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ORIGINAL ARTICLE

A systematic review of methods used to conduct decentralised clinical trials

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Aims: To evaluate, using quantitative and qualitative approaches, published data on the design and conduct of decentralised clinical trials (DCTs).

Methods: We searched MEDLINE, EMBASE, CENTRAL, PsycINFO, ProQuest Dissertations and Theses, ClinicalTrials.gov, OpenGrey and Google Scholar for publications reporting, discussing, or evaluating decentralised clinical research methods. Reports of randomised clinical trials using decentralised methods were included in a focused quantitative analysis with a primary outcome of number of randomised participants. All publications discussing or evaluating DCTs were included in a wider qualitative analysis to identify advantages, disadvantages, facilitators, barriers and stakeholder opinions of decentralised clinical trials. Quantitative data were summarised using descriptive statistics, and qualitative data analysed using a thematic approach.

Results: Initial searches identified 19 704 articles. After removal of duplicates, 18 553 were screened, resulting in 237 eligible for full-text assessment. Forty-five trials were included in the quantitative analysis; 117 documents were included in the qualitative analysis. Trials were widely heterogeneous in design and reporting, precluding meta-analysis of the effect of DCT methods on the primary recruitment outcome. Qualitative analysis formulated 4 broad themes: value, burden, safety and equity. Participant and stakeholder experiences of DCTs were incompletely represented.

Conclusion: DCTs are developing rapidly. However, there is insufficient evidence to confirm which methods are most effective in trial recruitment, retention, or overall cost. The identified advantages, disadvantages, facilitators and barriers should inform the development of DCT methods. We recommend further research on how DCTs are experienced and perceived by participants and stakeholders to maximise potential benefits.

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Principal Investigator: Professor Isla Mackenzie.

KEYWORDS
clinical trials, decentralised clinical trials, recruitment, retention, systematic review

1 | INTRODUCTION

Clinical trials are increasingly adopting technologies to allow trial activities to take place in or nearer to participants' homes.[1] These decentralised clinical trials (DCTs), where some or all elements of a trial are selected to reduce the need for clinical trial site attendance, aim to reduce the burden of trial participation, boost trial accessibility and recruitment, and improve the generalisability of trial-generated evidence.[2,3] Whilst the use of decentralised trial designs is not new, the tools and approaches available to achieve these have changed dramatically since the introduction of postal-based clinical trials in the 1980s.[4,5] This systematic review aims to summarise and evaluate published evidence on the conduct of DCTs to inform future clinical trial design.

More people than ever before own a mobile phone or smart device; 85% of Americans now own smartphones, and an estimated 85% of the European population are mobile subscribers.[6,7] The number of mobile devices operating worldwide is expected to reach 17.72 billion by 2024.[8] In 2019, an estimated 22% of the population owned wearable devices, such as smartwatches and fitness trackers, and 67% used them daily.[9] These enormous technological and social changes have opened new opportunities for researchers. Clinical trials must be ready to adopt new approaches and strategies to engage with a public who are increasingly at ease with technology and keep pace with a continually evolving digital climate. At the same time, it should not be forgotten that some people are either unable or unwilling to access or use digital technologies and online environments, the so-called *technologically disadvantaged*, which can lead to digital exclusion and selection bias.

DCTs are a pragmatic trial concept that combines participant-centred design with innovative technologies to reduce or remove the need for physical in-person interaction between participants and researchers. As a result, DCTs can make clinical trials more accessible to a broader demographic of participants who may not otherwise be willing or able to take part in more conventional research site-based trials. Whether fully decentralised (fully remote, participant never attends a clinical trial site) or combining conventional and decentralised elements (hybrid, still requiring some physical site attendance), DCTs offer an opportunity to improve recruitment and retention, enhance engagement and diversity, and lower the overall costs of clinical research and medicines and medical device development.

This review comprises 2 parts. Firstly, a focused review of randomised clinical trials using decentralised methods. The objective of this focused review was to identify the methods used to achieve fully remote and hybrid DCTs; and evaluate their effectiveness in terms of recruitment, retention and relative financial cost, compared to conventional (site-based) methods. Secondly, a wider review of the literature around decentralised clinical trials. The objectives of the wider review were identifying facilitators and barriers, advantages and benefits of DCTs, and summarising participant and stakeholder experiences and opinions.

This review was conducted as part of Work Package 1 (BEST) of the Trials@Home project (https://trialsathome.com) to inform best practices in designing DCTs.

What is already known about this subject

- Decentralised clinical trials (DCTs) have been suggested to improve participant centricity, recruitment, retention and generalisability.
- Many clinical trials already perform some trial activities away from conventional in-person investigational site visits.
- We do not know if DCTs are better for recruitment or retention than conventional site-based trials.

What this study adds

- DCTs using various operational and technological approaches have been used in many therapeutic areas and patient groups.
- There is a lack of published comparable data to determine if DCTs improve recruitment and retention.
- The convenience of at-home participation must be balanced against transferring burden to study participants.

2 | METHODS

A systematic review protocol was developed *a priori* and registered on the International Prospective Register of Systematic Reviews (PROSPERO, CRD42020166710).

2.1 | Literature screening

We developed a single search strategy based on all authors' knowledge and experience of conducting decentralised trials and an initial scoping search of MEDLINE. The search strategy comprised 2 search term sets: technical terms to search for remote or decentralised technologies and methods; terms to search for clinical studies and trials (see Supplemental File p4). The terms within each set were searched first using the Boolean operator OR. The results from each set were then combined using the Boolean operator AND to obtain the final search results. The search used both free-text words and Medical Subject Headings (MeSH), and the search strategy was modified as appropriate for each electronic database.

One reviewer conducted the database searches in MEDLINE, EMBASE, CENTRAL and PsycINFO on 11 and 12 February 2020. Additionally, 2 reviewers searched ProQuest Dissertations and Theses, ClinicalTrials.gov, OpenGrey, and Google Scholar during March 2020 to identify relevant grey literature. We also sought further grey literature by searching the public-facing websites of pharmaceutical companies and academic departments known to be involved in conducting or promoting DCTs. SCOPUS and Web of Science were also used for forwards and backwards citation searching from all included papers reporting clinical trials using DCT methods. We included articles published only in English, with no restrictions on age, therapeutic area or date.

2.2 | Inclusion and exclusion criteria

For the focused review, we included only reports of individually randomised controlled clinical trials using decentralised methods. We included trials where the intervention was a drug (licensed or investigational medicinal product), medical device or other medical intervention (including diagnostics and screening testing, and dietary supplements or herbal medicines). Studies evaluating only psychological, behavioural, educational or social interventions were excluded. We also excluded comparisons of remotely delivered healthcare delivery with usual care that used nonremote, site-based trial methods. For example, a trial comparing the acceptability of neurological assessment using telemedicine *vs*. in-person clinic-based examination for clinical care delivery would not be included. Many recent conventional trials already use some decentralised elements. This review only included trials if the decentralised element was explicitly used to minimise or replace in-person site visits. For example, a hybrid trial that used a smartphone-based e-diary to collect data between in-person visits would only be included if the available documentation indicated that the e-diary was being used to reduce site visits. A trial using an e-diary to replace a paper-based diary, reviewed with the participant at each visit, would not be included.

For the wider review, we included all publications reporting, discussing or evaluating decentralised methods; this included all types of clinical research (randomised, nonrandomised, qualitative studies and mixed-methods studies) as well as editorials, letters, commentaries, blogs, marketing/pharmaceutical reports, guidelines and reviews.

2.3 | Screening

All the articles identified from the individual database searches were exported to EndNote X9.2 reference management software.[10] After removing duplicates, the articles were imported to Rayyan QCRI, a web-based systematic review software tool.[11] Two reviewers independently screened titles and abstracts. Where there was disagreement, this was resolved by consensus with at least 1 additional reviewer. Full texts were then retrieved for all included sources and the process repeated. A study eligibility form (Supplemental file p5) was created to guide and record decisions on full-text inclusion. Reasons for exclusion at each stage were noted. Articles that met the eligibility criteria were included.

2.4 | Data extraction

We developed and pilot-tested a data extraction tool for the focused review using Microsoft Access (Supplemental file pp6–10). Data extraction was carried out independently by at least 2 reviewers, and discrepancies were resolved on discussion with a third reviewer. Two reviewers verified the extracted data for consistency.

For the wider review, we developed and tested a separate data extraction tool using Microsoft Forms. Two reviewers independently extracted qualitative data, in the form of text excerpts, from each source document. A third reviewer combined their data, removing duplicates and expanding excerpts when necessary to maintain context.

2.5 | Outcomes

A list of outcomes for the focused assessment is provided in Table 1. Outcomes included in the wider qualitative assessment are as follows:

1. Reported facilitators to conducting DCTs
2. Reported barriers to conducting DCTs
3. Perceived advantages of DCT methods (when compared to traditional trial methods)
4. Perceived disadvantages of DCT methods (when compared to traditional trial methods)
5. Participant experiences of taking part in DCTs
6. Stakeholder opinions of DCTs (including individuals or organisations affected by DCTs other than trial participants, investigators, research staff, or sponsors)

2.6 | Assessment of methodological quality

We assessed the risk of bias for the primary outcome of all trials included in the focused review as a proxy measure of the overall risk of bias. The risk of bias for the primary trial outcome of all completed

TABLE 1 List of outcomes and definition for focused assessment of decentralised clinical trials

Outcome	Definition/expression used
Primary outcome	
Number of randomised participants	Number (*n*)
Secondary outcomes	
1. Identification of potential trial participants	Number (*n*)
2. Potentially eligible screened participants	Number (*n*)
	Proportion of potential trial participants (%)
3. Randomised participants	Number (*n*, primary outcome)
	Proportion of screened individuals (%)
	Proportion of prespecified target sample size (%)
4. Recruitment rate	Mean number randomised/month during recruitment period (*n*/mo)
5. Retention	Proportion of randomised participants lost to follow up at 1 mo, 3 mo and 1 y (%)
	Proportion of randomised participants completing trial (%)
6. Cost	Total cost of trial (US$) Cost of trial per randomised participant (US$)
7. Remote methods used	Fully remote *vs*. partially remote
	Description of remote methods used, broken down by trial activity

and reported trials with full results was assessed using the Cochrane Risk of Bias (RoB 2) tool for randomised trials.[12] We created a modified version (mRoB) of Cochrane's RoB 2 tool to assess trials for which final results were not yet available (Supplemental file p11). These tools were also used, as applicable, to evaluate the risk of bias in any quantitative methodological comparison outcomes reported. Quality assessments for each outcome were carried out independently by at least 2 reviewers, and any disagreements were resolved by discussion with a third reviewer.

2.7 | Analysis

2.7.1 | Quantitative analysis

Due to the heterogeneity of the design and reporting of included trials, we decided a meta-analysis approach would be inappropriate; a narrative approach was adopted. Data were exported from Microsoft Access for analysis using STATA 15.1 for Windows.[13] The -metaprop- and -metan- commands were used for descriptive statistical analysis.[14,15]

2.7.2 | Qualitative analysis

Data were exported from Microsoft Forms (via MS Excel) to NVivo (Release 1.3) software for qualitative analysis.[16] Facilitators and barriers to DCTs, and advantages and disadvantages, were identified and categorised. Two coauthors identified initial broad themes with reference to an earlier qualitative analysis of DCT case studies performed as part of the Trials@Home project.[130] The data were first assessed using these broad themes, and the themes then adapted based on observed similarities, differences and clustering. Data were then coded to describe narrower themes agreed with a second author before presenting to all authors and refining until consensus was reached.

3 | RESULTS

Our searches initially identified 19 704 articles. After removing duplicates, 18 553 were screened for title and abstract, resulting in 237 eligible for full-text assessment. Of these, 138 met the inclusion criteria, from which 45 randomised clinical trials were identified for quantitative analysis and 117 source documents for qualitative analysis (55 documents about trials included in the quantitative analysis were included in the qualitative analysis). The results of this process are described in greater detail in a PRISMA flow diagram (Figure 1).

3.1 | Focused review

3.1.1 | Description of included trials

We extracted data from documents on the 45 randomised clinical trials included in the focused review. The reviewers sourced as many documents connected to the main study as possible (e.g., final reports, conference abstracts, protocols or methods papers, participant-facing materials, and blog posts) to extract all available information. A complete list of source documents identified can be found in the Supplemental file (p12). Table 2 summarises the included trials.

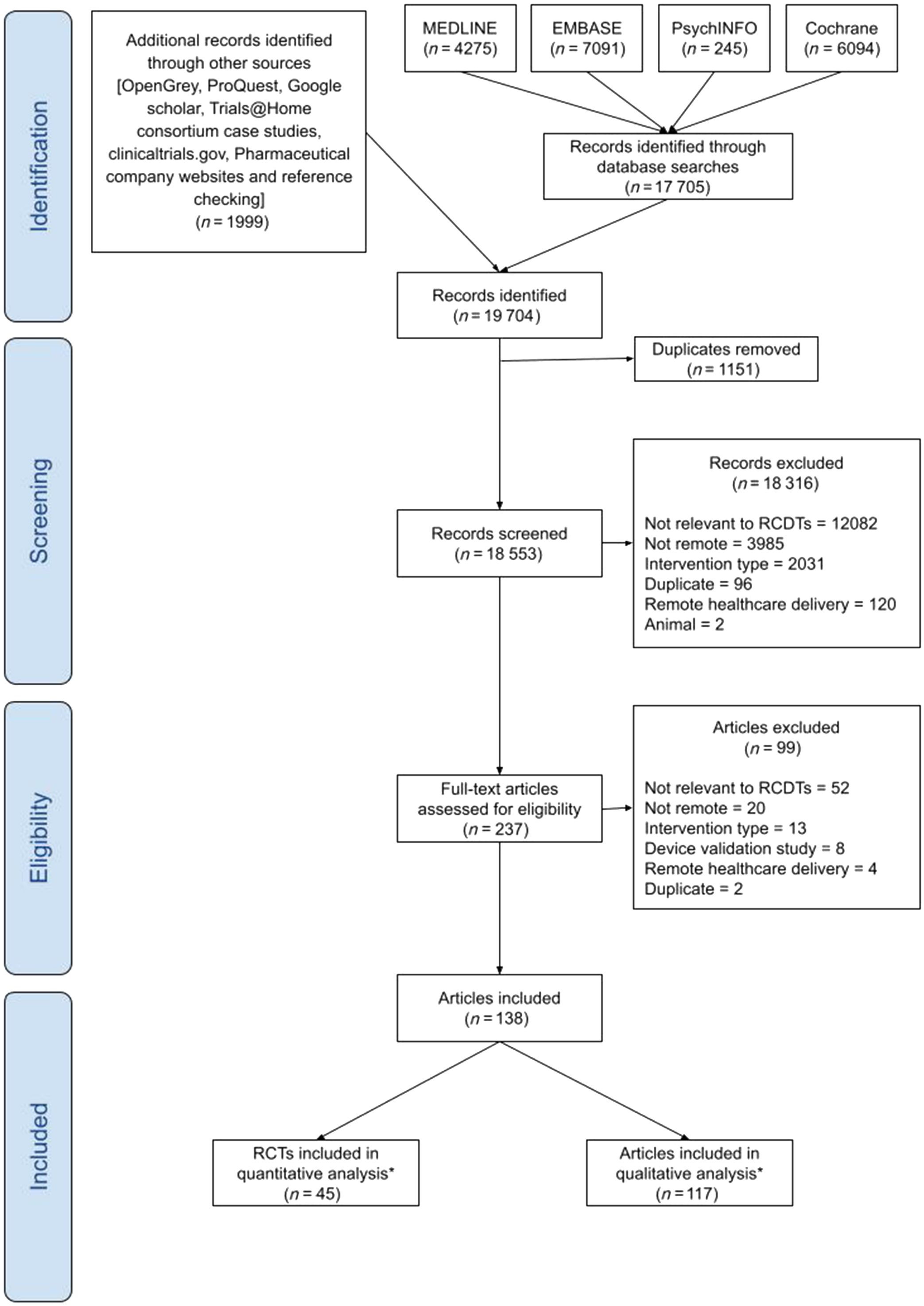

FIGURE 1 Prisma flowchart of systematic review. Fifty-five articles associated with the 45 randomised controlled trials included in the quantitative analysis also contained qualitative data and were included in the qualitative analysis

3.1.2 | Results of quantitative analysis

All sources were published between 1988 and 2020. At the time of data extraction, 29 studies (64%) had been completed, 13 studies (29%) were in progress and 3 studies (7%) had not yet started. Twenty-eight studies (62%) were conducted using fully remote methods, enabling at-home participation with no site-based physical interaction with the study team. Seventeen studies (38%) were performed using hybrid approaches.

Table 3 summarises the primary and secondary outcomes. We extracted data for our primary outcome for 34 trials; the remaining 11 trials did not report this outcome because they were yet to start or

TABLE 2 List of trials included in the focused review. Trials are identified by the first author; where multiple sources were identified for a single trial, the trial is identified by the first author of the published results, protocol, or other paper (in order of availability), or Academic Investigator/Company Sponsor if unpublished. Status is at the time of data extraction (8–25 May 2020). Year corresponds to the date of earliest publication or source identified for each trial

Trial	Year	DCT classification	Primary therapeutic area	Intervention(s)	Target population	Location of participants	Status
Peto et al.[48]	1988	Fully remote	Cardiovascular	Aspirin	Adults (18–60)	UK	Complete
Steering Committee of the Physicians' Health Study Research Group[22]	1989	Fully remote	Cardiovascular	Aspirin, betacarotene	Adults (18–60)	USA	Complete
Ulrich et al.[20]	1997	Hybrid	Musculoskeletal	Bisphosphonate	Elderly (>60)	USA	Complete
Ridker et al.[23]	1999	Fully remote	Cardiovascular	Aspirin, vitamin E	Adults (18–60)	USA	Complete
Pepine et al.[24]	2003	Hybrid	Cardiovascular	Verapamil, atenolol, trandolapril, hydrochlorothiazide	Elderly (>60)	USA, Australia, New Zealand, Germany, Canada, Mexico, Italy, France, Spain, Israel, South Africa	Complete
Eilenberg et al.[25]	2004	Hybrid	Urology	Tadalafil	Adults (18–60)	USA	Complete
Formica et al.[26]	2004	Fully remote	Dermatology	Dioctyl sodium sulfosuccinate ointment	Adults (18–60)	USA	Complete
McAlindon et al.[19]	2004	Fully remote	Musculoskeletal	Glucosamine	Elderly (>60)	USA	Complete
Jacobs et al.[27]	2005	Fully remote	Mental health	Kava, valerian	Adults (18–60)	USA	Complete
Cook et al.[28]	2007	Fully remote	Cardiovascular	Vitamin C, vitamin E, betacarotene	Adults (18–60)	USA	Complete
Oxman et al.[59]	2007	Fully remote	Sleep	Valerian	Adults (18–60)	Norway	Complete
Brophy et al.[49]	2008	Fully remote	Musculoskeletal	Oral probiotic	Adults (18–60)	UK	Complete
Sesso et al.[29]	2008	Fully remote	Cardiovascular	Vitamin C, vitamin E, multivitamin	Adults (18–60)	USA	Complete
Bailey et al.[51]	2011	Fully remote	Sexual health	Interactive website + screening test	Adolescents (12–18)	UK	Complete
Orri et al.[31]	2011	Fully remote	Women's health	Tolterodine	Adults (18–60)	USA	Complete
MacDonald et al.[50]	2011	Hybrid	Musculoskeletal	Febuxostat, allopurinol	Elderly (>60)	UK, Denmark	In progress
Manson et al.[63]	2012	Fully remote	Cardiovascular	Vitamin D, omega-3 fatty acids	Adults (18–60)	USA	Complete
Krischer et al.[33]	2013	Fully remote	Musculoskeletal	Prednisolone	Adults (18–60)	USA, Canada	In progress
Mackenzie et al.[52]	2013	Hybrid	Cardiovascular	Allopurinol	Elderly (>60)	UK	In progress
Bent et al.[34]	2014	Fully remote	Mental health	Omega-3 fatty acids	Paediatric (0–12)	USA	Complete
Blake et al.[35]	2014	Hybrid	Respiratory	Fluticasone/salmeterol	Adolescents (12–18)	USA	Complete
Rorie et al.[53]	2014	Fully remote	Cardiovascular	Anti-hypertensive dosing time	Adults (18–60)	UK	In progress
Steinhubl et al.[36]	2015	Fully remote	Cardiovascular	Screening test (ECG monitoring)	Elderly (60>)	USA	Complete
Woodcock et al.[56]	2015	Hybrid	Respiratory	Fluticasone/vilanterol	Adults (18–60)	UK	Complete
Dumbleton et al.[54]	2015	Hybrid	Gastrointestinal	Lansoprazole/clarithromycin/metronidazole	Elderly (60>)	UK	In progress

TABLE 2 (Continued)

Trial	Year	DCT classification	Primary therapeutic area	Intervention(s)	Target population	Location of participants	Status
Esserman et al[37]	2015	Hybrid	Oncology	Risk-based breast cancer screening	Adults (18–60)	USA	In progress
AOBiome[38]	2016	Fully remote	Dermatology	Ammonia oxidising bacteria topical spray	Adults (18–60)	Not Reported	Complete
Gelfand et al.[21]	2016	Hybrid	Neurology	Melatonin	Adolescents (12–18)	USA	Complete
Marquis-Gravel et al.[18]	2016	Fully remote	Cardiovascular	Aspirin	Adults (18–60)	USA	In progress
Pasman et al.[60]	2017	Fully remote	Neurology	Caffeine	Adults (18–60)	Not Reported	Complete
Sanofi[39]	2017	Fully remote	Diabetes	Insulin glargine	Adults (18–60)	USA, Canada	Complete
Olden et al.[30]	2017	Fully remote	Mental health	D-cycloserine	Adults (18–60)	USA	In progress
Preiss et al.[55]	2017	Hybrid	Diabetes	Fenofibrate	Adults (18–60)	UK	In progress
Charvet et al.[40]	2018	Hybrid	Neurology	Transcranial direct current stimulation	Adults (18–60)	USA	Complete
Bowman et al.[57]	2018	Fully remote	Diabetes	Aspirin, omega-3 fatty acids	Adults (18–60)	UK	Complete
Sharma et al.[42]	2019	Hybrid	Neurology	Transcranial direct current stimulation	Adults (18–60)	USA	Complete
Tarolli et al.[46]	2018	Hybrid	Neurology	Isradipine	Adults (18–60)	USA, Canada	Complete
Spartano et al.[47]	2019	Hybrid	Cardiovascular	Remote *vs.* in-person data collection device set-up	Adults (18–60)	USA	Complete
Liu et al.[62]	2019	Hybrid	Musculoskeletal	Herbal remedy	Adults (18–60)	USA	In progress
Tanner et al.[43]	2019	Fully remote	Neurology	Zoledronic acid, calcium, vitamin D3	Elderly (60>)	USA	In progress
NightWare[41]	2019	Fully remote	Mental health	Digital therapeutic device	Adults (18–60)	USA	Not yet started
Pfizer[44]	2019	Fully remote	Dermatology	Crisaborole ointment	Adults (18–60)	USA	Not yet started
Janssen Scientific Affairs[45]	2020	Fully remote	Cardiovascular	Canagliflozin	Adults (18–60)	USA	In progress
Redzic et al.[61]	2020	Hybrid	Dermatology	AV2-salicylic acid	Adolescents (12–18)	Belgium	In progress
Blis Probiotics[58]	2020	Fully remote	Infectious disease, ENT	Probiotic supplement	Adults (18–60)	Not reported	Not yet started

Abbreviations: DCT, decentralised clinical trials; ECG, electrocardiogram; ENT, ear, nose and throat.

TABLE 3 Summary of focused review outcomes (number of trials, $n = 45$)

Outcome	Median	Range
Primary outcome		
1. Number of randomised participants ($n = 34$, n)	375	10–39 876
Secondary outcomes		
2. Identification of potential trial participants ($n = 22$, n)	3350	31–453 878
3. Potentially eligible participants screened ($n = 31$, n)	456	401 605
• as proportion of potential trial participants identified ($n = 22$, %)	36	13.67–100
3. Randomised participants		
• as proportion of screened individuals randomised ($n = 30$, %)	71	2.59–100
• as proportion of prespecified target sample size randomised ($n = 24$, %)	100	6.36–190
4. Recruitment rate		
• number of participants randomised per month during recruitment period ($n = 22$, n)[a]	141	0–11 035
5. Retention		
• proportion of randomised participants lost to follow up at: (%) ○ 1 month ○ 3 months ○ 1 year	Insufficient data	Insufficient data
• proportion of randomised participants completing trial ($n = 21$, %)	93	1.1–100
6. Cost		
• total cost of trial ($n = 2$, US$)	-	*Less than* 13–14 million
• cost of trial per randomised participant ($n = 3$, US$)	914	155–3400

[a]Data for this outcome were strongly skewed; therefore, we have reported median (instead of the prespecified outcome mean).

were still in progress without any interim reporting. There were minimal data for 2 of the secondary outcomes: retention and cost. The proportion of randomised participants lost to follow up at 1 month, 3 months and 1 year was not specified in most trials, or retention was reported using different noncomparable metrics. We were, however, able to extract data related to the proportion of randomised participants completing 21 trials. Only 2 trials[17,18] reported a rough estimate of overall cost, and only 3 studies[19–21] reported the cost associated per randomised participant.

Stated trial target sample sizes varied between 30 and 100 000 participants ($n = 35$, median = 283), and just over half of trials reporting sufficient data ($n = 24$) met their recruitment target (54%). Eighteen trials that recruited both males and females reported separately by sex, ranging from 12 to 79% female (mean 51.75%). Thirty-five trials reported durations that ranged from 1 month to 13 years (median 11 mo). The lead investigators of over half (30) of the trials were based in North America,[18–47] 11 were in the UK,[48–58] 3 in other European countries[59–61] and 1 in Australia.[62] Most trials (40) included participants only in the country of the lead investigator; however, 4 trials included participants in 2 countries,[33,39,46,50] and 1 reported participants in more than 2 countries (11 countries, 5 continents).[24]

Forty trials reported methods used in recruitment; a wide variety of recruitment methods were used (Tables S1-3), with half of these trials ($n = 20$) using at least 2 recruitment methods and 7 trials having used 5 or more. Ten trials reported using routinely collected data to identify potential participants.[18,21,36,37,43,50,52,55–57] Sixteen trials reported using online participant registration[18,21,24–27,31,33,34,36,37,47,51,53,59,60]; other methods used included in-person registration, phone and postal. Seven trials offered an incentive to participants, such as money,[35,40,44] vouchers[51] or free herbal supplements.[27] Fifteen trials reported having verified participant identity,[18,19,25–27,31,35–37,49–53,55] with a range of different methods (Tables S4-6). Fifteen trials used online electronic consent,[18,24,25,27,33,34,36,37,39,43,47,51,53,59,62] but only 2 trials reported using a dynamic form of consent with functionality for participants to review and alter their consent to participation in line with changing preferences.[18,35]

Trials tested a variety of interventions: 14 trials used medicines prescribed within their licensed indications[17,18,22–25,31,33,35,39,48,50,53,54]; 12 tested dietary supplements[19,21,27–29,32,34,49,58–60,62] or herbal medicines; 6 tested licensed medicines for new or extended indications[43–46,52,55]; and 6 tested not yet licensed medicines.[20,26,30,38,56,61] Of the remainder, there were 3 device trials,[40–42] 3 screening trials[36,37,51] and 1 trial testing a methodological intervention (remote set-up of mobile health technology for a longitudinal cohort study).[47] Over half of trials ($n = 26$) used a placebo comparator, 6 used usual care or no additional treatment,[33,37,48,52,56,61] and 5, an active drug comparator.[18,24,35,39,50] The 3 device trials used sham device comparators. Screening intervention trials employed delayed screening,[36] attention control (educational website without screening test),[51] or usual care.[37] Thirty of the trials delivered the intervention directly to participants at home (Tables S7-13).

Six trials used a bring-your-own-device model, employing participants' own devices such as smartphones,[21,39–41,45,47] wearables[41] or blood pressure monitors[53] for data collection. Eleven trials used routinely collected healthcare or administrative data sources for study data collection[18,28,29,32,37,48,50,52,54–56]; 13 collected blood samples,[23,25,31,35,39,46,50,55,57] 6 collected urine,[31,39,46,51,55,57] and 8 collected other physical samples such as swabs or saliva,[30,35,37,38,53,54,58,61] all using a variety of collection methods (Tables S14–18). Most trials ($n = 37$) collected participant reported outcomes, using a variety of methods including postal and web-based questionnaires, and smartphone apps (Table S19).

Forty-four percent of trials ($n = 20$) reported using an external vendor to deliver all or part of the trial (Table S20).

Thirty-five trials were registered: 27 on ClinicalTrials.gov, 7 on ISRCTN.com, 2 on both registers and 1 on ANZCTR. Of the 9 trials for which we could find no trial registration, 3 were within the last 10 years.

3.1.3 | Risk of bias

Of the completed trials reporting only nonmethodological primary trial outcomes ($n = 24$), we assessed 5 as being at a high risk of bias.[21,26,38,42,60] Eleven trials presented some bias concerns,[19,22–25,27,28,31,40,48,56] and 8 were assessed as at low risk of bias.[29,34,36,49,51,57,59,63] Two trials reported methodological comparisons, 1 assessed as low risk,[39] and 1 high.[35] Three completed trials were feasibility studies with insufficient available information to allow risk of bias assessment.[20,46,47]

None of the incomplete trials ($n = 16$) was assessed as being at a high risk of bias. We evaluated 3 as being at low risk of bias,[54,61,62] while the remaining 14 presented some concerns, primarily due to limited available information.

A summary of the risk of bias assessments can be found in the Supplemental file, pp31–49.

3.2 | Wider review

3.2.1 | Description of included documents

Characteristics of source documents included in the wider review are summarised in Table 4. 117 publications were identified between 1988 and 2020; the median year of publication was 2017, demonstrating a clear skew towards recent years. Fifty-four publications discussed at least 1 of the 37 trials included in the focused review; 25 based in the USA, 11 in Europe (8 based in the UK) and 1 in Australia. A complete list of included documents can be found in the Supplemental file, pp 49–54.

3.2.2 | Advantages and disadvantages of DCTs

We identified 4 major themes in the advantages and disadvantages cited in source documents: research value, burden, safety and equity. Twenty-eight advantages and 25 disadvantages of DCTs were cited; we coded these under the major themes and broke them down into the narrower themes described in Table 5 (see Tables S34, 35 for representative quotations). Many authors cited ease of trial participation as a major advantage of decentralised methods; for example, "[enabling activities to be carried out at a time convenient to the participant] *dramatically reduces 1 of the major barriers to recruitment and retention—the time invested by a patient in a trial*",[64] and "*monitoring can occur passively without any additional work required of the participant beyond wearing and occasionally charging the device*".[65] However,

TABLE 4 Summary of types of documents included in the wider qualitative review

Description		Intended primary audience (n) Academic	Industry	Public
Source	Journal	88	7	0
	Institutional/company website	2	7	0
	News/magazine website	0	9	1
	Blog	0	2	0
	Public slide sharing website	1	0	0
Type	Research article	58	0	0
	Commentary	11	17	1
	Conference abstract	18	0	0
	Press release	1	3	0
	Promotional feature	0	2	0
	Report	0	2	0
	Slide set	1	1	0
	Recommendation/guidelines	1	0	0
	Research presentation (recorded)	1	0	0
Country	North America	68	16	1
	Europe	20	8	0
	Asia	1	1	0
	Australia	2	0	0

TABLE 5 Advantages and disadvantages of decentralised clinical trials

Broad themes	Narrow themes	Advantages
Value	Improving research quality	Generalisability of trial results (real-world data, representative cohorts)[67,72,86–88]
		Data quality (more data, timeliness, sensitivity, objectivity)[64,66,67,74,79,80,82,86,89–92]
		Novel biomarkers (new endpoints, multidimensional data)[76,88,89,93–96]
	Better participant engagement	Enabling self-management[65,95]
		Improved communication between participants and research personnel[97]
		Building trust[72,98]
	Enabling otherwise infeasible research	Permitting data-driven adaptive trial designs[99]
		Allowing trials in rare diseases with geographically dispersed patients[33,90]
	Knowledge generation	Improving scientific understanding of disease (new data types, real-world data collection, longitudinal and multidimensional data)[67,75,79,95,100]
	Improving healthcare	Better evidence for decision making[92,101]
		Generating useful individual patient data[54]
		Faster answers to clinical questions[21,92]
		Better understanding of patient experience[67]
		Promoting remote health care delivery[40]
	Commercial advantage	Faster drug development timelines[21,102]
Burden	Reducing burden of trial participation	Offering participants choice/flexibility in how to participate[72,103]
		Fewer in-person study visits[64,104]
		Passive data collection[65,90]
	Reducing burden of trial conduct	Less costly training (of staff and participants)[105]
		Less staff required to run each trial[106]
		Fewer investigative sites[106,107]
		Lower quality assurance/monitoring costs[25,106]
		Automation of tasks[76,89,105]
	Reducing waste (efficiency)	Data-informed trial management[66,92,97,108]
	Reducing burden of trials on healthcare professionals	Easier identification of eligible patients[26,54,91,109]
Safety	Maintaining privacy	Confidential nature of online interactions[72,73]
	Preventing physical harm	Continuous monitoring of potential adverse events[66,90]
Equity	Broadening access to clinical trials	Removing barriers to participation (geographical, time, travel)[36,42,72,90,97,104]
Broad themes	**Narrow themes**	**Disadvantages**
Value	Suitability for research question	Not suitable for all research questions[86,94,100,104,110]
	Risk to research quality	Difficulty ensuring eligibility[60,105,111]
		Lack of suitable devices to collect data remotely[74]
		Lack of researcher control over data collection[94,112,113]
		Risk of poor comprehension of study purpose by participants and resulting in reduced adherence[49,72,77,80,94,105]
	Commercial value of research	Lack of involvement of prescribing physicians in research may reduce familiarity of product and post-approval sales[106]
Burden	Increasing the burden of trial participation	Reduced participant choice[72,94]
		Limited communication opportunities[72]
		Financial cost of technology use[51]
		Volume of trial activities[66,77,93]
		Complexity of trial activities[47,60,81]
		Burden of wearing and charging devices[65,77,81]
		Emotional burden of responsibility for trial conduct[77]
		Lack of in-person support[107]

TABLE 5 (Continued)

Broad themes	Narrow themes	Advantages
	Increased burden on trial staff	Challenges in providing technical support to participants[60,77,80,81,95]
		Learning to manage trials using new technologies[104,106,114]
	Higher cost of trial conduct	Initial investments in equipment and training[77,94,106]
		Unforeseen costs[80,81,106]
Safety	Risk of physical harm to participants	Potential for inappropriate/unsafe administration of trial medicines[111]
	Risk of harm to autonomy	Lack of face-to-face interaction to check understanding[60,94,111]
		Loss of protective doctor-patient relationship[111]
	Potential for breach of confidentiality	Home delivery of trial materials may be identifiable[73]
		Vulnerability of electronic data transmission[60,72,96,105,107,114]
	Risk of harm to patients	Implementation of healthcare interventions based on potentially inaccurate research findings[111]
Equity	Excluding groups of potential participants	Differential technological barriers[80,91,115]

a few acknowledged a potential to simply transfer the burden of trial activities from site-based study staff onto individual participants; for example, "*Burden factors unique to remote study protocols include, for example, the imposition of recurrent performance of home-based tasks or requirement for consistent reporting on symptoms and drug intake times*"[66] and "*Participants having to activate, charge and wear the digital sensors for long hours may be a significant obstacle to success of the virtual trials*".[65]

3.2.3 | Facilitators and barriers of DCTs

We identified 25 facilitators and 34 barriers in the following categories: technological, logistical, regulatory, societal and other. These are summarised in Table 6.

3.2.4 | Participant, patient and other stakeholder opinions

Thirteen sources contained qualitative data on participant experiences or opinions of DCT methods gained from participant satisfaction questionnaires.[25,34,47,65,67–75] Fourteen had subjective assessments of participant experience,[30,34,47,51,72–81] e.g., "*The teleconsultation visits were well received by the patients in both the decentralised and conventional settings, especially when an effort was made to arrange calls outside the participant's working hours.*"[81] Only 3 sources contained verbatim quotations from patients or participants including experiences or opinions of DCTs[33,69,72]; these are summarised in Table 7.

While several sources suggested how DCTs may impact or be perceived by other stakeholders, such as usual healthcare providers, payers, regulators and ethical review boards, only 2 contained specific quotations from stakeholders other than participants and researchers (including pharmaceutical industry representatives). A qualitative study of a remote trial in a nursing home described in detail the specific burdens of the trial on nursing home staff in terms of comprehension, time, communication, emotional load, logistical burden and product accountability.[77] In a public-facing online magazine article, a Food and Drug Administration (FDA) representative was quoted as having written, "*The FDA is open to innovative trial designs that create efficiencies, serve the needs of patients while protecting their interests and safety, and create data that will be fit for use for regulatory decisions*".[82]

4 | DISCUSSION

To our knowledge, this is the first systematic review of both quantitative and qualitative literature on the strategies and approaches used to conduct decentralised clinical trials.

We identified 45 individually randomised clinical trials using a variety of wholly or partially decentralised methods ranging from relatively *low-tech* postal trials, with participants supplying their own medication and completing paper-based questionnaires, to trials deploying an array of wearable internet-connected devices to collect multi-dimensional longitudinal data. The trials were also diverse in their cohort size, therapeutic area, completion status, purpose and funding source. However, geographically, most trials were led by investigators in the USA and Europe (mainly UK).

Although we assessed several trials as being at high risk of bias, this does not necessarily indicate poor methodological quality as there were often insufficient data available to make a clear risk of bias assessment. Future adherence to applicable reporting standards, such as CONSORT and its extensions,[83,84] will improve transparency.

As with the included trials, sources eligible for the wider qualitative review were dominated by USA and European authors. While this

TABLE 6 Summary of decentralised clinical trial (DCT) facilitators and barriers

Facilitators of DCTs	
Technological	**Specific examples cited**
Devices with wireless connectivity	Tablet computers,[31] smartphones,[82,107] wearables,[45,60,64,65,74,77,79,82,88,91,95,101,104,113,116] other sensors,[21,47,64,67,79,82,93,95,100,102,108,117] wireless connectivity[35,74,79]
Software	Open-source app development platforms,[67,76,79,97,118] electronic health records (EHR) and patient portals,[54,56,88,91,101,114,119] electronic case report forms (eCRF),[35,95] integrated clinical trial platforms,[45,89,96,100,102,103,120] electronic participant-reported outcomes (ePRO),[21,66,91,116] online neurocognitive testing,[60] encryption,[65,114,121] social engagement platforms[99,107]
Telecommunications	Widespread and accessible internet infrastructure and mobile telephone networks,[69,82,90,108,118,122] cloud computing,[79] telemedicine[46,47,89,91,100,102,115,116]
Databases	Administrative healthcare datasets,[96,114,119] disease and procedure registries,[91] research biobanks and databases[47,105,119]
Data science	Blockchain,[113] natural language processing,[91] machine learning and artificial intelligence[66,91,97,101]
Regulatory	
Formal regulation/legislation	FDA Federal Regulations,[100] laws governing telemedicine,[94] FDA approvals of medical devices for home use[102]
Regulatory guidance	FDA guidance on electronic source data,[105] risk-based monitoring,[100] electronic signatures and informed consent,[99,100,105] mobile medical applications[79,105]; MHRA guidance on risk-adapted approaches to clinical trials[54]
Reflection papers	EMA reflection paper on risk-based quality management[100]
Initiatives and programmes	FDA Real-world Evidence Program,[91,97,113] FDA Digital Health Innovation Action Plan,[79,98] FDA Center of Excellence for Digital Health[91]; EMA workshop "Identifying opportunities for 'big data' in medicines development and regulatory science."[79]
Training	Training for ethics committees/IRBs[105]
Positive regulatory attitudes towards novel trials	"*Most companies are finding the FDA to be very supportive of virtual trials*"[99]
Independent legal/regulatory consultants	"[legal] *expertise may be obtained from external legal consultants and/or companies that track and report state-by-state changes in laws and regulations*"[94]
Logistical	
Speciality vendors	CROs with DCT capabilities[45,98,100,102,110,116,117]; home nursing and phlebotomy services[94,104,116]; temperature controlled courier delivery[113]; Cloud-based hybrid mail services[54]; speciality logistics companies[117]
Tech-enabled logistics	Tech-enabled IMP accountability systems, e.g., RFID tags[64,94,104,113,117,123]
Research networks	InSite platform (EU), CancerLinQ (US), PCORNet (US)[91,120]
Social	
Familiarity with DCT components	Internet usage,[35,36,69,105,107] telemedicine,[94,113] mobile and wearable devices[66,79,107,113,124]
Ownership of consumer electronic devices	Smartphones,[36,60,66,67,76,91,93,105] wearables[124]
Attitudes	Positive attitudes towards remote research[35]
Other	
International standards	International Council for Harmonisation,[100] Fast Healthcare Interoperability Standard (FHIR)[96]
Collaboration and knowledge sharing between stakeholders	Public–private partnerships, consortia and associations[97]; Clinical Trials Transformation Initiative,[79,94,100] Patient-Centered Outcomes Research Institute,[100] Transcelerate,[82,125] International Consortium for Health Outcomes Measurement,[86] Intensive Longitudinal Health Behavior Network[96]
Strategic research funding	US NIH "Strategic transformation of population studies" and "Digital clinical trials"[47,96]
Commercial investment	Pharmaceutical companies,[90,107] venture capital,[91] tech companies[91]
Recommendations	CTTI recommendations on Mobile Technology and Novel Endpoints,[79,94,100] reporting guidelines e.g., CONSORT extension for trials using cohorts and routinely collected data (forthcoming)[91]
Open Innovation	Crowdsourcing for protocol development and new indication finding[126]
Appropriately trained research workforce	Medical computer scientists, technically-trained clinicians[106]

TABLE 6 (Continued)

Facilitators of DCTs	
Technological	**Specific examples cited**
Barriers to DCTs	
Technological	**Specific examples cited**
Immature digital infrastructure	Lack of interoperability between EHR systems[91,97,105,113,119]; lack of high-speed internet coverage[26,59,68,69,90]
Lack of suitable devices	Limited battery life[66,79]; lack of ease in operation[65,66,82]; lack of simple user interface[31,66]; insufficient data storage capability[67,82]; inaccurate/inconsistent data[74,76,127]; wearables not comfortable in extended use[36,81]; frequent required firmware updates[80]
Difficulties in managing data	Difficulties transmitting large data files from devices to study database[67,74,81]; lack of data standardisation[79,97,105]; lack of accepted methods for analysis[79,82,91]
Novel endpoints	Lack of validated objective measures that can be captured electronically[67,91]; lack of suitable reference comparators[67]
Limitations of routinely collected data	Limited validation of clinical trial endpoints[91,119]; sub-optimal accuracy and completeness of data[91,105]
Regulatory	
Perceptions of regulatory barriers	Assumptions that regulation will prevent DCT use[71,94]; worries about meeting requirements[64]
Uncertainty about how to apply existing regulations	Unclear data ownership[79]; uncertainties about oversight and liability of mobile healthcare providers, and other vendors[94]; lack of clarity on validation requirements[94,100]; lack of clarity on the use of central monitoring systems and real-time data[100]; changing regulatory requirements and import procedures
Need to prove data reliability and validity to regulators	Uncertainty about the acceptability of novel endpoints[64]; complexity of hardware/sensors/algorithm interplay makes evaluation difficult[97,112]; proprietary/closed algorithms[97,112]
Variation of legislation between jurisdictions	Differing rules about distributing, returning and destroying IMP[31,94,100,104,117]; local physician licensing requirements (for prescribing and telemedicine)[94,100]; restricted shipping of devices[80]; app usage[92]
Lack of applicable regulatory provisions	Specific regulatory provisions for remote methods[82,87,100,103,105,111]; lack of explicit requirements for electronic data capture and transmission[100]; lack of standards for collection of subjective data[100]
Regulation or legislation that explicitly prevents DCT activities	Delivery of IMP or prescription of drugs across jurisdictions without local licensing not allowed in several US states[94,100]; prohibition of central distribution of IMP direct to study participants without local site dispensing in some countries[104]; current requirements for waivers[31]
Multiple responsible bodies	*Fragmented IRBs* requiring multiple approvals[119]
Regulatory standards for clinical trials increasing the cost of trial conduct	Resourcing requirements for quality (monitoring, event adjudication etc) and regulatory adherence[113,114,117]
Lack of evidence to support fully remote trials	Need for validation to confirm results obtained through remote and conventional trials are comparable[94]
Challenges in proving data attribution to individual participants	Perceptions that devices may be mis-used e.g., worn by nonparticipants[64]
Regulators unfamiliar with remote methods	"*Though the FDA has stated that they see benefits in the appropriate use of technology in clinical trials, they are still in the process of learning about virtual clinical trials, the bring-your-own-device (BYOD) model of provisioning and other aspects of today's tech-enabled research environment*."[99]
Logistical	
Availability of flexible, global, specialty logistics support	Smaller companies may have limited resources and/or local exposure to differing regulatory environments[117]
Scaling up existing research site capabilities	Sites may need additional resources to enrol larger numbers of participants[71,94]
Societal	
Limited experience with DCTs	Lack of patient and clinician familiarity with technology-enabled trials[87,92,99,105]
Inequalities in digital access	Excluding people in rural areas or on low incomes[69,92]
Privacy concerns	Concerns about identifiable mail or deliveries[51,73]; reluctance to enter personal information online[96,107,128]; perceptions of unrestricted access to medical information[91]; concerns about wearable visibility[47]

(Continues)

TABLE 6 (Continued)

Facilitators of DCTs	
Technological	**Specific examples cited**
Public attitudes towards digital/online activities	Tendency toward lack of prolonged engagement with digital apps[76]; cultural preferences against apps[76]; suspicion that unsolicited email contacts may be scams[72,80]
Healthcare system attitudes to research	Lack of recognition of value of research and financial incentives to increase care volume[119]
Poor computer literacy in target groups	Older people[64,92,115]
Participant preference	Preference for in-person trial activity[64,129]; perceived benefits of in-person trial activity[49]
Other	
Lack of consensus on data requirements	No widely accepted margin of error on data attribution[91]
Cost of investment	Investment needed to develop suitable technology platforms[91,106,107,119]; pharmaceutical companies and CROs will need to invest in upgraded systems to handle big data[82,107]; public investment in infrastructure[91,119]
Conservative corporate culture	Burden of innovation risk on single companies[82]; rigid systems[64]; "regulatory paralysis"[128]; "industry resistant to change"[64]
Information governance approval requirements for access to routinely collected data	Resource intensive approvals for EHR data access[114]
Lack of experience with DCTs	Limited methodological research[105]; lack of evidence to support remote recruitment, retention and engagement[93]; limited experience with remote clinical diagnosis[87]
Lack of suitable trained and experienced workforce and leadership	Lack of highly skilled interdisciplinary leadership and technology experts[97]; clinicians and PIs who are not confident using technology[92];
Current clinical trials financial arrangements	Conventional research generates revenue for research centres[64,96]
Conservative research funding agencies and decision makers	"*ongoing funding of clinical research depends almost solely on the decision of trial funders, whether grant reviewers or medical industry leaders, who historically tend to support the status quo rather than drive innovation*"[96]

Abbreviations: CRO, clinical research organisation; FDA, Food and Drug Administration; IMP, Investigational Medicinal Products; IRB, institutional review board.

may be due to the relative volume of trial activity in these places, there may be barriers to DCT development elsewhere, such as technological limitations, regulatory impediments or societal preferences. As many of the purported advantages of DCTs should be applicable worldwide, further specific investigation of DCTs in other countries may be warranted.

We identified comparable numbers of unique advantages and disadvantages. However, it should be noted that the literature was positive overall towards DCTs; this may well reflect publication bias as unsuccessful experiments with DCT methods may be less likely to be published, or there could be a bias towards novelty, particularly in news and commentary sources.

As might be expected, technology features heavily as both facilitators and barriers to DCTs; developments in this field are likely to continue to present new challenges and solutions. However, it is also clear that the regulatory climate, both formal legislation and its interpretations, impacts both perceptions and practicalities of DCT conduct. Regulators are now producing specific guidance addressing DCTs, e.g., "The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products".[3] We expect these and any future guidance to influence further DCT development. Similarly, the societal background against which DCTs take place can both encourage and discourage their use. For instance, the COVID-19 pandemic has had significant impacts on the use and perception of communications technologies and the willingness of people to attend busy clinical settings.[85]

While often referring to positive participant experiences of DCTs, the included papers contained minimal exploration of what it means to be a DCT participant. A deeper understanding of this, gained through qualitative research, could inform the successful implementation of DCTs. Similarly, we found little examination of how DCTs impact external stakeholders, such as healthcare providers, how funders and review boards view DCTs, or how the results of DCTs will be treated by decision-makers such as regulators and healthcare payers.

4.1 | Limitations

DCTs are a relatively new concept with terminology that has not yet settled. Despite including several known terms to describe DCT methods, our searches may have missed relevant source documents employing other terms, particularly where authors have not explicitly drawn attention to DCT elements. In addition, we restricted our searches to the English language only; this may have introduced bias. As noted above, our findings are likely to be subject to publication bias. The collected data were not suitable for a meta-analytic approach to publication bias assessment. The high variability in quantitative data availability and reporting also meant that we could not

TABLE 7 Participant experiences and patient opinions of decentralised clinical trials (DCTs)

Theme	Sentiment	Experience of taking part in a DCT
Burden	Positive	"I can choose the time of the day I'll answer the questions, and the environment is familiar (I do it at home or work, and not a hospital or clinic)."[72]
		"Despite the lack of physical presence, a warm, reassuring environment was established. To tell the truth, I was very surprised"[69]
		"Easy to participate as it was Internet-based. Also as a runner and researcher I was interested in the research question"[72]
		"The comfort of my own home… I felt more relaxed and felt I communicated better"[69]
	Negative	"I went through a bunch of hoops to get my doctor to say he would participate in it … I gave her the paperwork and stuff, and then I get e-mails from the TAPIR trial thing. They hadn't heard from her, and I'd call her and—or the next time I'd see her. And then eventually she said, well, she had given it to her people in her office to do it, and they would've—they only did them as they came in, and so they were working down the pile to mine"[33]
		"Just the time effort and 1 more task you, however little, you should do in a busy week."[72]
		"it is not as personal as being in the same room with a person"[69]
Safety	Positive	"But I felt that you guys did a good job in identifying yourselves as a legitimate group conducting a genuine research study and that eased my mind on the matter."[72]
Value	Negative	"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."[72]
		Opinion of DCTs
Burden	Positive	"I could be involved in more studies, as it is now I am limited to places real close or have my husband drive me"[69]
Value	Negative	"Organiser does not know who is really taking part—I could be 15 year old boy or 80 year old woman … (am neither!)."[72]
Value + Burden	Mixed	"My initial reaction was, 'gee, this is really great… it's gonna be a lot cheaper to be able to access the information used in computers than it is to have a 15 minute visit in a doctor's office every 3-6 months… I thought, 'this is really a great idea… but it also has a great problem'. To understand this, you have to think about what happens between a doctor and an individual patient. That patient is supposed to have a certain amount of trust and confidence in that doctor… an average patient is gonna say, 'why in the world should I do this?'… so it's very important to think of ways we can try to humanise this."[129]
Safety	Negative	"The disadvantage would be the fact that I may not be able to tell whether the study was genuinely conducted by the University or just a hoax. […] As you may know, the Internet has a lot of evil people trying to get access to personal information via similar methods."[72]
Equity	Positive	"I just think it's neat! Being able to use the Internet for medical surveys allows people all over the world to participate in studies that they would otherwise not be able to, especially when the surveys do not require extensive medical testing or histories. It's a small world after all."[72]

make meaningful comparisons between methods in terms of recruitment, retention, or other trial performance metrics. As a result, this review presents only a descriptive analysis. Data on the financial costs incurred in running trials were sparse; this is unsurprising given the potential commercial sensitivity of such information, but it does mean that we have not confirmed the oft-cited advantage of DCTs being less costly than conventional site-based trials.

We did not do a formal quantitative analysis of the number of times each advantage, disadvantage, barrier or facilitator was cited, nor have we made any assessment of their validity. Such judgements may be misleading because the number of times commentators say something, such as that DCTs will be better at recruitment than conventional trials, does not necessarily mean it will be proved true. Similarly, something perceived as an advantage by 1 person, such as not having any in-person contact with a study doctor, may be a disadvantage to another. By reporting all of the advantages, disadvantages, barriers and opinions that we found, we have produced a resource to inform DCT approaches.

5 | CONCLUSION

DCTs are a developing field with a wide variety of approaches that can be applied to various therapeutic areas and research questions. Many commentators have identified the great potential of DCTs in harnessing technological developments to improve the efficiency, generalisability and participant experience of clinical trials. However, there remains a lack of directly comparable data on key performance indicators such as recruitment, retention, adherence and cost metrics to confirm these benefits. We urge investigators conducting research using DCT methods to publish their findings, including negative results and data regarding the operational aspects of DCTs. Such data would allow investigators, sponsors and regulators to make informed decisions about future DCTs. By combining operational data with insights from patients, trial participants and other stakeholders, we stand to maximise the potential gains of this approach.

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COMPETING INTERESTS

The authors declare current or recent research income to their institution from Novartis, Pfizer, GSK, Menarini, IMI, EMA, NIHR HTA, BHF, Amgen, RTI, CSO Scotland, Tenovus Scotland, George Clinical, Sanofi and HDR UK, and consultancy income to their institution from AstraZeneca. ISM declares personal consultancy income from AstraZeneca. TMM declares consulting or speaking fees in the last 5 years from Novartis, Takeda, Servier, Shire, Menarini and AstraZeneca.

CONTRIBUTORS

All authors made a significant contribution to the concept, design, analysis, writing and revision of the manuscript, and have agreed to be listed as authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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