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

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1. Abstract

Background

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

Methods

An online survey was distributed to 53 UK Clinical Research Collaboration (UKCRC) registered CTUs to identify the adaptations that have been made to trials as a result of the pandemic up until early 2021 (work package 1, WP1). Case studies were then selected for further investigation by reviewing the survey responses, selecting relevant and promising adaptations whilst ensuring variation in key characteristics (e.g., CTU, disease area). Staff involved in the selected case studies were interviewed to discuss the changes that have been made, lessons learnt, and the potential for the adaptation to improve the efficiency of future trials post-pandemic (WP2). The interviews were transcribed verbatim and analysed qualitatively. Findings were reviewed by a group of CTU and patient representatives at an online workshop (WP3) that focused on the potential of these adaptations to improve efficiencies in trials post-pandemic.

Results

Forty studies, involving 86 adaptations were reported in the survey responses from 21 CTUs (WP1). Of these, 14 trials were selected as case studies for in-depth data collection, encompassing 36 adaptations (WP2). The workshop was undertaken with 15 CTU and 3 patient representatives. Adaptations were not seen as leading to direct efficiency savings for CTUs; however, three adaptations were seen as likely to directly improve trial delivery for sites and participants beyond the pandemic. These were: a **two-stage remote-first eligibility assessment**, **recruitment outside the NHS via a charity**, and **remote consent**. Other adaptations (**couriering of the IMP to the participant** and **adaptations related to the collection of follow-up data**) were thought to have benefitted participants and could be used as a back-up option in future trials, and therefore may indirectly improve trial efficiency through improving recruitment and retention rates. Other adaptations were perceived as only useful during the pandemic, or there was insufficient information to form a conclusion. All adaptations were only perceived to be applicable in specific contexts. Providing trial

participants with the flexibility to choose how to undertake a trial activity was key to allowing the trials to continue during the pandemic, which was also seen by interviewees as important to potentially increasing the representation of underserved groups in future trials. Barriers to using these adaptations include concerns around sampling biases and the validity of remotely collected outcomes.

Conclusions

Most trial adaptations to pandemic working were specific to certain trials and circumstances. Three trial adaptations were identified as potentially leading to cost savings in specific trial – a two-stage remote-first eligibility assessment, recruitment outside the NHS via a charity, and remote consent. Although not their primary aim, many adaptations provided participants with increased flexibility to undertake trial procedures, but we found concerns around potential biases created by mixing trial procedure modalities. It is currently uncertain whether the potential advantages of greater flexibility in trial procedures justifies the risk of different modalities of data collection eliciting different responses from participants whilst losing the known benefits of research champions and a clinician/researcher facilitating recruitment. Future research should focus on the acceptability of the adaptations to trial participants, the effect of the adaptations on the scientific integrity of the trial and quantitative evidence of efficiency. These adaptations could be incorporated into co-ordinated studies within a trial (SWAT) research to enable this.

2. Introduction

Many clinical trials were suspended in the UK due to concerns around COVID-19 related social distancing and in order to allow pandemic related studies to be undertaken [1]. Social distancing resulted in some clinical services pausing their delivery, and patients (especially older adults) self-isolating for long periods. In order to restart or to progress without stopping, trialists had to make pragmatic decisions to revise trials to permit them to continue while adhering to social distancing, with limited evidence or guidance regarding the best ways to achieve this. The main concerns for Clinical Trials Units (CTUs) were around maintaining recruitment of trial participants, intervention delivery, outcome assessment, and patient safety, all of which have the potential to be affected by social distancing rules.

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

3. Methods

This study comprised of three consecutive work packages (WPs):

Work package 1 (WP1) – survey of UK CTUs

All UK Clinical Research Collaboration (UKCRC) registered CTUs were surveyed to identify studies that have adapted their trial procedures in light of the pandemic. The survey was emailed to the Director of each CTU by the UKCRC in December 2020 and aimed to collect information regarding the adaptations made and lessons learnt. CTUs were asked to identify studies that were potentially good case studies for WP2, using the following criteria:

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

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

The results of the survey were used to select 14 cases, which were purposively sampled by RC to ensure diversity of type of change made, and other key variables (e.g., location of CTU, size of study, disease area). Only those adaptations that had the potential to increase the efficiency of trials in the future were selected.

An individual from each trial was contacted, and an in-depth qualitative interview undertaken online to understand how the adaptation was developed and implemented, and the challenges and benefits of doing so.

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

The findings from WP2 were presented to a group of fifteen CTU and 3 PPI representatives on 08/09/2021. The aim of the meeting was to discuss the generalisability of the findings, along with the contexts in which the adaptations may or may not work, and the potential for the adaptations to improve the efficiency of future trials. Only those adaptations that were deemed from WP2 to be potentially beneficial in future trials were discussed in the workshop. The discussions in this workshop were incorporated into this guidance document.

4. Results

Twenty-one CTUs responded to the WP1 survey (43% of CTUs), describing 40 studies that had made a total of 86 adaptations during the pandemic. From these, 14 case studies were selected and included in WP2. The selected case studies encompassed a total of 36 adaptations to trial procedures. An overview of the adaptations can be found in *Table 1*.

The adaptations included in WP2 can be split into those that were made to:

- Recruitment/consent:
    - two-stage remote-first eligibility assessment (two studies)
    - recruitment outside the NHS via a charity (two studies)
    - remote consent (nine studies)
- Intervention delivery:
    - central delivery of intervention by CTU (one studies)
    - delivery of the trial intervention by any interventionist at any NHS Trust (one study)
    - couriering the investigational medicinal product (IMP) to the participant's home (four studies)
- Follow-up:
    - remote collection of patient reported measures (PROMs) (ten studies)
    - remote collection of biological measures – including blood pressures (two studies) and spirometry and cough data (one study),
    - collection of outcomes from a routine source (two studies)
    - prioritisation of trial outcomes or in-person visits (two studies).

In the following sections, the findings of the study are summarised, the general considerations around adapting clinical trials are considered, and then the implications, future research priorities, and strengths and limitations of this study are discussed.

4.1. Summary of findings

4.1.1. Impact on trial efficiencies

There were a lack of adaptations that were thought to directly benefit CTUs – most adaptations made during the pandemic increased the CTU's workload, due to activities being transferred across from research sites. From the point of view of the interviewed CTU representatives, the benefit of the adaptations made during the pandemic was the continuation of the trial. Outside of the pandemic however, CTUs may benefit indirectly from these adaptations, through improvement to recruitment and retention rates, which may in turn reduce trial costs.

There were two main ways in which the adaptations could benefit the trial. Firstly, the adaptation could reduce the resources required at NHS sites, by moving the activity outside of the NHS (to a charity or a CTU), and therefore reducing trial costs by centralising the research procedure. Secondly, the adaptation could improve the trial participant's flexibility, which, according to the interviewees, was sometimes more important than increasing efficiency, and may enable the inclusion in the trial of underserved groups and those that were too unwell to attend a central location to undertake the trial activity. The improvement in the participant's flexibility may indirectly reduce trial costs by increasing recruitment or retention rates, therefore reducing trial timelines and costs.

Below, we discuss the potential efficiency of the adaptations in terms of whether the adaptation:

- May directly benefit participants and NHS trial sites and reduce the cost of the trial;
- May benefit participants and indirectly reduce the cost of the trial;
- Are inefficient or are only applicable during a pandemic;
- Has an unknown effect on efficiency.

Detailed information regarding the challenges, benefits, and further guidance can be found in *Table 2*.

4.1.1.1. Adaptations that may directly benefit participants and NHS trial sites and reduce the cost of the trial

Three adaptations relating to trial recruitment were thought to both directly improve trial costs by reducing NHS site workload, and indirectly reduce trial costs by making the trial more flexible for participants. These were: a **two-stage remote-first eligibility assessment**, **recruitment outside the NHS via a charity**, and **remote consent** (except postal consent, see *inefficient adaptations and those that are only applicable to the pandemic).*

A major concern regarding the implementation of the recruitment adaptations was the potential for bias. A complete shift in a recruitment procedure to a 'new' adaptation (e.g., replacement of in-person consent with remote consent) may shift the sampling frame of the research. It is therefore likely that these recruitment adaptations will be used as an adjunct alongside more 'traditional' techniques.

Below, further guidance for each adaptation is provided, with detailed guidance provided in *Table 2*:

A two-stage remote-first eligibility assessment (*a two-stage eligibility assessment, where eligibility is assessed remotely prior to an in-person eligibility assessment*) may reduce trial costs by potentially saving trial sites time and resources in avoiding in-person visits for those who are not eligible for the trial. However, this adaptation is only likely to be cost saving when a high number of participants are screened out at the remote screening stage (e.g., trials that recruit from social media platforms where a high number of individuals are likely to be ineligible). This adaptation may require significant resources at CTUs, and therefore, this adaptation may only be applicable to smaller studies. It may be infeasible for CTUs to undertake this adaptation where they do not have the necessary approvals to hold patient identifiable data or where clinical staff are required to conduct these assessments.

Recruitment from outside the NHS via a charity (*where charities are used to identify potential participants*) avoids the need for NHS sites to directly approach participants, and therefore may save the NHS time and resources. The use of this adaptation is dependent on a large disease specific charity existing. However, as described above, there were concerns that solely using this adaptation to recruit participants may alter the sampling frame of the trial.

Remote consent (*where consent is gained remotely, either via telephone or online*) may directly improve recruitment rates by making the recruitment process more flexible for potential trial participants. This therefore may reduce the recruitment period of the trial, thus reducing costs, although there is insufficient evidence to demonstrate this association. Online consent may be challenging for both participants and CTUs – both sets of individuals may have limited access to this technology; Telephone consent may therefore be preferable.

In the literature, remote consent is well represented, with four recent systematic reviews on this subject [2–5]. Remote consent was found to be acceptable to participants, however, some participants may prefer paper consent methods due to issues around trust, confidentiality, and lack of access to digital technologies [2,4,5].

4.1.1.2. Adaptations that benefit participants and may indirectly reduce the cost of the trial

Other adaptations were unlikely to directly reduce the cost of future trials (i.e., they did not directly save the trial sites or CTU time) but benefitted trial participants by making the trial less onerous, by reducing the need for in-person visits. This may indirectly reduce trial costs by making the trial more appealing to participants, therefore reducing recruitment and attrition rates. The adaptations that may indirectly benefit the trial were: **couriering of the investigational medicinal product (IMP) to the participant's home** (*where the study drug is sent to the participant, rather than having to attend a pharmacy*) and **remote collection of outcome measures** (*telephone or postal collection of PROMs, and remote collection of biological measures - blood pressures and a measure of blood glucose*).

Adaptations related to remote collection of outcome assessment

A barrier to the implementation of adaptations related to outcome assessment is the potential for bias. Undertaking an adaptation alongside the 'traditional' data collection procedure may cause two distinct populations to be formed, for instance where participants systematically undertake the outcome assessment procedure differently at home. This may be particularly true for the **remote**

collection of blood pressures, where participants at home may select the 'best' reading to report, or may be more relaxed in their home environment, thus creating a different measure to those whose blood pressure in measured in clinic. The **remote collection of PROMs** may not have been validated for specific measures, potentially eliciting different responses to the questions to those individuals who complete the measure in clinic.

It may be preferable to collect **PROMs** over the telephone, due to potentially reduced levels of missing data (compared to postal) and better access to this technology for both participants and CTUs (compared to online). However, telephone data collection may be unsuitable for long, sensitive, complex, or repetitive questionnaires, and requires significant CTU resources to follow-up participants out of hours and to administer reminders.

The literature reports differences in values reported by participants in questionnaires administered using different mediums, including those relating to quality of life and disease specific measures (e.g., in chronic obstructive pulmonary disease), when comparing telephone to mail, or paper to electronic versions, thus limiting the ability of study teams to allow participants flexibility [6,7].

The use of online data collection techniques was underrepresented in our sample, and the two trials that did use this adaptation did not use it extensively. However, there is extensive literature on the use of this medium - high response rates were identified when compared to other mediums (email, telephone or mail follow-up) and when tested alone [8–11]. In two studies, online data collection was also deemed to be the most acceptable to participants [11,12].

The **remote collection of blood glucose levels** may be less prone to bias and could be used to collect this outcome from those individuals who may find it difficult to attend a hospital. However, the process of sending and receiving the kits was time consuming for the CTU, and there may be barriers to vulnerable or unwell participants returning samples, e.g., accessing a post box.

Couriering of the IMP to the participant's home

Couriering the IMP to the participant's home may require extensive resources to create standard operating procedures (SOPs) and to administrate and manage the process. Concerns around the effect of this adaptation on the scientific integrity of the trial, 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) may mean that this adaptation may not be applicable to all trials involving an IMP.

4.1.1.3. Inefficient adaptations and those that are only applicable to the pandemic

Three adaptations were only applicable during the pandemic and were perceived to be unlikely to be used outside of this context – these are: **prioritisation in-person visits** (*where the trial team contact the participant prior to a scheduled in-person visit to ascertain the safety or necessity of undertaking the assessment),* **prioritisation of trial outcomes** (*where the need to collect trial outcomes is reviewed for the entire trial*) and **remote delivery of the intervention by CTU staff** *(where CTU remotely deliver the trial intervention, instead of site-based NHS staff).*

The use of **postal consent processes** (*where consent for participation in the trial is obtained through the participant sending the consent form via the postal service)* was considered inefficient by one interviewee, mainly due to the time it took to administer and receive participant responses.

4.1.1.4. Adaptations where the effect on efficiency is unknown

Some adaptations were not used extensively in the trials, had not yet been implemented, or were not discussed by the interviewees in detail, so their potential to improve efficiency was not possible to assess. These were:

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

These are promising adaptations that may have the potential to improve trial efficiency (see *Table 3* for more information).

4.2. General considerations

Limitations to the CTU's role

There are limitations to the activities that CTUs can undertake. CTUs may be unable to receive identifiable data from NHS sites, which may limit their ability to undertake certain adaptations. Regulations around the governance of clinical trials of investigational medicinal products (CTIMPs) may mean that only suitably qualified clinical staff are able to undertake certain trial procedures, including eligibility assessment and consent. In addition, the CTU may not have access to the technology (e.g., online platforms to facilitate online consent and data collection) in order to enable an adaptation to be successfully implemented.

Consider the needs and preferences of trial participants

The needs of the trial population were perceived to be an important factor, with the ability of participants to access and use technology particularly important. In some trials involving online interventions, an adaptation that involves technology that discourages participants from taking part may be acceptable. In other trials, this may drastically change (or skew) the sampling frame of the trial.

The needs of the participant should also be considered – including the need to form a relationship with the researchers, and preferences for being seen in person by a clinician, which may be especially important for chronic and life-limiting conditions.

Seek stakeholder involvement, but be aware of gatekeepers

Stakeholder involvement is important in the development of trial adaptations. Researchers may consider asking trial sites their opinion of the adaptation – this can be undertaken by either asking an individual site or surveying multiple sites. PPI representatives could also be consulted.

However, certain stakeholders may act as gatekeepers to using the adaptation in the patient population. Trial Sponsors may have differing levels of risk aversion and may struggle to support novel methods of undertaking trial procedures. NHS site staff may believe that a certain adaptation is not appropriate for a certain population.

Regulatory considerations

Those interviewed were sometimes surprised that a novel adaptation potentially seen as inferior to the previous way of undertaking a procedure was approved by the regulatory bodies (e.g., HRA, NHS REC). This was discussed for one adaptation, where the need for participants to sign a consent form was dispensed with and instead an independent witness at the site signed the form on their behalf.

Provide support and reminders to participants

Many adaptations involved the trial participant undertaking activities that would have previously been closely managed or undertaken by the trial site or CTU – e.g., taking of blood pressures, completion and return of a consent form. Across the different adaptations, participants often required reminders in order to complete a specific task. Support was often required, either in preparation for a certain activity (i.e., training) or ongoing support during an activity, in order to assist the participant in completing the trial task. This additional support may cancel out the efficiency savings in some circumstances.

Consider other benefits to making an adaptation

There are various other benefits to the identified adaptations that are not related to cost or efficiency gains. Adaptations to the consent process may improve the 'quality' of informed consent by starting conversations regarding the trial at an earlier time-point, therefore providing the participant with more time to consider the trial. Entry of data directly onto the trial database during telephone follow-ups was reported as being more accurate, resulting in less data queries and missing data, compared to returning questionnaires via the post or electronically. Collection of spirometry data, which was automatically uploaded to the database, allowed extra secondary outcomes to be collected. Many adaptations were described as improving the ability of participants to undertake trial procedures flexibly, potentially increasing the representation of underserved populations by improving access to trial procedures.

5. Discussion

5.1. 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 were thought to directly reducie 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.

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, in-person, 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.

5.2. Comparison to existing literature

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 [2–5], so could be incorporated into future studies. However, participants may prefer paper consent due to concerns around trust and data security – participants may need to be reassured regarding this [4,5]. The centralisation of research procedures, and the remote delivery of consent, may negatively affect consent rates by limiting the use of research champions, which has been found to be important in previous studies [3–5,13]. Previous literature provides some recommendations not identified in this study - including the clinician or researcher being present to answer questions [3–5] and using interactive features to aid comprehension [5]. These may have not been identified in this study due to the nature of the pandemic meaning that a researcher could not be present during recruitment, and the speed at which adaptations needed to be made meaning that there was not time to add interactive features.

There was a general view expressed in this study 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 [6,7], including differences in responses when comparing telephone to mail, or paper to electronic versions [6,7]. 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 [14].

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 [11,12]. 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.

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.

5.3. 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 moderate response rate, with 23 of 53 CTUs (43%) reporting adaptations which they considered could be used as 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 online systems 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.

5.4. Implications & future research

Implications

Clinical trials have previously been slow to implement new technologies, possibly due to concerns around confidentiality, data accuracy, and poor infrastructure [15]. However, prior to the pandemic, many clinical trials had already adapted their trials so that they were partially, or completely, undertaken remotely [16,17]. 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 may be implemented in specific circumstances, and understand the 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 may therefore consider trying to allow participants such flexibility. However, concerns around the effect of the adaptations on the scientific integrity of the trial, 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, 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 NHS trial sites is unknown. Future research should concentrate on the adaptations we identified in this study as having an unknown impact on trial efficiencies, including delivery of interventions by interventionists at any NHS Trust and the remote collection of spirometry and cough data.
- The impact of the adaptations on key variables should 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 [18,19]. 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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