POST-SCREEN (GREY)

Decentralised, patient-centric, site-less, virtual, and digital clinical trials? From confusion to consensus

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There is increasing interest in clinical trials that use technologies and other innovative operational approaches to organise trial activities around trial participants instead of investigator sites. A range of terms has been introduced to refer to this operational clinical trial model, including virtual, digital, remote, and decentralised clinical trials (DCTs). However, this lack of standardised terminology can cause confusion over what a particular trial model entails and for what purposes it can be used, hampering discussions by stakeholders on its acceptability and suitability. Here, we review the different terms described in the scientific literature, advocate the consistent use of a unified term, 'decentralised clinical trial,' and provide a detailed definition of this term.

Keywords: decentralised clinical trial; remote clinical trial; virtual clinical trial; telemedicine; direct-to-patient; patient-centric

Introduction

Clinical trials are indispensable in demonstrating the benefits and risks of new medicines, medical devices, and nonpharmacological interventions. However, many challenges can impact clinical trial conduct, such as slow participant recruitment, low participant retention, the burden of trial-related visits to the investigative site, high costs, and impact of the trial results, resulting from the limited generalisability of trial results to routine clinical practice [1–2]. The increasing implementation of digital health technologies, such as wearable devices, mobile applications, and telemedicine, in clinical trials now makes it possible to recruit, assess, and monitor trial participants without them having to leave their homes or their local healthcare environment. This reduces the time participants spend travelling to the investigator site and allows for the inclusion of participants who live further away and, as a consequence, might be unable to travel to the clinic. Additionally, the inclusion of digital health technologies could reduce the burden of participating in clinical trials, possibly facilitating recruitment, and increasing the diversity and subsequent generalisability of the trial findings [3].

The Coronavirus 2019 (COVID-19) pandemic, during which strict social distancing and travel restrictions were implemented, forced the clinical research community to adjust clinical trial management. As a result, investigators and sponsors had to implement diverse solutions, such as telemedicine, and other operational approaches to safeguard patient safety and guarantee

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clinical trial continuation without participants going to an investigator's site [4–6]. Regulatory authorities, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), responded by providing temporary flexibilities for various trials to ensure trial continuation [7–9], including guidance on obtaining remote (electronic) consent, distributing investigational medicinal products (IMPs) directly to the participants, and use of telemedicine visits.

This already increasing interest, catalysed by the COVID-19 pandemic restrictions and subsequent drive to implement digital and innovative operational approaches, now provides the opportunity to explore such alternative operational clinical trial models, which centre trial activities around trial participants rather than around investigator sites. The operational approach in clinical trials refers to the practical aspects of the implementation of the trial, including recruitment, staff training, data management, and operational details. A wide range of terminology has evolved to describe this operational model in clinical trials, such as site-less trials, digital trials, and decentralised clinical trials, to mention some (Box 1).

The lack of standardised terminology for describing this operational model impedes discussions between stakeholders, because identical terms can be used to describe different operational clinical trial models or even different methodological aims, hampering discussions of the scope, suitability, and acceptability of trial models and specific trial activities. For example, the term 'virtual clinical trial' has been used to describe not only technology-enhanced clinical trials involving participants, but also computer-modelled or *in silico* clinical trials in which no actual participants take part [10–12]. In addition, both 'decentralised' and 'virtual' clinical trials have been used to describe trials with a more pragmatic trial design [13–14], whereas the operational model of centring trials around participants could also be used for the more traditional explanatory clinical trials [15], which aim to show the isolated drug effect under strictly controlled circumstances [13–14]. Therefore, here we map the terminology on clinical trials that centre trial activities around the participant using technology and other innovative operational approaches, by exploring the definitions described in the scientific literature. We highlight differences between and (dis) advantages of the identified terms. In addition, we advocate the use of a single term to harmonise discussions concerning such clinical trials. Agreement on terminology and a description of what this type of clinical trial entails, including its limitations, could ease and improve stakeholder interaction, including regulatory and ethical processes.

Literature review of terms used to describe clinical trials

We conducted a literature review of terms used to describe clinical trials that utilise technology and other innovative operational approaches to centre the trial around the participant, using MEDLINE (via PubMed) as the main search engine. The search strategy included the following terms using both British and American English spelling: 'digital trials' or 'digital clinical trials'; 'virtual trials' or 'virtual clinical trials'; 'site-less clinical trials'; 'patient centred trials' or 'patient centric trials'; 'patient centric clinical trial' or 'patient centred clinical trial'; 'remote patient centred trials'; 'remote trials' or 'remote clinical trials'; 'decentralised clinical trials'; 'online clinical trials'; 'direct-to-patient' and 'clinical trial.' The search was conducted independently for each group of terms in August and September 2021. The literature search was supplemented by snowballing; that is, relevant references were searched from the identified literature. We included publications in English indexed in MEDLINE that included any of the aforementioned terms and stated a definition. We excluded articles in which 'virtual clinical trial' was used in the context of *in silico* trials. In addition, we excluded articles in which 'patient-centric trial' was used in the context of 'tailored to the patient's wishes' instead of referring to the physical proximity of the trial activities. The following information from the selected documents was extracted by two researchers (Y.S.A.T. and B.L.): publication title, year, term used to describe the clinical trial model, definition, and relevant references. The different definitions were summarised and descriptively analysed.

The search identified 211 articles, of which 26 articles were selected after applying the inclusion and exclusion criteria. The main reasons for excluding articles were the description of computer simulations ($N = 115$), studies that included a decentralised operational approach but not a trial definition ($N = 17$), studies without a term definition ($N = 22$), literature reviews of clinical trials with meta-analysis ($N = 9$), and the use of 'patient-centric clinical trials' in the context of patient wishes ($N = 3$). Eight additional references were identified through snowballing (Figure 1). Of the 34 articles that included a term definition and were included in the analysis, 12 (36%) defined 'virtual clinical trial', six (18%) defined 'remote clinical trial', six (18%) defined 'decentralised clinical trial', and three (9%) defined 'digital clinical trial'. Other terms that were identified and defined included 'site-less clinical trial' ($N = 2$), 'decentralised virtual clinical trial' ($N = 1$), 'remote decentralised clinical trial' ($N = 1$), 'patient-centric trial' ($N = 1$), 'internet-based trial' ($N = 1$), and 'web-based clinical trial' ($N = 1$). Table S1 in the supplemental information online presents the verbatim definitions as identified from the articles, and Figure 2 displays the terms in chronological order of the first appearance in scientific literature. Table 1 presents the condensed definitions of each term as identified from the articles.

The different clinical trial terms found through the search could be divided into three groups: terms focusing on use of technology; terms focusing on the participant; and terms focusing on the location of trial conduct.

Terms focusing on the use of technology

The term 'internet-based clinical trial' is one of the oldest terms noted in the conducted literature search. In 2003, McAlindon *et al.* reported on trial characteristics for which conduct over the internet is suitable and described 'internet-based clinical trials' as clinical trials in which the 'intervention is safe, the medical disorder can be confirmed by remote means, and the outcome measures can be applied by using electronically transmissible technologies' [16]. Furthermore, Paul *et al.* used the slightly different term 'online clinical trial' to discuss the potential of using the internet to conduct clinical trials [17]. The authors discussed

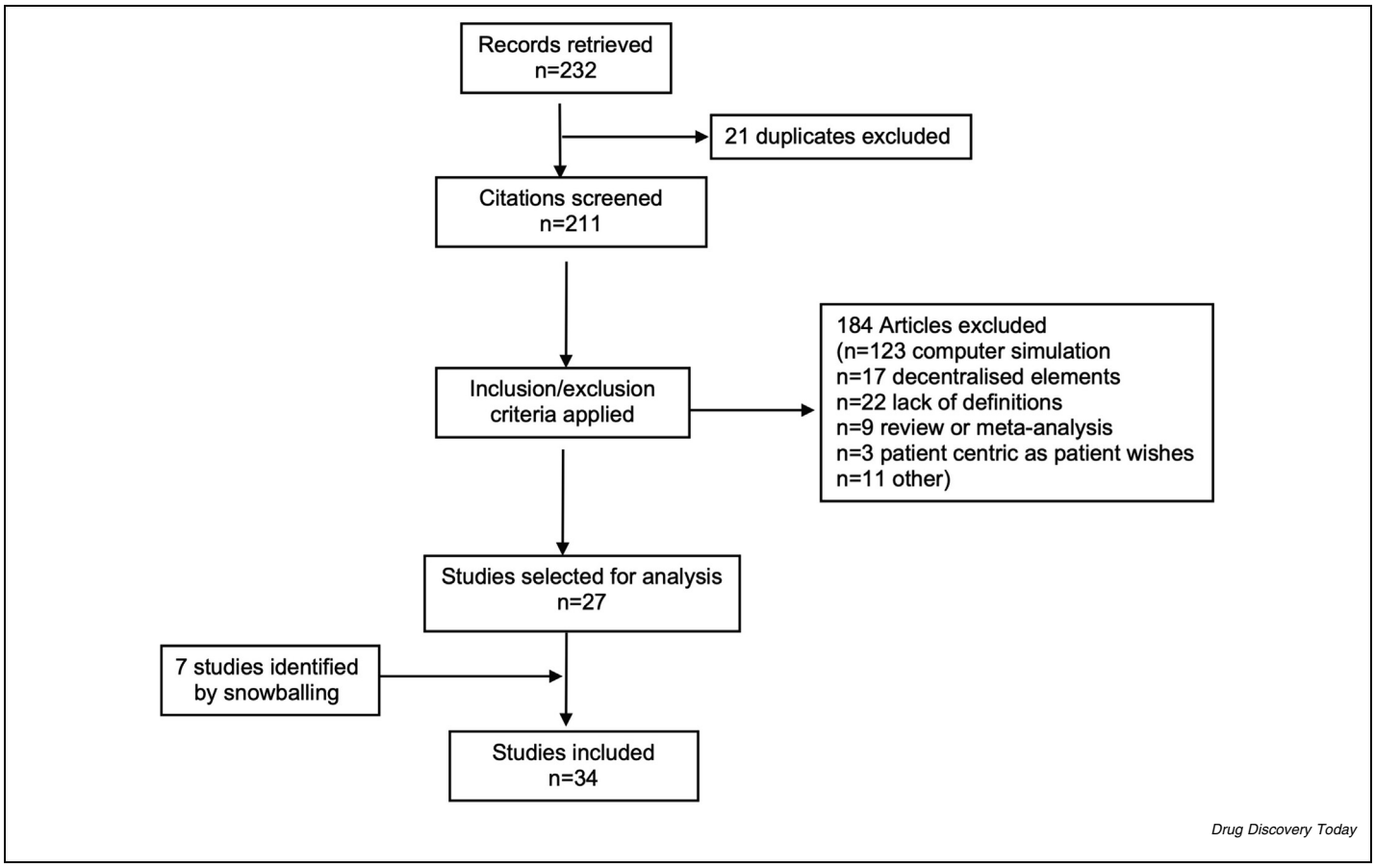

FIGURE 1
Literature search and review strategy.

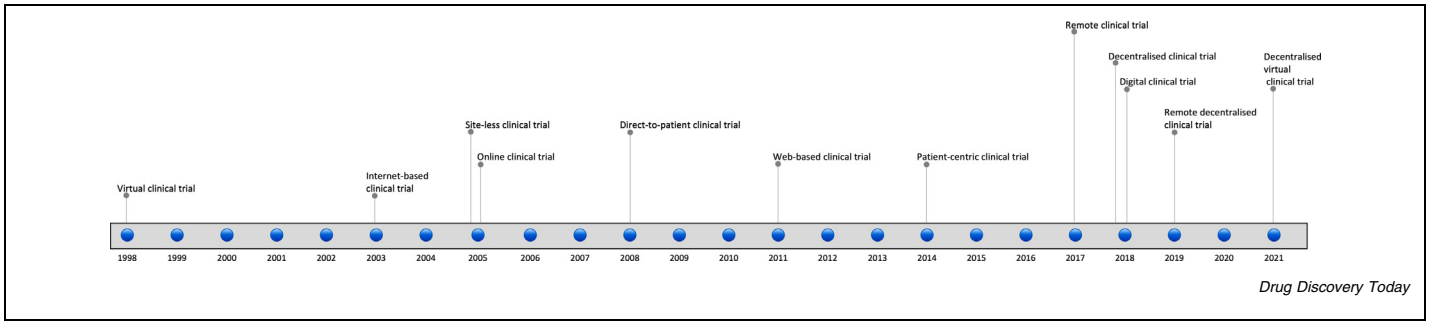

FIGURE 2
Chronological order of terms identified on their first appearance in the scientific literature.

examples, advantages, and disadvantages of online interventions, and concluded that, to be able to conduct online clinical trials, it would be necessary to pay extra attention to the security risks of electronic data administration with the advantage of improving the clinical trial conduct and reducing the cost of multicentre clinical trials [17]. Another related term, introduced in 2011, is 'web-based clinical trial', which was used to refer to the Research on Electronic Monitoring of Overactive Bladder Treatment Experience (REMOTE) trial [18]. This randomised clinical trial with an investigational medicinal product (IMP) was conducted solely using digital tools. Mobile phones were used to collect necessary data for the trial without clinic visits. When the results were published in 2014, the authors used the terms 'web-based' and 'participatory patient-centred' approach interchangeably without providing a definition [19].

In the included papers, 'virtual clinical trial' was most frequently defined (in 35% of papers). Several authors used the term interchangeably with 'online medical research' and 'remote clinical trials' [20–23]. The interchangeability of terms becomes apparent in a 2020 opinion paper by Nissen [24]. In this paper, Nissen describes 'digital clinical trial' and later refers to a definition of 'virtual clinical trials' by Andrews *et al.* from 2017, which summarizes the characteristics of 'virtual clinical trials' focussing on operational aspects, including the online identification of

TABLE 1

Terms and definitions, as described in the literature.

Term	Definition
Internet-based trial	Clinical trial in which the intervention, diagnosis, and outcome measurements are made electronically and remotely, primarily through the Internet
Web-based trial	Clinical trial that uses the Internet- or Web-based technologies to carry out various aspects of the trial, such as recruitment, screening, data collection, and consent with the active participation of trial participants and access to information throughout the study
Site-less clinical trial	Type of clinical research in which some or all trial activities are performed without the need for visits to investigative sites. This approach uses telehealth methods, such as phone and videoconferencing sessions, to provide counselling and ensure protocol compliance, and allows collection of data and administration of treatments directly from the participant's home
Virtual clinical trial	Type of clinical research that uses digital health technologies to conduct clinical trials entirely remotely, allowing participants to engage with research staff and complete study activities from their own location. These trials often involve evaluating effects of clinical interventions, such as medications, devices, and nutritional supplements. They are considered highly participant centred, because they eliminate the need for on-site visits
Digital clinical trial	type of clinical trial that uses technology to improve recruitment, retention, data collection, and analytics. This includes using online methods to identify potential participants, determine eligibility, obtain consent, administer treatment, and track progress. Digital trials can be characterised as those that use remote methods to collect data, whether it be through self-reported outcomes or laboratory measures
Patient-centric trial	Type of clinical trial that focusses on engaging and involving patients in their own healthcare management, typically conducted through a limited number of study sites that are coordinated by a central study coordination centre and data collection from multiple sources
Remote clinical trial	Type of clinical trial that utilises technology to shift some research activities away from traditional sites toward remote settings to improve recruitment, manage trial activity, report results, and ensure safety oversight. This approach aims to encourage participation of a more diverse group of participants, overcome geographic obstacles, and directly involve participants in the research process. The use of telemedicine and digital technologies in remote trials can improve the efficiency and geographic reach of the study. Remote trials are led and coordinated by a local investigative team, but are based remotely within a given community, state, or nation and have many benefits over multisite trials with fewer barriers and lower costs
Decentralised clinical trial[a]	Type of clinical research that utilises telemedicine, mobile/local healthcare providers, and/or mobile technologies to manage participants within their usual environment. DCTs are characterised by less dependence on traditional research facilities or specialist intermediaries for data collection. They leverage tools, such as telemedicine, sensory-based technologies, wearable medical devices, home visits, participant-driven virtual healthcare interfaces, and direct delivery of study drugs and materials to participants' homes

[a] This includes the terms 'remote decentralised clinical trials' and 'decentralised virtual clinical trials'.

potential participants, prescreening potential participants, shipping the drug or device to the participants, and participant-reported data collection, to enable the entirely remote conduct of clinical trials [20].

Most of the definitions highlighted that 'virtual clinical trials' involve few or no in-person visits to the investigator site, emphasising that such trials depend on technology for interaction between the participant and site staff, and data collection, transmission, and processing. The most recent definition identified in this review summarises 'virtual clinical trials' as 'one where patient assessment and data collection do not occur in traditional settings, such as a health centre or hospital, and are instead facilitated via remote interaction' [25]. However, 'virtual clinical trial' was also commonly used to describe *in silico* 'clinical trials' [26–27], which was an important reason for exclusion of those papers (Figure 1).

Three different publications used 'digital clinical trial' [24,28–29], of which two defined the term [28–29], whereas the third referred to a definition of a 'virtual clinical trial' [21]. These publications used the terms to describe the use of technology to facilitate and improve diverse trial activities, such as recruitment, data collection, and analysis. In addition, 'digital clinical trials' has been used to refer to clinical trials in which the (behavioural) intervention was delivered via digital means [29]. The papers defined a 'digital clinical trial' as 'one that uses technology to improve recruitment and retention, data collection, and analytics' [28] and clinical trials 'in which either the intervention and/or the outcome measures are collected remotely' [29].

Terms focusing on the participant

In 2013, Robbins *et al.* examined the patient-centricity concept and described how the discussion of the patient-centricity definition is broader than the context of clinical trials as 'patient-centricity is a dynamic process through which the patient regulates the flow of information to and from him/her via multiple pathways to exercise choices consistent with his/her preferences, values, and beliefs. This fundamentally transformative concept affects how health care decisions are made and who has the authority to make them' [30]. This definition explains patient centricity as a concept in which all facets of a clinical trial, including trial design and clinically relevant outcome measures, are centred around the participant. However, the term could also be used to focus on the operational model. For example, Covington describes 'patient-centred clinical trials' as clinical trials with open enrolment, limited sites, and centralised management and data collection facilitated by the study coordination centre [31].

Terms focusing on the location of trial conduct

The 'site-less trial' concept was initially used in 2017 by Hirsch *et al.*, who called for a framework that can incorporate trials without sites: 'the site-less clinical research organisation model, whereby pharmacists or other health care professionals provide

useful and timely counselling for protocol compliance by regular phone and videoconferencing sessions, is a flexible approach to managing clinical trial participants directly from their homes' [32]. Apart from opinion papers in which the term is used interchangeably with 'virtual clinical trials' [21,33], this term has not been frequently used in the publications that were reviewed.

One of the first 'fully remote clinical trials', conducted in 2014, aimed to assess and compare use patterns and clinical outcomes between three different self-guided mobile apps for depression in the USA [34] The authors described that the 'fully remote trial' involved remote conduct of treatment and assessment via smartphones and tablets with minimal contact with the study staff [34] In 2018, Donnelly *et al.* explored the burden of 'remote clinical trials' in nursing homes, stating that conducting a clinical trial remotely presents an opportunity to leverage mobile and wearable technologies to bring the research to the patient [35] In addition, Dahne *et al.* defined 'remote trials' as: 'trials (that) are led and coordinated by a local investigative team, but are based remotely, within a given community, state, or even nation' [36]. Most of the other papers emphasised the use of technology to describe remote clinical trial activities, including enrolment, electronic consent, and safety oversight (Table S1 in the supplemental information online). This term was used interchangeably with other terms, such as 'virtual clinical trials', 'web-based trials', 'mobile clinical trials', and 'decentralised clinical trials'.

Since 2018, 'decentralised clinical trial' has been increasingly used in various research articles and regulatory guidance documents [37–38]. In 2018, the decentralised clinical trial model was defined as a design with a 'single pivotal site managing patients within their usual environment by leveraging telemedicine, technology and local care providers' [39]. In the same year, the Clinical Trial Transformation Initiative (CTTI) defined DCTs as: 'those executed through telemedicine and mobile/local healthcare providers (HCPs), using procedures that vary from the traditional clinical trial model' [40]. The CTTI further distinguished completely remote (with no required on-site visits) from 'partially decentralised' or 'hybrid' (with some required on-site visits) and 'traditional trials' [40]. The identified definitions highlighted the use of technology for clinical trial conduct and emphasised that these trials are not bound by geography, possibly leading to the inclusion of more diverse participants [41].

Several derivatives of 'decentralised clinical trial' circulate in the literature including 'remote decentralised clinical trial', and 'decentralised virtual clinical trial'. The concept of 'remote decentralised clinical trials' is relatively new compared with the other terms and was introduced in 2019 by the Trials@Home consortium (https://trialsathome.com/), which defined 'remote decentralised clinical trials' as 'clinical trials that make use of digital innovations and other related 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'. The consortium has further put 'remote decentralised clinical trials' on a continuum from hybrid clinical trials 'that use only limited remote methods in combination with more conventional site-based methods' to fully virtual or digital trials 'where there may be no direct interaction between study personnel and participants'. In 2021, 'decentralised virtual clinical trial' surfaced in the literature when Ali *et al.* defined 'decentralised virtual clinical trials' as clinical trials 'that incorporate remote outcome assessments' that 'may accelerate clinical trials, increase adherence, reduce dropout rates, and bring new treatments to the market faster' [42].

Need for common terminology

Given the mix of the terminology used, there is a need for a common term to refer to trials that are centred around participants. The review of the published scientific literature allowed us to map the existent terminology on clinicals trials that include different technologies and other innovative operational approaches to centre trial activities around (potential) participants. We found that most of the definitions referred to mobile technologies, digital methods, or remote elements to ease the conduct of clinical trials. The definitions often emphasise advantages of these technologies for clinical trials, including increased recruitment rates, continuous data collection, and improved participant convenience. The terms described in the current paper are often used interchangeably and many of the analysed articles mention the interchangeability of the terms 'virtual', 'digital', and 'remote'. However, each term is slightly different, and subtle distinctions are expected to be a source of confusion. Furthermore, some papers describe the use of technology to centre clinical trial activities around participants but do not provide a clear definition for this type of trial [43], further obscuring the consistent use of terminology. The lack of clear terminology for clinical trials that centre trial activities around participants could impede discussions by stakeholders, including patients, investigators, sponsors, and regulators, on the suitability, acceptability, and implications of specific innovative trial-related activities and their locality.

Commonly used terms and their (dis)advantages

The three most frequently used terms in the current literature review were: (i) 'remote clinical trial'; (ii) 'virtual clinical trial'; and (iii) 'decentralised clinical trial'. The term 'remote clinical trial' emphasises the remoteness, that is, away from the investigator's site, administration of the intervention, interaction with study staff, and assessment of outcomes. As such, this term can be confusing because the activities are not conducted remotely from the perspective of trial participants. Rather, the opposite is typically envisioned, because trial activities are centred around, or moved close(r) to, the participants' surroundings. Although widely used to describe trials centring activities around participants, 'virtual clinical trial' is also used to refer to *in silico* trials and studies aimed to simulate pharmacokinetic and pharmacodynamic outcomes using historical patient data as opposed to prospective interventional clinical trials [10–12]. The last most frequently used term, 'decentralised clinical trials', was recently used by the FDA to describe trials in which 'patients participate at locations remote from the investigator's site' as described in a draft guidance document that is out for public consultation [44]. Furthermore, the EMA and national health authorities and ethics committees from Denmark and Switzerland recently adopted the term 'decentralised clinical trials' [37–38,45,46]. Fur-

thermore, the Danish Medicines Agency states that the use of 'decentralised clinical trial' is not synonymous with 'virtual clinical trial' because the latter is considered as retrospective data processing without participants [37]. Overall, 'decentralised clinical trial' is increasingly used and appears to be the prevailing term at present. However, this falls short of highlighting the envisioned benefits for the participants and the use of technologies to ease clinical trial conduct. In addition, 'decentralised', equal to the term 'remote', does not suggest that the trial activities are centralised from the participant's perspective. Furthermore, 'decentralised', 'remote', and 'virtual' are not specific to clinical trials, because they are used in other contexts, including '(de)centralised politics,' '(de)centralised computing', 'decentralised finance', 'remote jobs', 'remote access', 'virtual reality', and 'virtual assistance', with connotations other than those for clinical trials.

Toward a consensus definition

The previously described definitions of clinical trials centred around participants can be unified, because they describe recurring concepts, such as the monitoring of participants directly from their homes throughout the course of a clinical trial, the use of technological devices (apps and monitoring mechanisms) and web-based platforms to assist and enable its conduct, and the aim to improve participant recruitment, participant convenience, and protocol adherence. We have shown that none of the terms used is perfect and they all come with their own limitations.

The term 'decentralised clinical trial' can be preferred over 'patient-centric trial' when one focusses on how the conduct of trial activities away from the investigator's site contrasts with the currently most-used site-based clinical trial approach. However, 'patient-centric trial' emphasises that the trial is designed with the needs and preferences of participants in mind. Although this can include the centring of trial activities around trial participants, 'patient-centric trial' is used for a much broader scope than moving of trial activities, rendering the term less suitable for describing this new operational approach to trials. In addition, 'patient centric' is not inclusive of all possible trial participants, which might include healthy volunteers. In addition, 'patient centric' might not be preferred by individuals who do not regard themselves as patients.

Considering that 'decentralised clinical trials' is increasingly used and adopted by important stakeholders within the clinical research terminology, we advocate to collectively start using 'decentralised clinical trials', or DCTs, to refer to the operational model of clinical trials in which trial activities are designed to take place at, or in the vicinity of, the participant's home, rather than at a traditional clinical site. This approach might make use of technologies and other innovative operational approaches to facilitate data collection, such as telemedicine visits, direct delivery of study drugs to participants' homes, and mobile/local healthcare providers. This approach aims to increase participant engagement, recruitment, and retention while minimizing the burden of travel and increasing the representation of diverse participant population. However, DCT approaches do not per definition decrease the number of clinical site visits, because they could also be used to meet other goals, such as enriched data sets or more continuous data collection in the 'real-world'.

Notably, here, the investigator's site should be understood as sites where the investigator conducts the clinical work related to the trial, as opposed to trial site as defined in ICH E6R2, which defines a trial site as a 'location(s) where trial-related activities are actually conducted' [47]. The investigator's site of DCTs has the same responsibility as in traditional clinical trials. The degree of decentralisation depends on the specific design and objectives of the study [48]. Protocols of DCTs should thoroughly describe which technologies and other innovative operational approaches are decentralised. It is noteworthy that most clinical trials already have a degree of decentralisation by including technology that permits data collection outside of the clinical site, such as electronic diaries and wearables. This moves the definition of 'conventional clinical trials' toward 'decentralised clinical trials' on the continuum with 'completely decentralised clinical trials' on the one side, where no physical visits to a clinical trial site are required, and 'conventional' or 'traditional clinical trials' on the other side of the continuum, where most trial activities are conducted in person at the investigator's site (except for telephone follow-ups, for example) making the trend in clinical trials to move toward providing participants with greater degree of choice and flexibility. Furthermore, 'decentralised clinical trials' should be understood as an operational model that can use different trial methodologies that can be steered toward both 'explanatory' or 'pragmatic clinical trials' (Box 1)

> Box 1 DCT description.Decentralised clinical trials, or DCTs, is an operational model of clinical trials in which trial activities are designed to take place at, or in the vicinity of, the participant's home, rather than at a traditional clinical site. This approach can make use of technologies and other innovative operational approaches to facilitate data collection.

The advancement of technology has brought about a revolutionary change in the way clinical trials are conducted. While 'decentralised clinical trial' might not be perfect and could evolve in the future, a consensus on its use and understanding of its meaning will aid in harmonising future discussions on this topic within the clinical trials arena.

Concluding remarks

To ensure clear and effective communication among all stakeholders involved in clinical trials that use technologies and other innovative operational approaches to bring the trial closer to the patients, we call for the consistent use of 'decentralised clinical trial'. The current scientific literature includes a variety of terms that are used interchangeably, without clear definitions or examples, creating confusion and hindering critical discussions on the suitability and acceptability of these trial approaches. By adopting a unified terminology, we can avoid confusion and facilitate productive discussions on the implementation, benefits, and (potential) disadvantages of decentralised clinical trial approaches.

Authors' contributions.

Y.S.T., B. L., A.J.d.J, H. G., D. E. G., K. H., M.G.P.Z wrote the manuscript. Y.S.T. and M.G.P.Z designed the research. Y.S.T., B. L., and A.J.d.J analysed the data.

Data availability

Literature review; data is already available

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Declaration of interests

The authors declare no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.drudis.2023.103520.

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