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Which decentralised trial activities are reported in clinical trial protocols of drug trials initiated in 2019–2020? A cross-sectional study in ClinicalTrials.gov

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ABSTRACT

Objectives Decentralised clinical trial activities—such as participant recruitment via social media, data collection through wearables and direct-to-participant investigational medicinal product (IMP) supply—have the potential to change the way clinical trials (CTs) are conducted and with that to reduce the participation burden and improve generalisability. In this study, we investigated the decentralised and on-site conduct of trial activities as reported in CT protocols with a trial start date in 2019 or 2020.

Design We ascertained the decentralised and on-site conduct for the following operational trial activities: participant outreach, prescreening, screening, obtaining informed consent, asynchronous communication, participant training, IMP supply, IMP adherence monitoring, CT monitoring, staff training and data collection. Results were compared for the public versus private sponsors, regions involved, trial phases and four time periods (the first and second half of 2019 and 2020, respectively).

Setting Phases 2, 3 and 4 clinical drug trial protocols with a trial start date in 2019 or 2020 available from ClinicalTrials.gov.

Outcome measures The occurrence of decentralised and on-site conduct of the predefined trial activities reported in CT protocols.

Results For all trial activities, on-site conduct was more frequently reported than decentralised conduct. Decentralised conduct of the individual trial activities was reported in less than 25.6% of the 254 included protocols, except for decentralised data collection, which was reported in 68.9% of the protocols. More specifically, 81.9% of the phase 3 protocols reported decentralised data collection, compared with 73.3% and 47.0% of the phase 2 and 4 protocols, respectively. For several activities, including prescreening, screening and consenting, upward trends in reporting decentralised conduct were visible over time.

Conclusions Decentralised methods are used in CTs, mainly for data collection, but less frequently for other activities. Sharing best practices and a detailed description in protocols can drive the adoption of decentralised methods.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ By applying broad eligibility criteria, a large set of clinical trial protocols was identified and included in this study, which furthermore allowed for subgroup analyses.
⇒ The creation of a data extraction matrix allowed for manual ascertainment of both decentralised and on-site conduct of a broad range of operational trial activities.
⇒ This study only included protocols of drug trials that are publicly available from ClinicalTrials.gov.
⇒ The availability of more recent clinical trial protocols from ClinicalTrials.gov is limited.

INTRODUCTION

Clinical trials (CTs) are essential in the development of safe and efficacious medicines, diagnostics and medical devices and to evaluate clinical or behavioural interventions. In recent years, there has been a rise in the use of digital health technologies (DHTs) in clinical research.[1 2] These DHTs and other related operations, such as home health visits, enable decentralised (or remote) conduct of CTs, in which operational trial activities are organised around the trial participants and conducted away from investigative sites. Examples of such 'decentralised trial activities' include recruitment via social media, data collection using wearables and mobile applications, home nurse visits, and direct-to-participant (DtP) supply of the investigational medicinal product (IMP).[2–6]

The implementation of decentralised trial activities in CTs could address several issues

with CT conduct, including the high burden associated with participating in a CT and low recruitment and retention rates.[7–11] For example, (electronic) decentralised consent, telemedicine visits and DtP IMP supply could make CTs more participant centred by lowering the number of required on-site visits. Moreover, these decentralised trial activities could lead to increased participant understanding, participant satisfaction and enhanced protocol compliance.[12–16] Furthermore, data generated through wearables is less influenced by recall and observer bias and could lead to more continuous data collection, which may reduce trial timelines and improve safety monitoring.[17 18] Wearables could also lead to the introduction of novel digital endpoints, which is of particular interest in diseases for which no objective biomarker currently exists, such as disease progression in Parkinson's disease.[19]

Initiatives such as the Innovative Medicines Initiative Trials@Home consortium,[20] Clinical Trials Transformation Initiative[21] and TransCelerate[22] have advocated the uptake of decentralised trial activities in CTs and have researched the advantages and disadvantages of such approaches. The healthcare restrictions imposed by the COVID-19 pandemic have further affected the uptake of decentralised trial activities and attitudes of various stakeholders—including sponsors, investigators and regulators—regarding the incorporation of these activities in CTs.[22–24] For example, during the pandemic, regulators overseeing CTs have published guidance on decentralised trial activities for which no guidance or legislation was available before the pandemic, including DtP shipment of IMP and telemedicine visits.[23] Since then, the United States Food and Drug Administration,[25] the Danish Medicines Agency,[26] and Swissmedic and Swissethics,[27] among others, have published guidance specifically for the implementation of decentralised trial activities in clinical research. At present, however, there is limited information about the extent to which decentralised trial activities are implemented in CTs. In this article, we investigate the occurrence of decentralised and on-site conduct of trial activities as reported in publicly available protocols of drug trials with a study start in 2019 or 2020.

METHODS

Study design and eligibility

We analysed published CT protocols from the ClinicalTrials.gov database. Protocols from the ClinicalTrials.gov database were downloaded on 23 and 24 March 2021 using the advanced search box to retrieve phase 2, 3, and 4 protocols with an (estimated) trial start date (ie, first participant first visit) between 1 January 2019 and 31 December 2020 (the full search strategy is detailed in the online supplemental text). Because of the large number of protocols, phase 2 protocols with a start date in 2019 were downloaded on 23 March 2021, and the remaining protocols were downloaded on 24 March 2021. Trial phases were reported following the sponsor classification in ClinicalTrials.gov and verified using the CT protocol where possible. In accordance with previous studies,[28 29] we classified phase 1/2 as phase 2 and phase 2/3 as phase 3. Protocol eligibility was limited to CTs that investigated an IMP (drugs and biological products). In addition, protocols that included only a synopsis or a description of objectives were excluded.

Data collection

Operational trial activities

Decentralised trial activities used in CTs have been previously identified and described by the Trials@Home consortium.[30 31] Building on this work, we developed an extraction matrix including definitions and criteria to ascertain the decentralised and on-site conduct of the trial activities (table 1). The trial activities included in the extraction matrix were participant outreach, prescreening, prescreening through (electronic) medical records, screening, consenting, asynchronous communication with the participant (eg, email, chat), participant training, IMP supply, IMP adherence monitoring, CT monitoring, and data collection. Decentralised data collection was further specified into (1) participant-reported outcomes (PROs), (2) (wearable) devices or biomarker kits, (3) home health visits and (4) telemedicine visits, which encompass both telephone and videoconference calls.

CT characteristics

We collected data on CT characteristics including information on the (estimated) start date, type of sponsor (ie, public or private), trial location (ie, the number of countries involved, and the geographic regions per ClinicalTrials.gov classification—North America, Europe, East Asia, South America, Africa, Southeast Asia, Pacifica, Middle East, South Asia, North Asia and Central America), trial design (ie, trial phase, blinding and randomisation status, and number of sites), follow-up time (ie, the time a participant is expected to be involved in the trial), estimated sample size, type of participants involved (ie, healthy, patient, paediatric), and the therapeutic area (TA). The TA was classified using the International Classification of Diseases revision 11 of the WHO (https://icd.who.int/en). The trial characteristics and definitions are detailed in online supplemental table 2.

Extraction and verification

Data on the predefined trial activities and CT characteristics were obtained manually from the protocols by two researchers (AJdJ and RJG).[32] Data on CT characteristics were supplemented with data from the ClinicalTrials.gov registry. In case of a conflict between information from the protocol and the ClinicalTrials.gov registry, protocol information prevailed. Data from the first 15 analysed protocols were extracted in duplicate. The data from the remaining protocols were extracted by one researcher (RJG) and subsequently peer reviewed (AJdJ). An Excel sheet was used to record the reporting of decentralised

Table 1 Data extraction matrix

Trial activity	Activity definition	Examples from protocols
1.Participant outreach	Outreach to potential participants to raise awareness on clinical trial conduct and participation options.	On-site: *Patients will be recruited from the practice of [doctor] in the Division of Urology, Department of Surgery*. Decentralised: *Patients will be recruited(…)through printed and digital advertising media*.
2.Participant prescreening	Trial activity to describe participant identification activities before informed consent is obtained (1) for which participants' active involvement is required or (2) through the screening of (electronic) medical records.	On-site: *Once obtaining weight and size, we identify overweight or obese patients and risk factors for DM2, they will be invited to continue the counting (ie, glucose) phase*. Decentralised: *The research assistant will obtain verbal consent from patient in order to conduct a preliminary phone screen. Phone screening will be conducted as part of the Anxiety Disorders Clinic's pre-existing screening protocol*.
3.Participant screening	Trial activity to describe activities performed to ensure participant eligibility after informed consent is obtained.	On-site: *After obtaining informed consent, the investigator or sub-investigator will perform a screening examination*. Decentralised: *Screening(…)will be conducted through a web-based screening tool, HIPAA-compliant video conference (Telehealth), telephone, or text messaging*.
4.Consenting	Subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate or, in case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical trial.	On-site: *Clinical sites will receive referrals from rural locations, and potential participants will be transported to clinical sites where informed consent, randomization, and administration of [the drug] will occur*. Decentralised: *The informed consent form may be mailed, emailed or faxed to the participant. The consent discussion may then be conducted by phone, conference phone call or in person so that the participant can read the consent form during the discussion*.
5.Asynchronous investigator–participant interaction	Decentralised, asynchronous interactions between participants and investigator to provide study updates and to engage participants throughout the clinical trial (ie, after enrolment).	Decentralised: *To maintain updated contact details, participants will be contacted every two months by SMS(…)*.
6.Participant training	Trial activity to describe training of the trial participant by the investigator staff on study-related materials and/or procedures.	On-site: *Subjects randomized to [intervention] will be trained in intravenous technique by study nurses*. Decentralised: *A study team member calls the participant and reviews use of the study drug, establishes best contact information for response monitoring, and asks the patient to connect/wear the cardiac telemetry monitoring device.(…) A video will be sent to the participant's email address and texted to them providing visual instructions on use*.
7.IMP supply	Dispensing investigational medicinal products administrable in an at-home setting or other study-related materials to the participant.	On-site: *IMP will be distributed to the patient during each visit*. Decentralised: *Doses in between site visits will be administered at the patient's home (or other location convenient to the patient*).

Continued

Table 1 Continued

Trial activity	Activity definition	Examples from protocols
8.IMP adherence monitoring	Activity during which investigator staff (and/or a clinical trial monitor) monitors participant's IMP administration and dosing compliance according to the protocol. In case (e) Diaries were verified during an on-site visit by site study staff, this was considered 'on-site' IMP adherence monitoring.	On-site: *Compliance will be assessed by weekly pill count*. Decentralised: *The investigators (or appropriately qualified designees) are required to review the e-diary data online at frequent intervals to evaluate subject compliance and reported events as part of the ongoing safety review*.
9.CT monitoring	Quality control process to ensure participant safety and data integrity. Important activities include verification of documentation, protocol and regulation adherence, and source data.	On-site: *[Company] or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and GCPs are being followed*. Decentralised: *The sponsor's monitors will(…)communicate frequently via telephone, e-mail, and written communications*.
10.Investigator staff training	Activity that describes the training of investigator staff by the sponsor or contact research organisation. This encompasses training on the trial design, trial equipment, IMP, and investigator responsibilities	On-site: *All training and reads will be conducted by an imaging contract research organization (CRO) as described in the imaging review charter (IRC). Five readers will be trained in-person*. Decentralised: *The company coordinator will conduct the initial web-based system training sessions for study teams via online teleconferences*.
11.1 On-site data collection	In-person study visits at the investigator site by trial participants, during which the following data acquisition activities may take place: imaging, sample acquisition, and the collection of other clinical and safety data.	*Subjects will return to clinic for Visit 4, for history, physical exam, quality of life (QoL), Satisfaction, and Cost Effectiveness questionnaires, and AE assessment*.
11.2 Decentralised data collection through PROs	Participants are involved in the collection of data (by decentralised means) by filling out (e-)PROs	*Patient-reported outcome measures will be captured via an email sent to subjects with direct linkage to REDCap™ (Research Electronic Data Capture*).
11.3 Decentralised data collection through wearable devices, sensors or biomarker kits	Participants are involved in the collection of data (by decentralised means) using wearable devises and sensors, or biomarker kits.	*Subjects will perform home pregnancy testing on day 1 of Cycle 1 and Cycle 2*.
11.4 Decentralised data collection through home health visits	Study visits are performed at the participant's home. Data are collected by healthcare professionals, including sample acquisition, and the collection of other clinical and safety data.	*Blood and urine sample collection may be performed by a mobile nurse professional*.
11.5 Decentralised data collection through telemedicine visits	Decentralised study (follow-up) visits through teleconference or telephone calls during which data are collected by healthcare professionals (eg, AEs, verbal questionnaires).	*Telephone contacts will occur at Weeks 56, 64, 68, 76, 80, 88, 92, and 100*. *Study visits at weeks 0, 4, and 24 will be required in-person; the remaining visits optionally will be performed via secure videoconferencing using the Cisco Meeting app, between the investigator and the subject*.

The full data extraction matrix is included in the online supplemental materials (online supplemental table 1).
AE, adverse event; CT, clinical trial; DtP, direct-to-participant; GCP, good clinical practice; IMP, investigational medicinal product; PRO, participant reported outcome.

and on-site conduct of the trial activities. Conduct was labelled as 0 (ie, not reported or unclear), 1 (ie, explicitly stated), or 2 (ie, implicitly stated). Implicit reporting was based on the context of the CT protocol and determined by specific 'reporting rules' (online supplemental table 3). As an example, if participant screening was reported to be

conducted on-site, and obtaining informed consent was mentioned in the protocol but the locality of consenting was not detailed, it was assumed to be obtained on site and labelled as 2 (ie, implicitly stated).

Data analysis

Outcomes and rationales

The primary outcome was the occurrence of decentralised and on-site conduct (explicit and implicit) of the predefined trial activities reported in CT protocols. The exclusive reporting of decentralised conduct, the exclusive reporting of on-site conduct, the reporting of a combination of both, or no reporting at all was a secondary outcome. This secondary outcome provides more granularity to the primary outcome by describing whether decentralised conduct is reported complementary to, or separate from, on-site conduct.

Additionally, the occurrence of decentralised and on-site conduct of the trial activities reported in protocols was stratified and compared according to the trial sponsor (ie, public or private), geographic regions, trial phases, and four time periods (ie, the first and second quarters and third and fourth quarters of 2019 and 2020, respectively). These comparisons were motivated by the hypotheses that the sponsor type may affect the uptake of decentralised trial activities, as private sponsors have been suggested to be more risk-averse regarding implementation of technology in CTs[33 34]; the region may influence the incorporation of decentralised trial activities, as regulations differ between geographical regions[35]; the trial phase may affect the extent to which decentralised trial activities are implemented, as the safety profile of the IMP is typically more established in later phases[26]; and the implementation of decentralised trial activities may increase over time and may have been affected by the healthcare restrictions resulting from the COVID-19 pandemic.[1 23 36 37]

Statistics

Descriptive statistics were used to report on the collected data. Different denominators were used to report on the trial activity 'data collection', as detailed in the Results section. We performed χ^2 tests to analyse potential correlations. The occurrence of decentralised and on-site conduct of the predefined trial activities was defined as binary outcome variables (yes/no), and the trial characteristics used for the comparisons—type of sponsor, region, trial phase, and time periods—were defined as categorial determinants. To correct for multiple comparisons, the statistical significance level was set at p=0.0019, following the Bonferroni method. That is, 0.05 divided by 26, the number of on-site and decentralised trial activities that were analysed. Statistical analyses were performed using IBM SPSS Statistics V.27.

Patient and public involvement

No patient involved.

RESULTS

Cohort characteristics

Of the interventional phase 2–4 CTs registered in ClinicalTrials.gov that had a study start date in 2019 or 2020, 354 records had a protocol available when the search was conducted. Of these, 254 were included in this study. The main reason for protocol exclusion was the use of an intervention that was not a drug, such as cosmetics, food supplements and medical devices (online supplemental figure 1). Table 2 displays the characteristics of the included protocols.

Reported trial activities in publicly available protocols

Figure 1 summarises the proportion of protocols in the study cohort that explicitly (dark green) and implicitly (light green) reported decentralised and on-site conduct of the predefined trial activities. In general, only a small portion was implicitly reported, with implicit on-site consenting occurring most frequently (17.7%). For all trial activities with an on-site equivalent, on-site conduct was more frequently reported than decentralised conduct. On-site data collection (98.4%) and consenting (95.3%) were most frequently reported in the protocols. Decentralised conduct was most frequently reported for data collection (68.9%) in the 254 included protocols followed by CT monitoring (25.6%) and participant outreach (25.2%). Specifically, protocols reported decentralised data collection through telemedicine visits (52.4%), PROs (41.7%), devices or biomarker kits (15.8%), and home health visits (7.9%). Of note, the analysed protocols included 23 hospital-based trial protocols—defined as trials in which CT data were collected during one hospital stay—that did not report the collection of CT data by decentralised means, while these protocols could report other decentralised trial activities. Similarly, of the 254 protocols, we considered only 138 suitable to implement 'DtP IMP supply' and 'decentralised IMP adherence monitoring' as (at least one) IMP was administered in an at-home setting in these protocols (ie, by the participant or by a home nurse).

Clinical studies can apply both on-site and decentralised conduct of an activity. Table 3 presents the proportion of protocols that exclusively reported decentralised conduct, on-site conduct, or a combination of both or did not report the trial activity at all. The majority of decentralised data collection (67.3%) was used to complement on-site data collection. Data collection exclusively by decentralised means was reported in 1.6% of the protocols and data collection exclusively by on-site means in 31.1% of the protocols (table 3). Consenting was reported to be exclusively on-site in 89.0% of the protocols, whereas a combination of both on-site and decentralised consenting was reported in 6.3% of the protocols. Only 2.8% of the protocols exclusively reported decentralised consenting. Trial activities that were frequently 'not reported' at all include staff training (86.2%), participant prescreening (61.8%), participant training (57.9%), CT monitoring (51.2%) and participant outreach (44.9%).

Table 2 Protocol cohort characteristics

Cohort characteristic		Number (%)
Year	2019	191 (75)
	2020	63 (25)
Sponsor	Private	99 (39)
	Public	155 (61)
Trial location	North America	155 (61)
	Europe	66 (26)
	East Asia	23 (9)
	South America	14 (6)
	Africa	11 (4)
	Southeast Asia	11 (4)
	Pacifica	6 (2)
	Middle East	6 (2)
	South Asia	5 (2)
	North Asia	2 (1)
	Central America	2 (1)
	Single country	221 (87)
	Multicountry	33 (13)
Trial design	Phase 2	116 (46)
	Phase 3	72 (28)
	Phase 4	66 (26)
	Randomised	190 (75)
	Non-randomised	64 (25)
	Open label*	126 (50)
	Participant blinded	15 (6)
	Participant and investigator blinded	112 (44)
	Multicentre	124 (49)
	Single centre	130 (51)
Follow-up time	Median number of days (IQR)	90.5 (30–305.75)
Sample size	Median (IQR) number of participants included	
	Overall	90 (40–285.5)
	In CTs with healthy participants	187.5 (60–962.5)
	In CTs with patients	86 (34–216)
	In paediatric CTs	174 (58–450)
Trial participants	Healthy participants	38 (15)
	Patients	216 (85)
	Paediatric clinical trial (patients and healthy)	27 (11)
Therapeutic area	Infectious and parasitic diseases	30 (11.8)
	COVID-19†	30 (11.8)
	Neoplasms	26 (10.2)
	Endocrine, nutritional, or metabolic diseases	23 (9.1)
	Diseases of the skin	16 (6.3)
	Mental, behavioural, or neurodevelopmental disorders	14 (5.5)
	Others‡	115 (45.3)

*One clinical trial protocol was omitted here as it described a subsequential design in which the first intervention 'round' was open and the second was double blinded.
†Categorised under 'codes for special purposes' following ICD-11.
‡Others include 'conditions originating in the perinatal period'; 'developmental anomalies'; diseases of 'blood and blood-forming organs'; 'the circulatory system'; 'the digestive system'; 'ear and mastoid process'; 'the genitourinary system'; 'the immune system'; 'the musculoskeletal system or connective tissue'; 'the nervous system'; 'the respiratory system'; 'the visual system'; 'factors influencing health status or contact with health services'; 'injury, poisoning or other consequences of external factors'; 'pregnancy, childbirth or puerperium'; and 'symptoms, signs, or clinical findings not elsewhere classified'.
CT, clinical trial; ICD-11, International Classification of Diseases revision 11.

Reported trial activities per trial sponsor

Figures 2A and 3A depict the decentralised trial activities stratified per sponsor type (ie, public and private). With regard to on-site conduct, public sponsors reported more on-site outreach (63.9% vs 17.2%; p<0.001) and prescreening (34.2% vs 14.1%; p<0.001), whereas private sponsors reported more on-site screening (95.0% vs

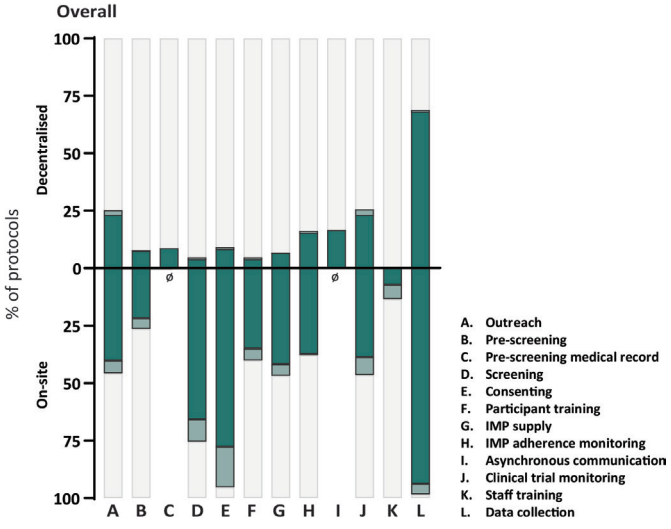

Figure 1 Frequency of decentralised and on-site trial activities reported in the protocols (n=254). The lighter green parts of the bars display the proportions that were implicitly reported. Prescreening through medical records (C) and asynchronous communication (I) do not have an on-site equivalent. IMP, investigational medicinal product.

Table 3 Decentralised conduct, on-site conduct, a combination of both, or no report of the trial activity in the protocols (n=254)

Activity	Exclusively decentralised (%)	Exclusively on-site (%)	Combination (%)	Not reported (%)
Outreach	24 (9.4)	76 (29.9)	40 (15.7)	114 (44.9)
Prescreening	29* (11.4)	57 (22.4)	11* (4.3)	157 (61.8)
Screening	3 (1.2)	183 (72)	9 (3.5)	59 (23.2)
Consenting	7 (2.8)	226 (89)	16 (6.3)	5 (2.0)
Participant training	5 (2.0)	95 (37.4)	7 (2.8)	147 (57.9)
IMP supply†	7 (2.8)	108 (42.5)	10 (3.9)	13 (5.1)
IMP adherence monitoring†	12 (4.7)	67 (26.4)	29 (11.4)	30 (11.8)
Clinical trial monitoring	6 (2.4)	59 (23.2)	59 (23.2)	130 (51.2)
Staff training	1 (0.4)	34 (13.4)	0 (0)	219 (86.2)
Data collection	4 (1.6)	79 (31.1)	171 (67.3)	0 (0)

Explicit and implicit reporting were aggregated.
*Includes prescreening through medical records.
†Proportions do not add up to 100%, as these trial activities were considered to be 'not applicable' for 116 protocols that investigated an IMP that was not administered in an at-home setting.
IMP, investigational medicinal product.

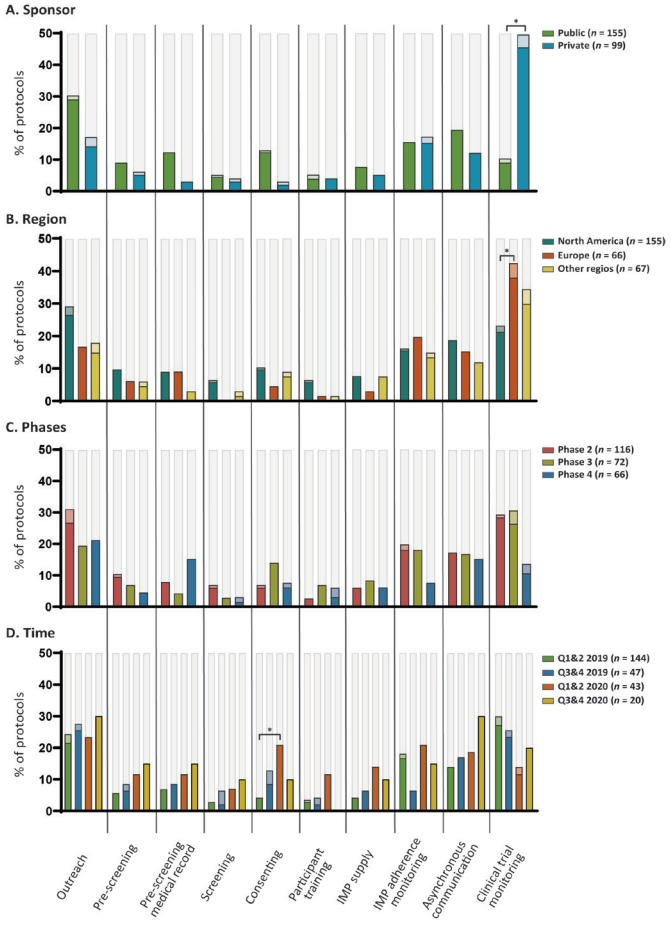

Figure 2 Frequency of decentralised trial activities reported in different strata. The lighter parts of the bars display the proportions that were implicitly reported. IMP, investigational medicinal product; Q1&2, first and second quarter; Q3&4, third and fourth quarter.

63.3%; p<0.001) (online supplemental figure 2). Public sponsors reported more decentralised conduct of trial activities related to recruitment and enrolment than private sponsors. Namely, public sponsors reported more decentralised outreach (30.3% vs 17.1%), decentralised prescreening (9.0% vs 6.1%), prescreening through medical records (12.3% vs 3.0%), decentralised screening (5.1% vs 4.0%), and decentralised consenting (12.9% vs 3.0%) (figure 2A). Private sponsors reported more data collection by decentralised means than public sponsors (figure 3A).

Reported trial activities in the geographical regions

We compared the protocols of trials conducted in the regions of North America (n=155), Europe (n=66) and other regions (n=67) (figures 2B and 3B). Because protocols for trials conducted outside of North America or Europe were less prevalent (table 2), these were aggregated. Of note, the number of protocols assessed for the geographical regions exceeds 254, as trials can be conducted in multiple regions. It became apparent that on-site conduct of CT monitoring was more frequently reported in protocols for trials conducted in Europe (65.2%) than protocols for trials conducted in North America (42.5%) (online supplemental figure 3). Similarly, figure 2B shows that decentralised conduct of CT monitoring was reported in 42.4% of the European protocols vs 23.2% of the North American protocols (p<0.001). Protocols for trials conducted in North America more frequently reported, among others, decentralised outreach (29.1% vs 17.9% in other regions and 16.7% in Europe) and DtP IMP supply (7.7% vs 7.5% in other regions and 3% in Europe) (figure 2B). Decentralised screening was not reported in protocols for trials conducted in Europe. Of the non-hospital-based

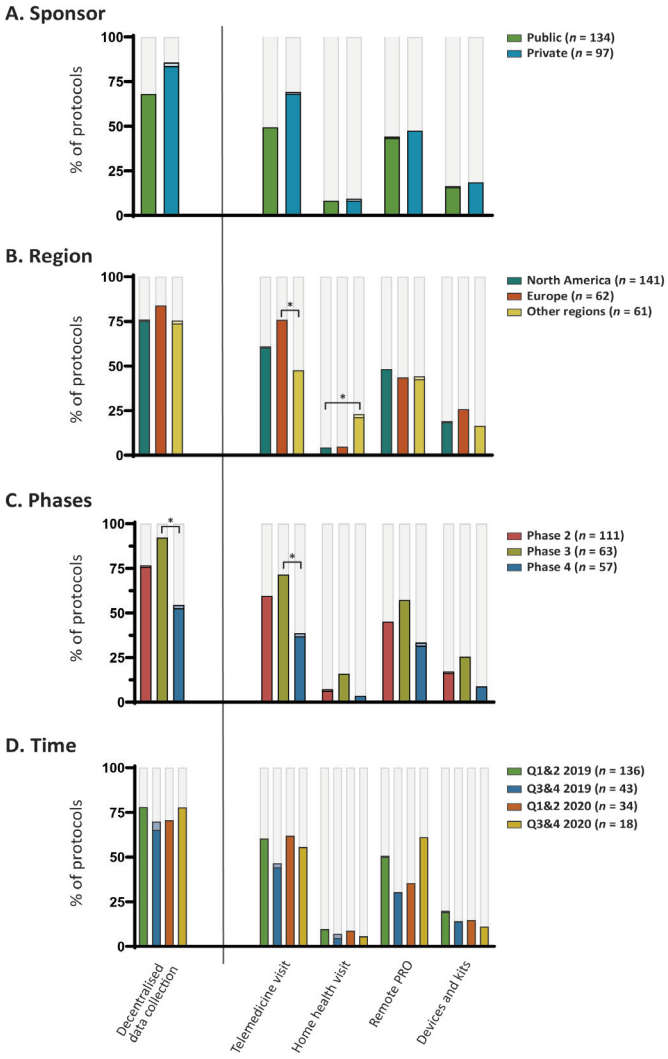

Figure 3 Data collection by decentralised means reported in the different strata. Data are presented for non-hospital-based trials (n=231). The lighter parts of the bars display the proportions that were implicitly reported. PRO, participant-reported outcome; Q1&2, first and second quarter; Q3&4, third and fourth quarter.

protocols (n=231), 'other regions' reported more decentralised data collection through home health visits (22.9%) compared with Europe (4.8%) and North America (4.3%; p<0.001), whereas protocols for trials conducted in Europe reported most telemedicine visits (75.8%) compared with North America (61.0%) and other regions (47.5%, p<0.001) (figure 3B).

Reported trial activities per trial phase

No clear trend across trial phases in the reporting of on-site (online supplemental figure 4) and decentralised conduct was observed (figures 2C and 3C). However, on-site and decentralised 'IMP adherence monitoring' and 'CT monitoring' were reported less frequently in phase 4 protocols. Specifically, on-site CT monitoring was reported in 28.8% of the phase 4 protocols compared with 61.1% of the phase 3 protocols (p<0.001) and 47.4% of the phase 2 protocols. Similarly, decentralised CT monitoring was reported in 13.6% of the phase 4 protocols, whereas this activity was reported in 30.6% and 29.3% of included phase 3 and 2 protocols, respectively (figure 2C). Additionally, on-site IMP adherence monitoring was reported in 22.7% of the phase 4 protocols compared with 37.5% and 45.7% of the phase 3 and phase 2 protocols, respectively. Decentralised IMP adherence monitoring was reported in 7.6% of the phase 4 protocols compared with 19.8% of the phase 2 and 18.1% of the phase 3 protocols (figure 2C).

On-site data collection was frequently reported in all trial phases (98.3%, 97.2%, and 100% for phase 2, 3, and 4, respectively), whereas decentralised data collection was most reported in phase 3 protocols (81.9%) compared with phase 2 (73.3%) and phase 4 protocols (47%). Of the non-hospital-based trial protocols (n=231), 92% of the phase 3 protocols reported at least one means of decentralised data collection, compared with 77% of the phase 2 protocols and 54% of the phase 4 protocols (figure 3C).

Reported trial activities over time

Trends in reporting over time were visible for the several decentralised (figure 2D) and on-site (online supplemental figure 5) trial activities. For example, decentralised prescreening increased by 3 percentage points, on average, per half a year (figure 2D), whereas on-site prescreening was stable over time (online supplemental figure 5). Additionally, decentralised consenting increased from 4.2% in the first half of 2019 to 20.9% in the first half of 2020, whereas on-site consenting decreased from 99.4% in the first half of 2019 to 81.4% in in the first half of 2020. Figure 2D further shows that for several decentralised trial activities, reporting increased until the first half of 2020 but declined in the second half of that year. For example, DtP IMP supply increased to 14.0% in the first half of 2020 but then it decreased to 10.0% in the second half of 2020. Decentralised data collection did not show clear trends over the four time periods (figure 3D).

DISCUSSION

Decentralised trial activities in CT protocols

This study aimed to quantify the reporting of on-site and decentralised conduct of trial activities in CT protocols. We found that on-site conduct was more frequently reported than decentralised conduct. Nevertheless, decentralised conduct was commonly reported in CT protocols, mainly for data collection (68.9%), particularly in phase 3 CTs (81.9%). However, decentralised conduct of other activities such as obtaining consent (9.1%), and participant screening (4.7%) was less frequently reported. Decentralised methods were typically used to complement on-site conduct. For example, data collection was reported in 68.9% of the analysed protocols, but was reported to be conducted exclusively decentralised in only 1.6% of the protocols—although mobile devices are available for a broad variety of outcomes, such as

physical activity, sleep-related outcomes, cardiac-related outcomes, and glucose monitoring.[2]

COVID-19 and trends over time

On 11 March 2020, the WHO declared COVID-19 a global pandemic.[38] Subsequently, the initiation of non-COVID-19 CTs declined from 2019 to 2020 by 11.1% and 13.2% in Europe and the USA, respectively.[39] Furthermore, the increased workload due to the pandemic may have affected the registration of new CTs in ClinicalTrials.gov by sponsors,[39] which could partially explain the fewer number of protocols available for 2020. Previously, the use of wearables and telemedicine visits in interventional CTs has been demonstrated to increase only slightly (~1%) during the first 10 months of the COVID-19 pandemic compared with trials initiated 10 months before the pandemic,[34] despite regulatory flexibilities and the need to move trial activities away from investigative sites.[23] Similarly, we have observed that the reporting of decentralised data collection methods did not increase over time. However, other decentralised trial activities including prescreening, screening, consenting and DtP IMP supply were increasingly reported over time. Despite this temporal increase, reporting of decentralised consenting, and DtP IMP supply decreased again in the second half of 2020. This is in agreement with a previous study that, based on data from the Mayo Clinic sites in the USA, described an increase in telemedicine visits and decentralised electronic consent during the COVID-19 pandemic until the peak in April 2020, after which activities reverted again to investigative sites.[40] The authors suggested that this reversion to on-site activities could be due to sponsors wanting to adhere to original (on-site) protocols.[40]

Trial characteristics and reporting decentralised trial activities

Interestingly, phase 4 CT protocols reported less on-site and decentralised 'IMP adherence monitoring' and 'CT monitoring', which could be due to the elucidation of the safety profile of the IMP in phase 4 CTs. Nevertheless, we did not observe an increased frequency of reporting other decentralised trial activities, such as decentralised consenting or decentralised data collection, which could also be expected when the safety profile is more elucidated in late-phase CTs. Moreover, phase 4 protocols reported less decentralised data collection than phase 2 and 3. Differences in reporting data collection by decentralised means were also observed for the compared regions. Despite the heterogenous group of regions included in the 'other regions' category, we hypothesise that impeded access to participating sites in the 'other regions' is one of the reasons that decentralised data collection through home health visits was reported most in trials conducted outside of North America and Europe. Furthermore, it would be interesting to research whether the difference across the regions in reporting telemedicine visits has to do with limited internet access in certain regions.

Comparing the trial sponsors, trials conducted by private sponsors have previously been found to incorporate wearables and telemedicine visits less frequently than publicly funded trials.[34] Nevertheless, we found that private sponsors reported more telemedicine visits. However, it should be noted that private sponsors employed fewer phase 4 CTs (n=14)—which reported less decentralised data collection—than public sponsors (n=52).

Completeness of CT protocols

The results of this study suggest that publicly available protocols are often incomplete, as several trial activities are frequently 'not reported'. For example, information about the training of staff and participants, CT monitoring, and participant outreach was frequently not reported. The incomplete reporting of these activities may be partly explained as CT protocols are supplemented with additional study-related documents, such as a monitoring plan or a data management plan,[41] which were not included in our analysis. Nevertheless, hiatuses in protocols identified in this study may affect the interpretation of the CT results, and the design of future CTs. As an example, if the outreach strategy is not sufficiently clear from the protocol, deducing whether the trial results are generalisable can be difficult, particularly if these strategies are not discussed in CT publications. Because of the novelty of decentralised approaches, on-site conduct may often be assumed. However, future protocols should clearly distinguish on-site and decentralised conduct. The problem of incomprehensive CT protocols is well established and has been previously addressed by the Standard Protocol Items: Recommendations for Interventional Trials initiative, which has described a protocol checklist that could assist sponsors and investigators in drafting a comprehensive CT protocol.[42 43]

Strengths, limitations and future research

This study provides insight into the implementation of a broad set of operational trial activities, which can be executed in a decentralised fashion. A careful review of publicly available protocols allowed us to compare the reporting of decentralised and on-site conduct of predefined trial activities in different strata. Further, by manually extracting data from the protocols, the use of potentially incomplete or inaccurate information from the ClinicalTrials.gov records was circumvented.[44]

Nevertheless, it should be noted that the failure to report specific trial activities in CT protocols does not imply that these trial activities are not used, either decentralised or on-site. Second, we limited our search to protocols of drug trials because regulations regarding these trials are typically most stringent. However, decentralised conduct of trial activities may be more apparent in trials investigating other interventions such as behavioural interventions. Although 254 CT protocols were included in this study, the number of protocols were sometimes relatively small when comparing subgroups. We saw a limited availability of 2020 protocols, which may be due to

the fact that protocols become available over time, after the CT is conducted and results are disseminated.[45] As a consequence, this may have caused protocols for trials with a longer follow-up time to be underrepresented in the dataset. Additionally, compliance with obligations to publish information on ClinicalTrials.gov is known to be inadequate.[46] Third, most CTs included in this study were conducted in North America and Europe (155 and 66 protocols with≥1 site in these regions, respectively), as ClinicalTrials.gov is a database maintained by the US National Library of Medicine at the National Institutes of Health,[47] thereby limiting generalisability to other geographical regions.

Future research could gauge the experiences of the stakeholders involved in decentralised conduct of trial activities, including participants and investigators. Moreover, further analysis of the various trial populations and TAs that would benefit the most from these approaches is warranted. Lastly, lessons learnt during the COVID-19 pandemic regarding decentralised trial activities from sponsors, health authorities and investigators should be collected to identify the best practices for employment of decentralised trial activities in CTs.

CONCLUSIONS

Trial activities are commonly conducted using decentralised means, typically to complement on-site conduct. On-site conduct is more frequently reported for operational trial activities than decentralised conduct. Of the analysed trial activities, decentralised data collection was most frequently reported. Decentralised conduct of other trial activities, such as participant outreach, consenting, and screening was less frequently reported, whereas these activities were (more) frequently reported to be conducted on site. An interesting additional finding is that several trial activities are not reported at all in CT protocols including participant outreach and participant and study staff training. Innovation in CTs should therefore be followed by improved reporting on trial activities and the way these activities are conducted. Sharing experiences on trial activities frequently and infrequently executed in a decentralised fashion—including participant outreach, obtaining informed consent, supply of IMP, and data collection—can now progress future use and drive mutual learning among clinical research stakeholders, to consequently benefit trial participants.

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