831458 – Trials@Home

Centre of Excellence – Remote Decentralised Clinical Trials

WP1 – BEST

D1.1 First set of recommendations for RDCTs (to be implemented in the pan-EU pilot RDCT)

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Document History

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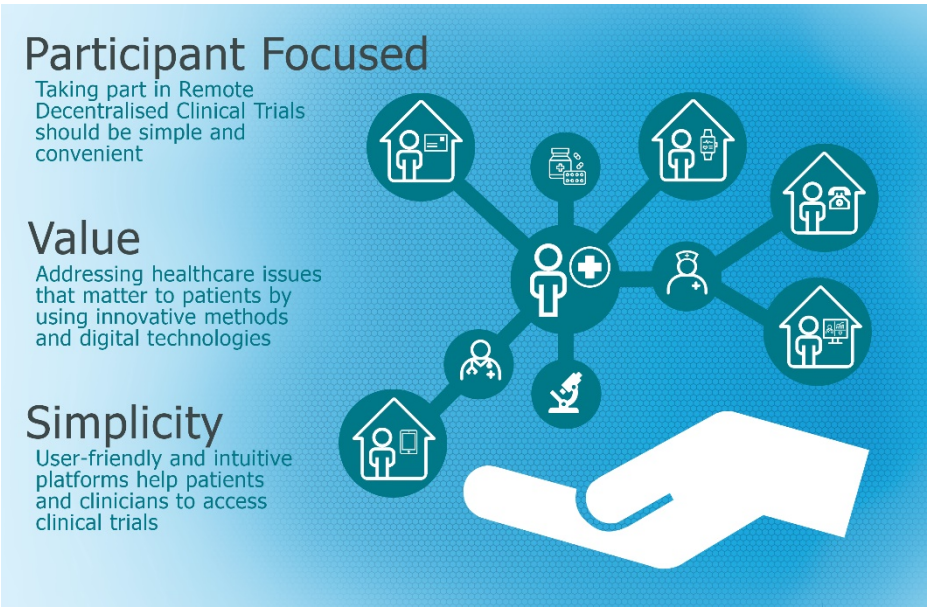
The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking (H2020-JTI-IMI2) Trials@Home grant n° 831458.

Lay Summary

Clinical trials are a crucial step in the development and testing of medical treatments. They are essential to ensure that new treatments are safe and effective.

Traditionally, clinical trials have taken place in hospitals or other research sites, often requiring participants to attend several face-to-face study visits. While these trials produce results, they can do so at a great burden to participants and risk excluding people who are unable or unwilling to travel to study visits.

Remote decentralised clinical trials (RDCTs) are one way to make trials more accessible. RDCTs are centred around participants. Using technology can allow people to take part in clinical trials in their own home with no need to travel to attend study visits or to take substantial time off work or away from family. RDCTs have the potential to make taking part in a clinical trial simple and convenient.



These draft recommendations are based on in-depth research, conducted over a 12-month period, into remote decentralised clinical trial methods. They apply to all aspects of RDCTs from design, planning and set-up to close-out and reporting.

3 Key Recommendations

1. Answer an important research question
2. Keep the focus on participants
3. Simplify the participant experience whilst maintaining quality and scientific rigour

Full recommendations will be published at the end of the IMI Trials@Home project in 2024.

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Executive Summary

Remote Decentralised Clinical Trials (RDCTs) are an innovation in clinical trials that combine technological solutions and user-centred design to improve accessibility for participants. By moving trial activities nearer to the participant and allowing individuals more choice in how to participate, they offer the promise of improved recruitment and retention, better engagement and superior generalisability of results when compared to more conventional, or traditional, site-based clinical trials.

The Trials@Home consortium of public and private partners is exploring the opportunities and benefits of RDCTs, as well as the challenges and solutions. By working together to share knowledge and experience we aim to improve the understanding and delivery of RDCTs across Europe and worldwide. One year after the start of the five-year Trials@Home project, we publish our preliminary recommendations for RDCTs in Europe. The final Trials@Home recommendations for RDCTs will be published in 2024 based upon project activities exploring the methodological, technical, ethical, legal, regulatory, and practical aspects of implementing RDCTs.

It is important to note that RDCTs are not separate from clinical trials and should instead be considered a further development of trial methods incorporating new tools. For this reason, the recommendations within this document are applicable, to an extent, to all clinical trials. We highlight throughout why the recommendations have particular importance to RDCTs.

This first report on best practices in RDCTs contains three key recommendations. Firstly, as with all clinical research, it is vital to start with an important research question of value to participants and public health. Secondly, keeping the focus on participants when making decisions about trial design and conduct is essential to fostering meaningful engagement outside of traditional research or healthcare settings. Thirdly, the expertise and experience of clinical trial teams should be directed towards simplifying the participant experience in RDCTs whilst maintaining quality and scientific rigour. In support of these key recommendations we also advise that investigators and sponsors embarking on RDCTs do the following: involve other stakeholders early, share knowledge and experience gained with others in the clinical trials field, and continue to research ways to improve remote decentralised clinical trial methods.

These preliminary recommendations are the result of extensive evidence gathering over the last 12 months aimed at establishing current best practices and summarising existing knowledge on RDCTs. The research methods used include detailed study of selected illustrative case studies of clinical trials using remote methods from within the Trials@Home consortium and beyond. These have included in-depth interviews with key

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personnel and other stakeholders including patient representatives. An extensive systematic literature review has also been conducted to identify ongoing and completed clinical trials using remote methods as well as to summarise the current state of the RDCT landscape. The academic research underpinning these recommendations will be published in due course.

RDCTs are an exciting field with enormous potential to improve participant experience and efficiency in clinical trials. Full realisation of this potential will be dependent upon sharing knowledge and experience gained from RDCTs so that processes can be continually improved, keeping quality, safety, privacy, and participant experience at the forefront.

These recommendations reflect current best practice in RDCTs and should act as a springboard for future development in this area.

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Contents

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Methods

These recommendations are primarily based on two scientific research studies: a systematic review and a qualitative analysis of selected case studies. The research methods used to generate these draft recommendations for best practice in RDCTs are described in more detail in Appendix B. The full results of these research activities will be published in peer-reviewed journals in due course.

The systematic review includes published literature on clinical trials, and other clinical research, conducted using remote and/or decentralised methods. It should be noted that these results will likely be subject to publication bias as investigators and sponsors are less likely to publish on trials that have not completed or met their objectives. In-depth interviews with clinical trial staff and other stakeholders, including patient representatives, have contributed to a greater understanding of the practical advantages and challenges of RDCT methods. The recommendations also take into account existing applicable guidelines and developments in the wider clinical trials landscape including Quality by Design[1] and ICH E8 General considerations for clinical studies[2].

The recommendations are intended to enable everyone involved in designing, planning and managing clinical trials to make decisions that will maximise the chances of benefitting from the advantages associated with using RDCT methodologies, to the ultimate benefit of patients and the public.

Notes on terminology

RDCTs are an emerging field in clinical trials. There are many terms currently in use to describe identical, or very similar, concepts and activities. Throughout this document, we use terms that have been agreed and defined by the Trials@Home project. The glossary for the Trials@Home project is published and can be found here: https://trialsathome.com/trialshome-glossary/

For example:
RDCTs themselves have been described using many synonyms including virtual trials, online trials, digital trials, direct-to-patient trials. The following is the definition currently used in the Trials@Home Project:

Definition: Remote Decentralised Clinical Trials (RDCTs) are trials that make use of digital innovations and other novel methods to make them more accessible to participants. By moving clinical trial activities to the participant's home or to other local settings this minimises or eliminates physical visits to a clinical trial centre.

[1] https://www.ctti-clinicaltrials.org/projects/quality-design
[2] https://www.ema.europa.eu/en/ich-e8-general-considerations-clinical-studies

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An Introduction to Remote Decentralised Clinical Trials (RDCTs)

Remote decentralised clinical trials, i.e. those that involve no or minimal clinical site-based interaction with participants have been suggested as a way to improve clinical trials for participants, investigators, and other stakeholders. Potential advantages of RDCT approaches are listed in Figure 1 below.

Figure 1. Potential advantages of RDCT approaches

Trials using remote methods have been conducted since the 1980s when several large long-term postal trials of medicines and supplements started.[1–3] These streamlined mail-based studies were accomplished without most of the modern digital technologies available to clinical trials today. The lessons learned from these early mail-based studies, and the internet-enabled trials that have come along since, can and should be applied in the digital age moving forward.

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A Framework Approach to RDCTs

While it may be tempting to categorise trials as conventional or remote, it is more helpful to think of a spectrum of remoteness. Most modern clinical trials already lie somewhere to the right of a conventional face-to-face clinical trial by incorporating digital technologies in some way e.g. using social media for recruitment, using a web-portal to collect and manage data, or collecting eDiary data from participants. Figure 2 illustrates examples of how differing degrees of remoteness can be achieved by combinations of methods.

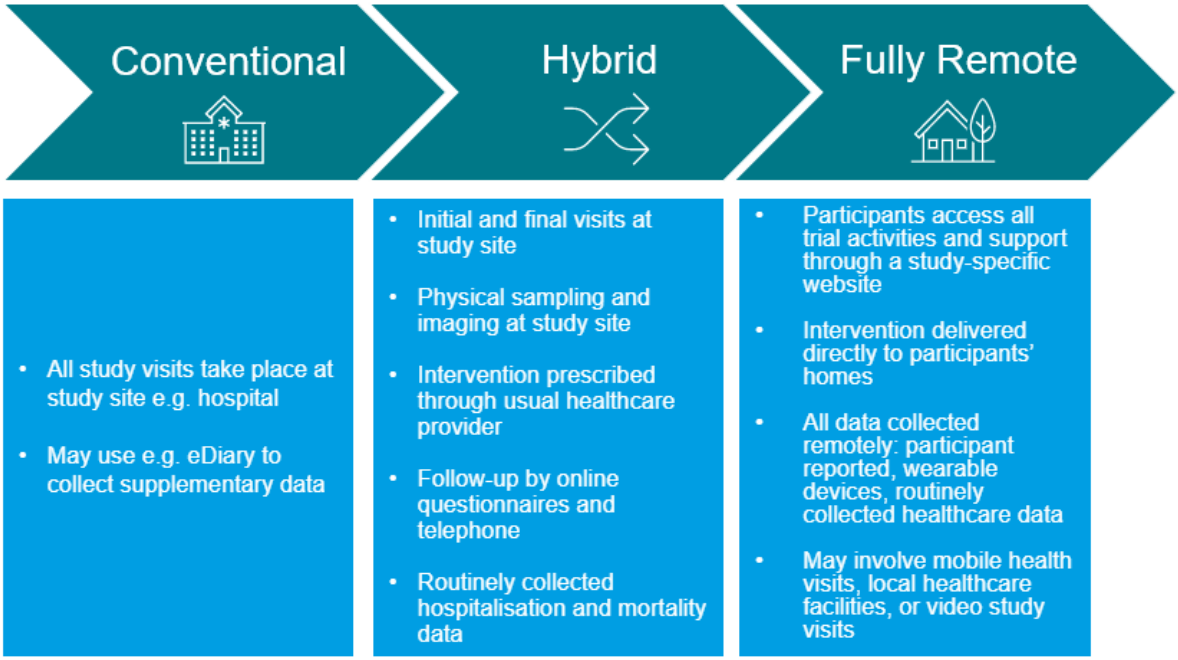

Figure 2. Examples to illustrate degrees of remoteness in clinical trials

In addition to remoteness, an important feature of RDCTs is their potential for a high level of focus on participants' needs and wishes. Again, this is not a binary categorisation; conventional trials may have high degrees of participant involvement (e.g. co-production) and adjustable visit schedules whereas a fully remote trial may be entirely protocol driven with minimal participant-centred flexibility. However, the methods used in RDCTs do lend themselves to participant-centric trial design.

It is important to recognise that RDCTs are diverse and no single model will be suitable to answer every clinical question. Remote decentralised clinical trial methods are a collection of tools that can be used when planning and conducting a clinical trial. Decisions about which, if any, of these tools to deploy at each stage of trial activity should be determined by the needs of the research question and participant population and not simply by a desire to use remote methods. Trials@Home Deliverable "D1.2 Criteria for selection of appropriate trials" accompanies these recommendations and is intended to support such decision making.

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The Basic Building Block approach

Clinical trials are complex projects with many different stages involving various stakeholders. The Trials@Home project uses a *basic building block* approach to facilitate thinking about the many different stages involved in planning and conducting a remote decentralised clinical trial. This is summarised in Figure 3.

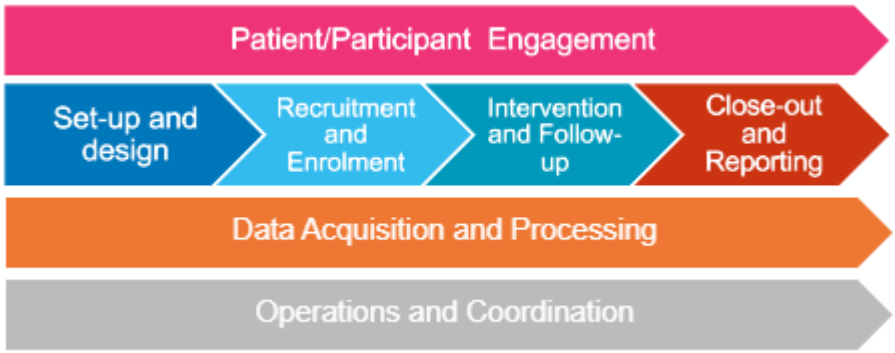

Figure 3. Summary of high-level basic building blocks of clinical trials

Each building block can be further broken down into specific trial activities. Each individual trial activity is an opportunity to select the best method for the trial and participants in question. The most remote or technically advanced method may not always be feasible or acceptable to participants and other stakeholders.

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The Recommendations

Each recommendation is presented as a general principle followed by explanation and guidance on how it can be applied. Examples of experiences from previous clinical trials and excerpts from interviews are included as illustrations.
There are 3 key recommendations (1-3) and 3 supporting recommendations (4-6):

Key Recommendations

1. Answer an important research question
2. Keep participants at the centre
3. Simplify the participant experience whilst maintaining quality and scientific rigour

Supporting Recommendations

4. Involve stakeholders early
5. Share knowledge and experiences
6. Research implementation and improvement of remote decentralised clinical trial methods

For readers wishing to refer to the Trials@Home basic building blocks, the following key applies. A matrix of recommendation applicability can also be found in Appendix D.

High-level basic building block	Symbol
Set-up and Design	SD
Recruitment and Enrolment	RE
Intervention and Follow-up	IF
Data Acquisition and Processing	DP
Close-out and Reporting	CR
Patient/Participant Engagement	PE
Operations and Coordination	OC

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1. Answer an important research question

SD RE IF DP PE

Start with a clear research question SD

As with all clinical research, RDCTs should be designed to answer a clear and important research question. This is essential in planning an RDCT as the research question will determine which methods can and should be used.

While methodological questions are important to the research community, completely new trial methods or operations may be best appraised by feasibility testing or as sub-studies within a larger clinically relevant trial. This investment in testing can enable a wider implementation and smoother roll-out of innovative methods without risking an early trial termination. Similarly, decisions to incorporate new technologies should be driven by the research question and tested appropriately.

Research questions should lead to the decision of the type of remote methods that could be used for the trial, not the other way around. RDCTs methods lend themselves to late phase trials and pragmatic trial approaches but their use should not be ruled out in earlier phase, or more explanatory, trials, should they be appropriate to the research question.[4, 5]

The PICO mnemonic, often used in evidence-based medicine, can be a helpful way to structure a research question.[6] The following table below uses PICO to prompt consideration of whether RDCT methods might be applied to a given research question.

		Factors to consider when designing RDCTs
P	Patient, Problem or Population	An RDCT approach may suit the target population better than conventional methods e.g. People with restricted mobility or fatigue may prefer to take part in a home-based trial. People who work or have other commitments may find it easier to participate in a remote trial. RDCTs may make it easier for parents and other caregivers to assist children, elderly or other participants with added support needs. A remote method may allow recruitment from a much wider geographical area; this could be invaluable in rare diseases. Is the target participant group likely to have specific features or difficulties that might affect their interaction with planned trial

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		activities? e.g. People with severe hand arthritis may have difficulty using home sampling kits. Cultural factors and local healthcare provision may also affect preferences for remote vs. conventional site-based approaches.
I	Intervention	Are there special considerations about the planned intervention and comparator(s) that may make remote trial delivery more challenging, or can these challenges be overcome? e.g. temperature storage requirements, parenteral administration, need for close monitoring for safety purposes
C	Comparison, control, or comparator	
O	Outcome(s)	Can the proposed outcome be reliably measured using remote methods? e.g. Participant reported outcome measures lend themselves to remote capture. Complex imaging-derived endpoints may require a hybrid trial approach. Could new technologies capture richer data? Wearable devices can provide continuous longitudinal data that could allow new insights into chronic health conditions and enrich more traditional data.

Table 1 The PICO framework with examples of how it can be used to assess the suitability of an RDCT approach

The chosen intervention and outcome will determine whether remote methods can be used and how they can be implemented. Table 1 in Appendix A summarises remote methods that have been effectively used in clinical trials. We have not provided a similar list of remote methods that have been perceived to be unsuccessful as our research has found that, where available, reasons for failure were often related to overall study design and management decisions rather than the specific methods themselves.

Choose a research question that is important to participants SD● RE● PE●

The importance of a research question and the potential to produce benefit for participants are often cited as reasons for taking part in clinical research. Choosing a research question that is perceived as important should, therefore, improve recruitment. For example, in a trial of prevention of progression of diabetic retinopathy, participants reported that the clear research question, addressing a topic of high importance to people with diabetes (their vision) motivated them to take part (source: case study).

Priority setting partnership initiatives, such as the James Lind Alliance (https://www.jla.nihr.ac.uk/), have been set up to bring patients, carers and clinicians together to identify and prioritise research questions.

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In all clinical research it is important to be transparent with participants about the reasons for the research. In the case of pivotal, or marketing authorisation trials, this may require explaining the medicines licensing process, as well as the research question, to prospective participants. Similarly, the reasons for post-marketing pharmacovigilance trials, and trials to support reimbursement decisions, should be clearly explained to potential participants.

Involve clinicians and other stakeholders e.g. policymakers in choosing and refining the research question. SD●
A well-chosen and clearly defined research question will result in evidence that is useful and important to the people who will implement it. Early involvement of stakeholders may also facilitate dissemination of results.

Consider how the study will integrate with other planned and ongoing research. Remote methods can be ideal to complement more conventional drug development. For example, the efficiency of remote methods can facilitate large-scale post-licensing safety studies or long-term follow-up studies to collect clinical outcomes after conditional approvals based on surrogate biomarkers.

Seek statistical and design advice SD● IF● DP●
Data collected using digital technologies may be more reliable than traditional transcribed data sources but there are valid concerns regarding the validity of unsupervised data collection and entry by participants. Specialist statistical or methodological advice will be necessary to ensure that the study outputs are valid and reliable. Remote study designs may require sample size inflation to account for missing data, data variability and higher participant attrition[7]. Statistical input will be particularly important when planning a study using large longitudinal datasets or continuous data, as may be collected using wearable devices.

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2. Keep the focus on participants

SD RE IF DP PE CR OC

Participant engagement is arguably even more important in RDCTs than in conventional trials. This is because the remote nature of these trials and the lack of in person study visits means that they rely heavily on participant understanding and active participation.

"They [patients] began their involvement early and did a protocol design, making sure that it was a question that was important to the community of patients, making sure that the design was one that would be engaging for patients."
Case study interviewee, Project Leader

Involve patients and the public in choosing the research question SD PE

Engaging with existing patient support groups e.g. chronic disease-specific groups or service user groups is a good way to ensure that the proposed research question is important to patients as well as clinicians and researchers. The choice of which patient or public group(s) to approach should be determined by the research question and therapeutic area. For example, a trial aiming to recruit people with a long-term condition may choose to involve a disease-specific support or advocacy group to ensure that the research question addresses their needs. Whereas, a vaccine study may aim to involve members of the wider public to ensure legitimacy and to support applications for funding and ethical approval. Public or patient groups who have been involved in choosing and defining the research question may also be willing to assist in recruitment.

Communicate clearly RE IF CR PE

Clear messaging about the purpose of the trial can assist in effective trial recruitment by enabling participants to adopt the aims of a trial as their own. In a trial without face-to-face contact with study staff it is essential that recruitment materials clearly highlight the importance of the research question and what the trial involves to potential participants. Clear communication is also vital for maintaining retention and protocol adherence where fewer or no in-person study visits are taking place to reinforce these.

Involve patients/potential participants in study design early SD PE

Patient input into study design can ensure that proposed methods and activities will be acceptable to potential participants. Care should be taken to ensure processes are in place to integrate such input and avoid tokenism. Patients should be involved as early as possible to avoid useful ideas being "too late" for incorporation. For example, a large US study of aspirin for cardiovascular disease prevention found patient involvement invaluable but the team was unable to act upon all their recommendations due to approvals having already been granted.[8]

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Involve patients and/or the public in the design of recruitment materials and strategies RE PE

Studies that have involved patient and public participation (PPI) groups in planning recruitment have reported fast recruitment and more engaged participants.

"Our patient partners were also really critical in the design of the recruitment materials. So again you think a lot of recruitment materials there's a lot of language…they felt that if we were going to be approaching patients remotely…we really had to let a patient know very quickly this is a clinical study, this is the goal of the clinical study and who we are looking to enrol… They also wrote letters about their personal journey and many of the sites included the personalised letters with their recruitment material. I think it helps you humanise what we were doing."

Case study interviewee, Project Leader

Present a streamlined approach to potential participants RE IF PE

Keeping a trial simple for participants may mean accepting some additional complexity behind the scenes. Similarly, programming of user-friendly software may be more complex but can improve the participant experience, improving study participation and retention. For example, routinely collected data can be used to prepopulate research databases to minimise baseline data entry by participants. Participant-facing web portals should be user-friendly and user-tested.

For example, a trial of asthma medications in adolescents used patient involvement and extensive user testing to design a multimedia information and consent website.[9, 10]

Minimise requirements for participant data entry SD RE IF DP PE

Each piece of data or supporting documentation that a participant must supply increases the burden of enrolment and increases the possibility of losing engagement early. Consider alternative sources of information or whether it is needed at all. For example, a multi-step screening process requiring participant data entry is thought to have been a major factor contributing to early drop-out from a web-based trial of a medication for overactive bladder.[11]

Use familiar technologies SD RE IF DP PE

Many people are already familiar with some technologies such as electronic health record patient portals, telehealth, disease-specific self-management websites and apps, widely used videoconferencing and messaging services. Consider the proposed trial population; factors such as age, employment experience, geography and local amenities may influence how familiar prospective participants are with technologies. These patterns of familiarity may change over time and should be reassessed regularly. Use of familiar technologies and devices already used in daily living or routine healthcare (e.g. in a bring-your-own-device (BYOD) model) will ease participant engagement. Where participants

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do not already own suitable devices, or where they are shared with other members of the household, a study supplied device with appropriate support/training may be preferred.

For example, a trial of blood pressure lowering in people with diagnosed hypertension has used participants' own blood pressure monitors.[12] A US-based trial of breast screening encourages participants to register on a local app that facilitates access to medical records for the trial but also for ongoing personal use.[13]

Despite evidence that commercially available consumer health devices, such as smart watches with heart rate measurement, can be as accurate as those used in conventional site-based trials, bring-your-own-device data collection has been limited by a lack of standardised data outputs across manufacturers.[14, 15] This reduces the utility of such approaches for trials in support of marketing authorisation applications. Future developments in data standardisation and regulatory standards may facilitate wider use of this cost-effective approach.[16]

Provide useful information for participants, clinicians, and caregivers SD● DP● CR● PE●

RDCTs can facilitate the provision of useful health information to participants and their usual healthcare providers and caregivers. For example, feeding back home blood pressure measurements to participants can enable ongoing self-management and facilitate future management decisions.[12]

"That study was not well organised…. One never got information back from it. One would go to the hospital… every time you had your blood taken and weight and all kinds of stuff. You spent a lot of time there. But you never got any kind of results, any kind of inkling…You never got anything at all at the end of it, and that I thought, was pretty bad." Case study interviewee, Patient Representative (talking about previous experience of participating in a non-remote clinical trial)

Data visualisations and intuitive interfaces can be used to present information to participants in a user-friendly way. Investigators should be aware that some types of sharing of data with participants may risk biasing results. However, this should not prevent sharing of general study information (e.g. in the form of newsletters) or providing clinically useful data at the end of a study.

Provide support to participants SD● RE● IF● PE● OC●

Remote set-up of technologies with participants who may not be confident in their use is challenging. Dedicate sufficient resources to participant support for this process. Consider including initial study site or home visits for set-up and training. For example, a study where data were collected using multiple devices found that participants who were randomly assigned to a study site visit for device set-up were far less likely to drop out of

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the study early.[17] Pre-randomisation run-in periods can be a useful opportunity to provide a supported introduction to remote trial methods.

"I think we struggled a little bit with who the right person was to do that home visit and we had hired home nurses…. We probably needed a Geek Squad, there's a company in the US if you buy a computer they'll come to your house and they'll hook up your computer and get you on your Wi-Fi and basically teach you how to use your computer…We had the wrong skillset…We needed tech trainers and cheerleaders to help the study participants to feel comfortable. So that was a good learning."
Case study interviewee, Vendor

Several studies have reported that participants have benefited from accessible contact with study staff by email, telephone, or video-call. Peer-support has also been used successfully.[8] Study coordinators may require specific training to deliver these non-traditional roles.

"The lack of feedback. If my response had been given in person or over the phone, there would probably have been some chat about how the survey was going. Because of the lack of this, I never really felt part of the research"
Participant in an online trial of stretching to prevent exercise-associated injury.[18]

Consider alternatives for participants with differing needs SD RE IF PE
Consider the needs of participants who may not have access to their own technological devices or reliable internet connectivity. For example, one study supplied mobile hotspots to participants whose home did not have suitable Wi-Fi and to those who needed to travel during the study period.[10] Participants' own home environments may also influence their ability to take part in a remote study. For example, home blood testing or online cognitive testing will require participants to have undisturbed time and space to complete study procedures. Study information should highlight these considerations to potential participants.

"The concentration is going to be very important. And the concentration can be affected by the environment… I think the role of patients and people like me, is to try and think of all these other issues such as which room do you do your RCT in? Your kitchen? Your bathroom? Your bedroom? Somewhere else? Where do you keep either the tools or devices, or the medicine?"
Case study interviewee, Patient Representative

Some studies have offered telephone participation to participants unwilling or unable to use the standard online methods.[19] This flexibility may allow wider study participation but must be balanced against potential bias introduced by differential uptake of alternative models of participation.

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Try to mimic usual life activities SD IF PE

As much as possible within the constraints of the research question, interventions and data collection should be implemented as they would be in usual practice. Participants are likely to be more at ease with receiving interventions in this way, reducing the cognitive burden of participation. Embedding trial activities in usual care is one pragmatic way to achieve this.[20] Another option is to use measurement protocols that are already familiar to patients from their clinical care such as home blood pressure or peak flow rate measurement.[10, 21] Where local healthcare services have adopted telehealth, this presents an opportunity to use the same technology in trials and avoid imposing new hardware and software on patients and clinicians.

Consideration should be made as to the best mode of participant follow-up. This should be informed by participant needs and preferences, data requirements and availability of local study staff and premises. Table 3 in Appendix A gives examples of digital technologies that have been used to facilitate remote follow-up and lists some key advantages and disadvantages of each.

Occasionally, it may be necessary to bring a participant to a healthcare or research setting for a face-to-face visit, for example to obtain physical samples or imaging. Ideally these will take place in a familiar location near to a participant's home. For example, a trial of osteoporosis treatment used mobile imaging that could be delivered remotely in local healthcare settings.[22] A trial assessing whether a gout medication improves cardiovascular outcomes in people with heart disease used study nurse visits at participants' usual local healthcare centres to take safety blood samples.[23]

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3. Simplify the participant experience whilst maintaining quality and scientific rigour

SD RE IF DP CR PE OC

RDCTs have a greater chance of success when presenting participants with a simple trial experience. A streamlined approach is also preferable for sites and sponsors.

"There is a temptation with increasing technology to increase complexity. That would be a huge mistake. Keep it simple. Get the basics right. Then add if you need to."
Case study interviewee, Project Lead

Modern clinical trials using conventional methods have developed into complex networks of processes and paperwork. RDCTs offer an opportunity to consider what is essential for a successful trial and to dispense with activities and processes that do not address the core clinical questions (e.g. safety, effectiveness) or add value. For example, money saved by reducing or eliminating in-person study site visits could be used to pay for additional participant support resources or devices for passive data collection.

Use tested and validated technologies SD RE IF DP PE OC
In this period of rapid technological development, it is tempting to employ new software and hardware in the hope of improving trials. Experience has shown that this approach presents risks to the successful completion of a trial.

"It would encounter an error at every juncture and oftentimes the cause of these errors just weren't apparent …little failures where either the data wouldn't transfer, a menu wasn't accessible… When you're dealing with the patient's and investigator's tolerance for having these types of errors… it was death by a thousand papercuts"
Case study interviewee, Operations Manager

If the proposed technologies have not been used successfully in the same context for previous clinical trials or health care settings, feasibility testing with patient groups and study staff is vital. In studies where a vendor is being used to provide some remote capabilities, it is preferable to use vendors with experience of clinical trials unless extensive feasibility testing is planned. Testing should include endpoint validation, data flow feasibility, technology usability and reliability, and assessment of user support needs. A plan for systems and escalation procedures to satisfy Good Clinical Practice should be put in place when contracting with vendors.

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"The lack of knowledge that they had of clinical trials itself was a problem because we felt we would tell them one thing and that they understood exactly what we were asking them to do but until later some of these things didn't become apparent."

Case study interviewee, Operations Manager

Aim for seamless integration of technological platforms SD IF DP

When using multiple devices and software solutions, test before deployment, involving vendors, where necessary, to achieve seamless integration. Minimise the number of steps required for participants and study staff to register, login and accomplish tasks. The development and adoption of standardised digital health data structures should be encouraged to facilitate this. As with all data concerning identifiable persons, all data collection, transfer, storage, and handling processes must satisfy local applicable legislation e.g. General Data Protection Regulation (GDPR) in the EU or the Health Insurance Portability and Accountability Act (HIPAA) in the US. Trials operating across international borders should anticipate the need to comply with differing national requirements. Technical platforms used in trials to support applications for marketing authorisation will be required to comply with additional local regulations such as EU Good Manufacturing Practice (GMP) Annex 11 or US Food and Drug Administration Code of Federal Regulations (CFR) 21 part 11.

Plan for ongoing technical support SD IF CR PE OC

In long-term studies, ongoing technical support will be required and should be planned for. Non-technical staff, as well as participants, can benefit from step-by-step instructions on using any unfamiliar software or devices. Any such documentation and support should be made available in local languages for multinational trials. The US Clinical Trials Transformation Initiative[3] found that patients preferred technical support to be provided directly by study sites over other support providers.

Studies have reported a need to plan for the following technology issues:

- Ongoing technical support for participants, especially if there are long intervals between study activities
- Processes for repair or replacement of faulty, damaged, or lost hardware
- Set-up and training for new staff members
- Contingency planning in case of vendor or manufacturer withdrawing device, or device support

[3] https://www.ctti-clinicaltrials.org/

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking (H2020-JTI-IMI2) Trials@Home grant n° 831458.

Collect the minimum necessary data SD RE IF DP

It is good practice to collect only data sufficient to satisfy the needs of safety, science, and regulation. For RDCTs using digital technologies for data collection it may be tempting to collect vast amounts of data with only limited additional resources. This should be avoided as minimising unnecessary data collection facilitates a simpler trial experience for participants and allows investigators to concentrate on ensuring data quality is sufficient to answer the core research question(s).

Use existing data sources SD RE IF DP

Data collection is resource intensive. Where feasible and appropriate, using routinely collected data and other existing datasets can reduce the required activity by study staff and participants. The effort required to access, and process, routinely collected data can be traded off against simpler trial data entry and fewer study visits. International efforts to bring healthcare data into standardised formats should make this more straightforward in future.

Routinely collected data such as primary care electronic health records (EHRs), national or regional health databases and disease registries are valuable resources containing data that can be used to identify potential trial participants manually or algorithmically, minimising the amount of information that potential trial participants and their healthcare providers have to provide. Existing research databases, cohorts and biobanks can also be used to increase efficient recruitment.

Routinely collected healthcare and administrative data can also be used for follow-up, pharmacovigilance, and endpoint identification. If necessary, these data can be validated by adjudication using source data. Where routinely collected data is used to supplement trial-collected data, consideration should be given as to how to integrate the two, and how to reconcile conflicting data. For example, a hybrid post-licensing safety study of a gout medication used both participant reports and routinely collected data to ensure that significant adverse events were not missed despite infrequent study site visits. Potential cardiovascular endpoint events were independently adjudicated using source data.[24]

Table 2 in Appendix A gives examples of how various data types can require alternative approaches in RDCTs.

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4. Involve stakeholders early

SD● DP● OC●

Until RDCTs become commonplace it will remain essential to engage with stakeholders when planning a trial using non-traditional methods.

"So, the ethics committee would ask about the investigator oversight, what about this, what about that. So, it was like creating the narrative for them about what is the patient journey… What do they see? What do they click? What happens next? What does the investigator do here? The setup was a little bit complicated with the diabetes device and interfaces…so we kind of had to explain the patient journey… in a language that anybody will understand."

Case study interviewee, Project Lead

Discuss plans for RDCTs with relevant authorities SD● DP●

RDCTs may challenge current regulatory frameworks. Early discussion with stakeholders including clinical trial regulators, licensing authorities, ethics committees, and sponsors can avoid unforeseen barriers to trial completion. This is particularly important when planning to use new methods or novel endpoints. For example, where a trial uses remote monitoring of an intervention it may be necessary to delineate clearly with licensing authorities whether the remote monitoring should be considered part of the intervention.

"My advice would be to create plans around virtual trial operations, share those plans and do a risk management session. Meet with your sponsor and think about everything that could go wrong in a virtual study and have a medication[sic] *behind it."*

Case study Interviewee, Project Lead

Allow time and resources to consult relevant authorities in all planned study locations SD● OC●

Although the EU Clinical Trials Directive 2001/20/EC still applies across the EU at the time of writing (to be replaced by Regulation (EU) No 536/2014[25] when implemented) national interpretations and legislation varies across member states. *NB The Trials@Home project is mapping these variations. This will be a useful resource for trial planning that the final recommendations will refer to.*

Similar considerations will apply in non-EU states.

Table 4 in Appendix A summarises some specific issues that have been reported as requiring discussion with stakeholders with their accepted (trial-specific) solutions.

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5. Share knowledge and experiences

SD RE IF DP CR PE OC

RDCTs are an emerging and rapidly developing field. Practitioners can learn from the experiences and expertise of others by sharing methods and learning points across all trial activities. Investigators and sponsors are encouraged to publish protocols, methods papers, methods evaluations and, most importantly, all trial results. Open access publication is preferred.

Consideration should be made towards maximising the utility of trial data while protecting the interests of trial participants. Adherence to FAIR (findability, accessibility, interoperability and reusability) data principles will facilitate later data sharing and reuse.[26, 27]

RDCTs should be reported and published in accordance with applicable existing clinical trial reporting frameworks e.g. CONSORT[28] or TransCelerate's common clinical study report (CSR)[29]. Where applicable, method-specific reporting guidelines should also be adhered to, for example, the CONSORT PRO Patient-Reported Outcomes extension.[30]

As well as formal publication, increased interaction between all RDCT-interested parties should be encouraged to maximise learning and avoid repeating mistakes.

Interdisciplinary collaboration will continue to be key to combining technical expertise with clinical trial experience in industry and clinical academia.

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6. Research implementation and improvement of remote decentralised clinical trial methods

SD RE IF DP CR PE OC

There is a scarcity of evidence on how best to implement RDCTs. While our qualitative findings have highlighted successes and opportunities in RDCT methods there remains a lack of directly comparable data to support many of the claims that have been made for RDCTs in terms of reduced costs and better recruitment and engagement.

RDCTs are not a magic bullet, rather they are a set of tools that will be best deployed in the hands of skilled clinical trial teams. It is essential that the clinical trials community tests and evaluates new developments to ensure that they live up to early promises.

The academic research underpinning these recommendations will be published in peer-reviewed journals and will contribute to the ongoing development of RDCT methods. The Trials@Home project, which includes a pilot remote decentralised clinical trial, will contribute further knowledge and experience on RDCTs. The final Trials@Home RDCT Recommendations will be published in 2024. With further expected developments in technology and trials methods, we anticipate that expertise will develop significantly over the next few years.

Note on COVID-19

These draft recommendations and the research underpinning them were developed before and during the first few months of the COVID-19 pandemic. This pandemic, and the resulting restrictions on physical contact, have driven clinical trial operators and regulators to rapidly appraise and adopt more remote methods and already planned rollouts of RDCT methods have been expedited. Most ongoing clinical trials have been affected in some way but those using RDCT methods may have been less vulnerable to restrictions on face-to-face activities such as recruitment and study visits.

Time will tell what the long-term effects of this pandemic will be on the clinical trials landscape, but it seems likely that the pandemic will accelerate the adoption of RDCT methods for future trials.

The final recommendations of the Trials@Home project will include experiences and learnings from clinical trials during and following the COVID-19 pandemic.

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking (H2020-JTI-IMI2) Trials@Home grant n° 831458.

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The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking (H2020-JTI-IMI2) Trials@Home grant n° 831458.

Appendix A - Supplementary Tables

Table 1 - Remote methods that have been used in clinical trials SD●

RDCT specific intervention and follow-up challenges	**Remote methods that have been used***
Getting the intervention to the participant (medicines, devices, therapies)	Trial-specific pharmacy[24, 31], postal delivery with letterbox-safe packaging[24, 32], overnight courier with recorded delivery[33–35], temperature-controlled packaging, prescribing through usual healthcare[20, 23, 36], self-purchase by participants[19], delivery by mobile healthcare e.g. visit to participant's home by nurse or other healthcare providers[37, 38], telehealth physician/therapist-delivered intervention e.g. psychological therapy, physical therapy[39]
Supporting the administration of: Medications	Online educational videos and text instructions[9], telehealth supported administration[39], mobile health visits to administer injections/infusions[37]
Devices	Online or telephone technical support, telehealth supervision of device use[40], mobile health device set-up[17]
Assessing Compliance	Online participant self-reporting[12, 41], postal/courier return of packaging and excess medicines[24], blood or urine testing of a random sample of participants remotely or local to study centre.[42]
Safety monitoring	Blood testing by usual local healthcare provider (non-study laboratories[23] or by supply of collection kit for return to centralised research laboratory[42]), mobile healthcare visit
Pharmacovigilance requirements	Participant reported adverse events (online, telephone)[19, 43, 44], routinely collected hospitalisation and mortality data[12, 23, 24, 45], electronic health record querying[13, 19, 20].
Validating remotely obtained data	Pre-trial validation studies, adjudication of remotely identified events.[12, 23, 24, 46]

*NB citations are added for information only and are not intended as an exhaustive list of where remote approaches have been used.

Return to the recommendations

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Table 2 - Data collection options for RDCTs SD IF DP

Data Type	Conventional Approach(es)	Remote Approach(es)*
Baseline Demographics	Collected from participants during a face-to-face (F2F) visit, extracted from physical healthcare records.	Direct online data entry by participants[21, 35, 47], manual or automated data extraction from Electronic Health Record (EHR)
Baseline Past Medical History	Collected from participant during a F2F visit, extracted from physical healthcare records	Direct online data entry by participants[21, 35, 47], manual or automated data extraction from EHR
Medication History	Collected from participant during a F2F visit, extracted from physical healthcare records	Direct online data entry by participants[19, 21], manual or automated data extraction from EHR, routinely collected pharmacy dispensing records[48].
Physiological Measurements	Measured by study nurse during F2F visit	Reported manually by participant online, measurement using a participant-owned or study-provided device[17, 21], wearable or other connected devices with direct data upload[10, 17, 49, 50], guided measurement during telehealth visit[51], mobile health visit
Physical Specimens	Collected by study nurse during F2F visit	Collection by usual healthcare staff[11, 32], extraction of results from EHR, collection during mobile health visit[11, 42], testing during mobile health visit. Participant collection using a home kit for postal/courier return or manual entry of result by patient[13, 52, 53].
Assessing Compliance	Inspection of returned packaging and medicines during F2F study visit. Directly	Participant reported compliance[23, 46], postal return of unused medication [24], telehealth supported

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	administered or observed therapy at study visit.	administration[39], mobile health administration[54]
Clinician-assessed outcomes	Assessed during F2F visit	Telehealth assessment[39, 55], teledermatology (telehealth + imaging)[56], mobile health visit
Participant Reported Outcome Measures (PROM)	Questionnaires administered during F2F visit	Postal[23], telephone[23],online[12], smartphone app[10, 11, 40], elicited during telehealth visit
Imaging	Performed at study site	Extraction of images or reports from healthcare records[13], referral for imaging in usual healthcare setting[57], telehealth, mobile health, guided participant photography[53, 56].
Outcome/endpoint and pharmacovigilance event reporting	Elicited directly from participants during F2F visits, manual extraction from physical health records, reporting by study staff using faxed forms	Reported by participant by return of questionnaire, by email, telephone or online[1, 2, 10, 11, 21, 23, 24, 34, 36, 41, 42, 45, 46, 58, 59], remote access to EHR[23], routinely collected data[13, 19, 21, 60], elicited during a telehealth visit[39], or mobile health visits.

*NB citations are added for information only and are not intended as an exhaustive list of where remote approaches have been used.

Return to the recommendations

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Table 3 - Advantages and disadvantages of RDCT technologies for follow-up

SD IF DP

Technological Solution	Advantages	Disadvantages
Participant-facing web-portal	Affordable, flexible, uses familiar hardware	Excludes participants who do not have suitable IT devices and internet connectivity. Requires ongoing IT support. Privacy and security concerns (submitting personal information), clinical research software has not traditionally focused on user experience - may require additional training/personnel.
Smartphone apps	Affordable, flexible, many participants will have own device, devices can be supplied to participants, can collect geospatial data, push notifications can prompt data entry	Device cost, interoperability, IT support, internet connectivity and/or mobile network coverage issues, privacy, and security concerns (GPS, personal information)
Wearable devices	Portable, unobtrusive, can automatically collect longitudinal data and/or continuous passive data, convenient, provide feedback to participants, can collect novel biomarkers such as sleep, steps, and heart rate variability	Cost, interoperability, IT support needed for set-up and use, unfamiliar user interface, need charging, smartphone and Wi-Fi or data connectivity, comfort, compliance, stigma with people not wishing others around them to know they are participating in a trial, privacy and security concerns (GPS, personal information), regulatory acceptance of devices.
Scheduled telehealth visits	Widely used platforms for video conferencing, patients may already be familiar with telehealth, personal connection	Cost (may need to supply devices), IT support needed for set-up and troubleshooting during visits, connectivity issues, security, and privacy concerns, less convenient, variable national and local regulations, physician licensing limitations.

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Scheduled mobile health visits (home visits by health professionals)	Nursing expertise, physical sampling, and treatment administration, personal connection	Cost, scheduling may be inconvenient, geographical coverage, unfamiliar staff,

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Table 4 - Issues requiring stakeholder engagement SD● OC●

Issue	Conventional Approach(es)	RDCT solutions
Verification of participant identity	Proof of identification (ID) presented at face-to-face (F2F) study visit	Recruitment with healthcare system (using system identifier), confirmation of eligibility with usual healthcare provider, participant supply of copies of ID documents e.g. passport by mail, display of ID during initial telehealth visit, requirement for unique Internet Protocol (IP)/email address, credit report-based challenge questions, biometric logins.
Documenting informed consent	F2F visit with discussion and wet ink signature of paper consent form	eConsent (subject to local regulations, with or without telephone, online and email support), mail return of completed paper consent form, verbal consent during telehealth visit, paper consent at initial mobile health visit
IMP handling and delivery	Handover at F2F study site visit	Direct-to-participant delivery is admissible in some countries but not all. It may be necessary to distribute first to local sites. Alternative approaches (as listed in the earlier table) may need to be considered, depending on local regulations.
Medical software legislation	It remains unclear where the boundary lies between consumer devices for personal use and medical device legislation e.g. smart watch apps. Discuss with local regulators.	
Telemedicine	Local regulations may restrict telemedicine use. For example, in the US, physician licensing is at state-level and some states will not allow out-of-state physicians to conduct telemedicine. Discuss with local regulators and vendors.	
Mobile health	Local regulations on the required training and certification of mobile health practitioners may vary. Discuss with local regulators and vendors.	
Acceptability of novel and digital endpoints	A fast-moving field. Investigators and sponsors should familiarise themselves with the latest guidance from regulators and discuss	

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	early with them and other stakeholders. Intention to use a novel endpoint in a regulatory study should be supported with a strong rationale for use, details of the intended context of use and evidence of reliability and validity of data.[61]	
Monitoring	Monitors visit sites physically	Risk-based monitoring can be adapted for remote use and should be discussed with the relevant authority. Access to digital systems by monitors should be considered during their design, paying attention to protecting the privacy of participants.
Regulatory Inspection	Inspectors visit sites physically	Processes to allow compliance with inspection should be considered and discussed with relevant authorities.

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Appendix B - Research Methods

Systematic Review

Aims and Objectives

A systematic review of quantitative and qualitative literature was conducted to summarise and evaluate published evidence on strategies used to conduct remote decentralised clinical trials. This comprised two approaches:

1. A focused assessment of remote and hybrid randomised controlled trials to describe and summarise methods used and to quantitatively evaluate recruitment and retention strategies (including all age groups and therapeutic areas)
2. A wider assessment of the literature around remote decentralised trials to address the following question: what are the perceived benefits and challenges of using remote trial methods by investigators, participants, and other stakeholders?

The objectives of the systematic review were as follows:

1a. To identify remote methods reported as having been used in various stages of trial conduct in fully remote and hybrid RDCTs

1b. To evaluate the effectiveness of remote decentralised methods in terms of recruitment, retention and relative financial cost when compared to traditional methods

2a. To identify facilitators and barriers to conducting RDCTs

2b. To identify advantages and disadvantages of RDCTs

2c. To summarise patient and stakeholder experiences and opinions regarding remote decentralised methods.

The protocol for this review was prospectively registered on the PROSPERO International prospective register of systematic reviews and can be viewed here: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020166710

The full methods and results of this systematic review will be formally published in due course. The following is a summary of the methods used to identify relevant literature.

Search Strategy

A search strategy was developed with the involvement of subject matter and methodological experts. The search strategy had two sets (concepts) of search terms: (i) technical terms to search for remote/decentralised technology; (ii) terms to search different types of study design. The results from each concept were combined to obtain the final search results. The search used both free-text words and Medical Subject Headings (MeSH) (see below) and was modified for each electronic database. Databases searched included MEDLINE, EMBASE, the Cochrane Central Register of Controlled

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Trials (CENTRAL), PsycINFO, ProQuest Dissertations and Theses, and ClinicalTrials.gov. OpenGrey and Google Scholar were also searched to identify relevant grey literature. Scopus and Web of Science were used to facilitate forward and backward citation searching. We also conducted hand searches of the websites of pharmaceutical companies and organisations/research centres known to be involved in conducting and promoting remote decentralised clinical trials.

The following search terms were adapted for use in different databases:

Technical search terms
remote
remote trial
decentralised trial
decentralized trial
hybrid trial
site-less trial
direct-to-patient
direct-to-participant
direct-to-subject
patient-centric trial
patient-centric study
patient centered trial
patient centered study
patient centred trial
patient centred study
home-based trial
virtual trial
digital trial
digital medicine
e-medicine
emedicine
online trial
internet based trial
web-based trial
tele-visit
e-health
ehealth
electronic health
m-health
mobile health
mobile application
mobile applications
e-clinical
eclinical
e-clinical health
eclinical health
electronic clinical health
e-clinical technology
eclinical technology
e-clinical technologies
eclinical technologies
electronic clinical technologies
wearable electronic device
wearable electronic devices
e-consent
econsent
electronic consent

Search terms for study design
clinical trial
randomised trial
randomized trial
randomised controlled trial
randomized controlled trial
interventional study
cluster-randomised trial
cluster-randomized trial
non-interventional study
augmented clinical trial

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Types of Study included

For the focused assessment, only reports of randomised clinical trials using remote decentralised methods were included. For the wider assessment, all publications reporting, discussing, and/or evaluating remote decentralised methods were included. These included all types of clinical studies: randomised, non-randomised, qualitative studies, and mixed-methods studies; as well as editorials, letters, commentaries, blogs, marketing/pharmaceutical reports, guidelines, narrative and systematic reviews.

Inclusion criteria:
Focused assessments of randomised controlled trials using remote methods.
Articles that:
• Describe the methods of a completed or ongoing randomised clinical trial of using fully remote or partially remote methods.
• Compare traditional clinical trial methods with hybrid or fully remote decentralised clinical trial methods within a randomised clinical trial.

Wider assessment of remote trial methods:
All articles included in the focused assessment as well as articles that:
• Describe methods that have been used to conduct remote decentralised (both hybrid and fully remote) clinical trials.
• Report feasibility testing of remote decentralised clinical trial methods.
• Report experiences and/or lessons learned in conducting remote decentralised clinical trials.
• Report facilitators and barriers in conducting remote decentralised clinical trials.
• Discuss the feasibility of conducting remote decentralised clinical trials.
• Report the patient experience of participating in remote decentralised clinical trials.
• Report the costs of running remote decentralised clinical trials.
• Report stakeholder opinions on conducting remote decentralised clinical trials.

Exclusion criteria:
• Articles describing or reporting the use of technologies in clinical research without reference to remote decentralised trial methods, such as using wearable devices to collect supplemental participant data in a trial but uploading the data from the device during a formal study site visit;
• Randomised trials testing online behavioural, educational, or psychological interventions only.

Brief Results

The full results of the systematic review will be published separately in a peer-reviewed scientific journal. Almost 20,000 potentially relevant records were identified and screened. 138 articles were included in the review and 46 randomised clinical trials using fully remote or hybrid methods were identified.

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Case Study Interviews

A case study selection tool was developed to collect summary data on potential case studies from Trials@Home consortium partners as well as potential cases identified from initial literature searches. The tool was used to facilitate discussions within Trials@Home work package 1 to identify a group of studies that demonstrated a wide range of therapeutic areas, study methods, participant characteristics and site locations.

20 case studies were identified across the following therapeutic areas:

Therapeutic Area	**Number of case studies**
Cardiovascular	5
Endocrine, diabetes	4
Neurology	3
Rheumatology	3
Women's health	2
Oncology	1
Respiratory	1
Rare disease, unspecified	1

One case study was a trial exclusively in adolescents. The remainder had adult and older adult cohorts

The following organisations contributed case studies:
University of Dundee
eClinicalHealth (Janssen)
Novartis
Sanofi
UCB
Bayer
The George Institute for Global Health, University of Oxford
AstraZeneca
Duke Clinical Research Institute
University of Oxford
Janssen

All interviews were conducted using an interview schema that was developed to explore:

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- Perceived advantages of RDCTs and aspects that had worked well in case studies
- Key challenges encountered and the reasons for them
- Responses and solutions to challenges encountered
- Potential ways to mitigate future challenges

The following open questions were asked of all interviewees:

CONTEXTUAL INFORMATION

1. Please tell me a little bit about the [name the study].
2. What were (or are) the study's objectives?
3. Tell me a bit about the remote aspects of the study? What did (or do) they involve?
4. Why did you choose to use this approach – choose to use these remote aspects?
5. What do you think were (are) the advantages?
6. What would you say worked well? (or Is working well?)
7. Are there particular patient populations that this type of approach is best suited to? Why do you say that?

PROBLEMS AND CHALLENGES

8. What were (are) the **main** problems in conducting your remote research? (Probe – descriptions of **all** problems. Some examples might be Technological, Regulatory and Ethical, Legal, Cultural and Logistical and others).
9. What do you feel caused these problems? (probe each one – 'tell me more about that')
10. Out of these, which was the biggest most difficult challenge? Why was this? Help me to understand why this was.

RESPONSES AND SOLUTIONS

11. How did you respond to these problems, what did you do? (or How **are** you responding? What **are** you doing?) (Probe responses and solutions for each problem).
12. How far do you feel you are able to solve these issues? Prompt: Why do you say that? (Probe solutions, partial solutions, unresolved issues)
13. (Note to interviewer: If unable to find a solution, probe reason). 'Tell me a little bit about what prevented you, or what is preventing you? How did (or do) you feel about that?'

ADVICE AND RECOMMENDATIONS

14. In hindsight, what if anything, would you do differently? Prompts: For what reason(s). That's interesting, tell me more.
15. What advice would you give to other investigators just starting out on a remote clinical trial?
16. How could they avoid the problems you've talked about (or minimise them?) Go through each one.
17. What is the single most important thing you've learned about conducting a remote clinical trial? Then probe for all they've learned.

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The schema was adapted during the interviewing process to explore developing themes, notably the impact of COVID-19 on ongoing trial conduct.

47 semi-structured qualitative interviews (including one joint pair interview, at the request of the interviewees), from 20 case studies, were conducted and analysed. Between 1 and 6 people were interviewed for each case study (median = 2) dependent on availability and experience. Interviewees had the following broad job roles:

Role	Number of Interviewees
Senior Manager	16
Trial Project Manager	10
Chief or Principal Investigator	5
Research Nurse	3
Clinical Research Scientist	3
Senior Manager (vendor)	2
Investigator	3
Patient Representative	2
Trial Pharmacist	1
Administrator	1
Data Manager	1
Software Developer	1

Although most case study interviewees mentioned ethical and/or regulatory issues, we were unable to interview specific individuals involved in the ethical or regulatory overview of the included case studies due to availability issues.

All interviews were audio recorded and fully transcribed. Thematic analysis was used to identify themes, or patterns, in the data and involved the following stages:

- Familiarisation
- Generating initial thematic coding
- Searching for preliminary descriptive themes
- Reviewing and modifying themes
- Final refinement of themes

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Appendix C - Other Useful Resources

RDCTs -general
https://trialsathome.com/
https://www.ctti-clinicaltrials.org/projects/decentralized-clinical-trials
https://www.nationalacademies.org/event/11-18-2019/virtual-clinical-trials-challenges-and-opportunities-a-workshop#sectionEventPublications

Digital technologies
https://transceleratebiopharmainc.com/initiatives/patient-technology/
https://www.ema.europa.eu/en/documents/other/questions-answers-qualification-digital-technology-based-methodologies-support-approval-medicinal_en.pdf
https://www.iso.org/iso-13485-medical-devices.html
https://www.ctti-clinicaltrials.org/projects/digital-health-technologies

eConsent
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-informed-consent-clinical-investigations-questions-and-answers
https://transceleratebiopharmainc.com/initiatives/econsent/
https://www.hra.nhs.uk/documents/1588/hra-mhra-econsent-statement-sept-18.pdf

Patient engagement
https://imi-paradigm.eu/
https://eupati.eu/
https://www.nihr.ac.uk/explore-nihr/industry/pecd.htm

General clinical trial design and conduct
https://www.ctti-clinicaltrials.org/projects/quality-design
https://www.ema.europa.eu/en/ich-e8-general-considerations-clinical-studies

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Appendix D - Basic Building Block Matrix

	Set-up and design	Recruitment and Enrolment	Intervention and Follow-up	Data Acquisition and Processing	Close-out and Reporting	Patient/Participant Engagement	Operation and Coordination
Answer an important research question:	✔	✔	✔	✔		✔	
Start with a clear research question	✔						
Choose a research question that is important to participants	✔	✔				✔	
Involve clinicians and other stakeholders e.g. policymakers in choosing and refining the research question.	✔						
Seek statistical and design advice	✔	✔		✔			
Keep the focus on participants:	✔	✔	✔	✔	✔	✔	✔
Involve patients and the public in choosing the research question	✔					✔	
Communicate clearly		✔	✔		✔	✔	
Involve patients and/or the public in study design early	✔					✔	
Involve patients and/or the public in the design of recruitment materials and strategies		✔				✔	
Present a streamlined approach to potential participants		✔	✔			✔	
Minimise requirements for participant data entry	✔	✔	✔	✔		✔	
Use familiar technologies	✔	✔	✔	✔		✔	
Provide useful information for participants, clinicians and caregivers	✔			✔	✔	✔	
Provide support to participants	✔	✔	✔			✔	✔
Consider alternatives for participants with differing needs	✔	✔	✔			✔	
Try to mimic usual activities	✔		✔			✔	
Simplify the participant experience whilst maintaining quality and scientific rigour:	✔	✔	✔	✔	✔	✔	✔
Use tested and validated technologies	✔	✔	✔	✔		✔	✔
Aim for seamless integration of technological platforms	✔		✔	✔			
Plan for ongoing technical support	✔		✔		✔	✔	✔
Collect the minimum necessary data	✔	✔	✔	✔			
Use existing data sources	✔	✔	✔	✔			
Involve stakeholders early:	✔			✔			✔
Discuss plans for RDCTs with relevant authorities	✔			✔			
Allow time and resources to consult relevant authorities in all planned study locations	✔						✔
Continued overleaf							

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continued	Set-up and design	Recruitment and Enrolment	Intervention and Follow-up	Data Acquisition and Processing	Close-out and Reporting	Patient Engagement	Operation and Coordination
Share knowledge and experiences	✔	✔	✔	✔	✔	✔	✔
Research implementation and improvement of remote decentralised trial methods	✔	✔	✔	✔	✔	✔	✔

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