trial involved individuals with cancer – they were shielding due to the pandemic, so were unable to attend the hospital pharmacy to collect the IMP. At the baseline visit 4 months' worth of IMP was provided to the participants. However, at other time points post randomisation, the IMP sometimes had to be couriered to the participants, in which case 3 months' worth of IMP was couriered at each time-point. The research site contacted the courier to arrange collection of the study drug. The drug was then delivered to the participant, the courier informed the site that delivery had been made, which the site then confirmed back to the CTU. In this trial carers could also consent to provide data for the trial, in which case, the consented carer could also collect the IMP.

Remote collection of PROMs – Study E

This trial involved lengthy questionnaires with participants, often involving sensitive questions. Sites undertook follow-ups in different ways. Some sites preferred to post the questionnaires to participants, therefore allowing the participant time to work through the questions. In other sites, follow-up was undertaken via the telephone; often the follow-up was split into multiple appointments due to the length of the questionnaires. A lot of flexibility was required for both the participants and site staff.

In order to allow for data to be collected in this manner, the follow-up windows were extended from two weeks. Cut offs were required for when a participant was no longer contacted after no return of the questionnaires, and the follow-up was regarded as a missed visit.

The questionnaires were collected from parents, and therefore it was easier to undertake the questionnaires when the children were at school. It was easier to undertake the session earlier in the morning or later in the evening.

Remote collection of blood pressures – Study C

In this study, the investigator decided whether the participant required their blood pressure to be monitored closely due to their medical history. The majority of participants already had their own blood pressure monitors at home, due to already monitoring their blood pressures routinely. If the participant did not have a monitor at home, one was provided for them by the trial team. In some cases participants were able to borrow a monitor from their GP practice, and in other cases the participant could go to their GP practice for a blood pressure reading to be taken for the purposes of the trial. When a blood pressure was measured at home by the participant it was collected over the telephone by a researcher.

Remote collection of blood glucose measure (HbA1C) – Study N

A batch of kits to enable the participant to take their blood, store it in a tube, and send the sample to the lab was first obtained by the CTRU. The pack and return documents had to be labelled with the participant's details, including their name and study ID. In order to ensure the participant needed to complete a self-kit test, the trial team had to work closely with NHS sites to ascertain which participants were likely to attend the site for in-person routine measures to be collected, and which participants already had a recent blood glucose measure taken by their GP. Before sending a kit to the participant via the post the CTU team would contact the participant to ensure they were happy to complete the measure remotely. If they agreed to it, the participant received the kit, which included a short instruction flyer, and placed a sample of their blood in the test tube provided. The participant had to add the date the sample was taken to the materials that were sent back to the laboratory. The sample was sent back to a central laboratory via the post the same day in which the sample was taken. The results from the laboratory were received via email by the CTRU – the CTRU contacted the participant in order to pass on the results and forwarded the results to their clinical team. If three to four weeks passed without the kit being returned to the laboratory the CTU contacted the participant to confirmed they had received the kit, and to ask if there were any questions.

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