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).3–6
with CT conduct, including the high burden associated with participating in a CT and low recruitment and retention rates.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{19}

Initiatives such as the Innovative Medicines Initiative Trials@Home consortium,\textsuperscript{20} Clinical Trials Transformation Initiative\textsuperscript{21} and TransCelerate\textsuperscript{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.\textsuperscript{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.\textsuperscript{23} Since then, the United States Food and Drug Administration,\textsuperscript{25} the Danish Medicines Agency,\textsuperscript{26} and Swissmedic and Swisstherics,\textsuperscript{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 25 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,\textsuperscript{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.\textsuperscript{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, Pacific, 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).\textsuperscript{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...
| 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 organisation (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 devices 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; the region may influence the incorporation of decentralised trial activities, as regulations differ between geographical regions; 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; 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.

**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 $\chi^2$ 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 supplementary 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 inventor 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) |

### Table 2 Continued

| Cohort characteristic | Number (%) |
|-----------------------|------------|
| 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 67.8%; p<0.001). Asynchronous communication (11.1% vs 2.0%; p=0.003) and data collection (31.2% vs 13.6%; p=0.001) were more frequently reported by private sponsors. The differences in prescreening and on-site screening for private sponsors may be related to differences in the nature of the diseases that were studied, as private sponsors conducted more trials for ‘the nervous system’ (10.2% vs 1.7%; p=0.01), ‘the digestive system’ (10.2% vs 1.7%; p=0.01), and ‘the circulatory system’ (10.2% vs 1.7%; p=0.01).

CT, clinical trial; IMP, investigational medicinal product.

### 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.
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).

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

| 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.

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

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.
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 2C).

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 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, DiP 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. 

COVID-19 and trends over time
On 11 March 2020, the WHO declared COVID-19 a global pandemic. 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. Furthermore, the increased workload due to the pandemic may have affected the registration of new CTs in ClinicalTrials.gov by sponsors, 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 intervention. Prevalously, the increased workload due to the pandemic may have affected the registration of new CTs in ClinicalTrials.gov by sponsors, 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, despite regulatory flexibilities and the need to move trial activities away from investigative sites. 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. The authors suggested that this reversion to on-site activities could be due to sponsors wanting to adhere to original (on-site) protocols.

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. 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, 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 incomplete 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.

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.

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. 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. 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. 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, 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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SUPPLEMENTARY MATERIAL

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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Supplementary Text. Full search strategy

To identify protocols for phase 2, 3, and 4 clinical trials investigating an investigational medicinal product (IMP) with a start date in 2019 or 2020, the ClinicalTrials.gov database was searched on 23 and 24 March 2021 by one researcher (R.J.G.) using the advanced search box. Protocols of trials with an (estimated) start date (i.e., first participant first visit) between 1 January 2019 and 31 December 2020 were eligible to be included. 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 (i.e., phase 3 and phase 4 protocols with a start date in 2019 and phase 2 to phase 4 protocols with a start date in 2020) were downloaded on 24 March 2021. To that end, the following filters were applied in the advanced search box in ClinicalTrials.gov:

- Study type: Interventional Studies (Clinical Trials)
- Study results: All Studies
- Phase: Phase 2, Phase 3, Phase 4
- Study documents: Study Protocols
- Study start from: 01/01/2019 to 12/31/2019 and 01/01/2020 to 12/31/2020 (MM/DD/YY)

No other filters were applied, and we were interested in all the protocols regardless of therapeutic area, availability of results, recruitment status, participant characteristics, location, and funder type. The protocols were manually screened for the other eligibility criteria by one researcher (R.J.G.) and this eligibility screening was peer-reviewed by another researcher (A.J.d.J.). That is, we assessed whether the trials described in the protocols aimed to investigate an IMP, and we excluded other interventions (e.g., cosmetic products, medical devices). Additionally, we excluded duplicate protocols and protocols that solely comprised of a synopsis or description of the objectives. Phase 1/2 and phase 2/3 were classified as phase 2 and phase 3 protocols, respectively. Data were extracted from the protocols as described in the manuscript.
**Supplementary Table 1. Data extraction matrix.**

| Category                          | Specific activity         | Activity definition                                                                 | Questions for “decentralised” ascertainment                                                                 | Examples from protocols                                      |
|-----------------------------------|---------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| 1. Recruitment and enrolment      | 1.1 Participant outreach  | Outreach to potential participants to raise awareness on clinical trial conduct and participation options. | Are potential participants informed of trial participation opportunities through websites or other forms of digital or remote contact (e.g., radio advertisements, telephone calls, e-mail)? | 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.                        |
|                                   | 1.2 Participant prescreening | Trial activity to describe participant identification activities before informed consent is obtained, (i) for which participants’ active involvement is required or (ii) through the screening of electronic medical records. | Were participant identification activities performed in a decentralised/remote fashion requiring participants’ active involvement, e.g., through telephone questionnaires, teleconference, or online surveys? Were participant identification activities performed by checking (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 (i.e., 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. |
|                                   | 1.3 Participant screening | Trial activity to describe activities performed to ensure participant eligibility after informed consent is obtained. | Is screening performed in a decentralised fashion (e.g., through telephone, teleconference, or via home visits)? | 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. |
| 1.4 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. | Is informed consent obtained from the participant whilst participant and investigator staff were not physically at the same location, for example through the use of telephone contact or online means? | 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 call or in person so that the participant can read the consent form during the discussion. |
| --- | --- | --- | --- |
| 2. Participant engagement | 2.1 Asynchronous investigator-participant interaction | Decentralised, asynchronous interactions between participants and investigator to provide study updates and to engage participants throughout the clinical trial (i.e., after enrolment). | Are participants updated or reminded of trial activities through the use of asynchronous interactions, including text messages, e-mail, or mobile applications? | Decentralised: To maintain updated contact details, participants will be contacted every two months by SMS [...]. |
| 2.3 Participant training | Trial activity to describe training of the trial participant by the investigator staff on study-related materials and/or procedures. | Are participants trained on study-related materials and/or procedures in a decentralised manner, for example through a telemedicine visits, home nursing, or mobile applications? | 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... |
| 3. Trial operations | 3.1 IMP supply | Dispensing investigational medicinal products administrable in an at-home setting or other study-related materials to the participant. | Is IMP delivered directly to participants, for example from the investigator site or central depot to the participants’ homes, a local pharmacy, or through the use of home nurses? | sent to the participant’s email address and texted to them providing visual instructions on use. |
|---------------------|---------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| 3. Trial operations | 3.2 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. | Is IMP adherence evaluated in a decentralised manner, for example through the use of smart caps, ingestible sensors, or photographing? Were eDiaries used as a means to monitor IMP adherence, and were these eDiaries reviewed independent of on-site visits? | 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). |
| 3. Trial operations | 3.3 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. | Are clinical trial monitoring activities performed remotely/centrally, for example through telephone interactions with site staff, and/or remote access to study 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. |
| 3. Trial operations | 3.4 Investigator staff training | Activity that describes the training of investigator staff by the sponsor or contact research | Is investigator staff trained on clinical trial conduct or trial-related material in a decentralised fashion, for | On-site: All training and reads will be conducted by an imaging contract research organization (CRO) as specified in the protocol and as per the investigator site’s policy. |

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| 4. Data collection | 4.1 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. | NA | Subjects will return to clinic for Visit 4, for history, physical exam, quality of life (QoL), Satisfaction, and Cost Effectiveness questionnaires, and AE assessment. |
|-------------------|-----------------------------|------------------------------------------------------------------|-----|----------------------------------------------------------------------------------|
|                   | 4.2 Decentralised data collection through PROs | Participants are involved in the collection of data (by decentralised means) by filling out (e-)PROs | NA | Patient-reported outcome measures will be captured via an email sent to subjects with direct linkage to REDCap™ (Research Electronic Data Capture). |
|                   | 4.3 Decentralised data collection through wearable devices, sensors or biomarker kits | Participants are involved in the collection of data (by decentralised means) using wearable devices and sensors, or biomarker kits. | NA | Subjects will perform home pregnancy testing on day 1 of Cycle 1 and Cycle 2. |
|                   | 4.4 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. | NA | Blood and urine sample collection may be performed by a mobile nurse professional. |
|                   | 4.5 Decentralised data collection | Decentralised study (follow-up) visits through teleconference or telephone calls during which | NA | Telephone contacts will occur at Weeks 56, 64, 68, 76, 80, 88, 92, and 100. |
through telemedicine visits | data are collected by health care professionals (e.g., AEs, verbal questionnaires). | 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.

Definitions are adopted from the Trials@Home basic building block framework (Work package 2 (TECH) D2.3 – Technology scan. (2020) (available from: https://trialsathome.com/wp-content/uploads/2020/10/D2.3-Scanning-results_Master.pdf) and * Regulation (EU) no 536/2014 of the European parliament and of the council (2014) (available from: https://eur-lex.europa.eu/legalcontent/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN). Abbreviations: AE, adverse event; CT, clinical trial; DtP, direct-to-participant; GCP, good clinical practice; IMP, investigational medicinal product; PRO, participant reported outcome; QoL, quality of life.
### Supplementary Table 2.

**Supplementary Table 2A. Definitions of trial characteristics.**

| Category          | Trial characteristic            | Definition                                                                                                                                                                                                 | Adapted from                  |
|-------------------|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Study timeline    | Study start date               | The date on which the first participant was enrolled in a clinical study (i.e., first participant, first visit)                                                                                         | ClinicalTrials.gov            |
|                   | (Estimated) study completion date | (Estimated) date on which the last participant in a clinical trial was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events (i.e., last participant last visit). | ClinicalTrials.gov            |
|                   | Therapeutic area               | Classification of the disease of interest in the clinical trial based on the international statistical classification of diseases and related health problems (ICD-11).a                                                                 | WHO ICD-11                    |
| Trial location    | Region(s)                      | Regions as presented by ClinicalTrials.gov. ClinicalTrials.gov defines the following regions: Africa, Central America, East Asia, Europe, Middle East, North America, North Asia, Pacifica, South America, South Asia, Southeast Asia.b | ClinicalTrials.gov            |
|                   | Countries                      | All countries with at least one investigator site detailed in the protocol or on ClinicalTrials.gov.                                                                                                        | Current study                 |
|                   | Number of sites                | Maximum number of (planned) investigator sites where study activities are performed.                                                                                                                                 | Current study                 |
| Intervention      | Investigational medicinal product | Pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. | EMAc                          |
| Term | Definition | Source |
|------|------------|--------|
| Drug (medicinal product) | A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action. | EMA<sup>d</sup> |
| Active comparator | An investigational or marketed medicinal product used as a reference in a clinical trial. | EMA<sup>e</sup> |
| (Active) placebo | An inactive substance or treatment that looks the same as, and is given in the same way as, the active drug that is being study. | ClinicalTrials.gov |
| Administrable IMP | Participant is able to administer (at least 1 IMP in case of multiple IMPs) the IMP his/herself without the help of investigator site staff or other health care professional. | Current study |
| Trial design | Phase 2 trial | A phase of research to describe clinical trials that gather preliminary data on whether a drug works in people who have a certain condition/disease (that is, the drug’s effectiveness). For example, participants receiving the drug may be compared to similar participants receiving a different treatment, usually an inactive substance (called a placebo) or a different drug. Safety continues to be evaluated, and short-term adverse events are studied. | ClinicalTrials.gov |
| | Phase 3 trial | A phase of research to describe clinical trials that gather more information about a drug’s safety and effectiveness by studying different populations and different dosages and by using the drug in combination with other drugs. These studies typically involve more participants. | ClinicalTrials.gov |
| | Phase 4 trial | A phase of research to describe clinical trials occurring after a regulatory authority has approved a drug for marketing. These trials gather additional information about a drug’s safety, efficacy, or optimal use. | ClinicalTrials.gov |
| Randomization | A type of allocation strategy in which participants are assigned to the arms of a clinical trial by chance. | ClinicalTrials.gov |
| Blinding | A clinical trial design strategy in which one or more parties involved in the trial, such as the investigator or participants, do not know which treatment participants receive. | ClinicalTrials.gov |
not know which participants have been assigned which interventions. Types of masking include: open label (no blinding), single blind (participant-blinded), and double-blind (participant and investigator-blinded). For the purpose of this study, other denotations such as ‘triple blinding’ were categorised under double blinding.

| Primary objective | The primary objective(s) is the main question to be answered and drives any statistical planning for the trial (e.g. calculation of the sample size to provide the appropriate power for statistical testing). | CDISC |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------|-------|
| Hospital-based trial | Trials in which all clinical trial data were collected during one hospital stay. For example, trials with acute diseases. | Current study |
| Trial participants | (Estimated) sample size | (Estimated) maximum number of subjects (to be) consented as described in the protocol or detailed in ClinicalTrials.gov. | Current study |
| Follow up time | Maximum time (in calendar days) that a subject is expected to participate in the trial as detailed in the protocol. If the follow up time was not detailed, the duration was calculated from the information in the protocol or ClinicalTrials.gov. That is, the time between consenting (first visit) until the day on which the final data was collected (last visit). Years were defined as 365 days, months as 365*(1/12) days, and weeks as 7 days. | Current study |
| Subject minimum age | Minimum age of subjects (in years) as detailed in the eligibility criteria. | Current study |
| Subject maximum age | Maximum age of subjects (in years as detailed in the eligibility criteria. In case no age limitation was detailed in the protocol, this is presented as ‘no maximum’. | Current study |
| Healthy participants | Participants included in the study are healthy volunteers. | Current study |
| Pediatric clinical trial | All participants included in the study are up to and including (≤)18 years of age as detailed in the eligibility criteria. | Current study |
| Trial sponsor | Private | A private/commercial company, institution, or organization that takes responsibility for the initiation and management of a clinical trial. The sponsor is the applicant for the regulatory clinical trial authorization. It may or may not be the main funder. | CDISC |
|--------------|---------|-------------------------------------------------------------------------------------------------|-------|
| Public       | Public  | An public person/investigator, institution, or organization that takes responsibility for the initiation and management of a clinical trial. The sponsor is the applicant for the regulatory clinical trial authorization. It may or may not be the main funder. | CDISC |
| Other        | Data Safety Monitoring Committee | Group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical trial. The DSMC advises the sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. | CDISC |

Definitions were adopted on 11-Aug-2021 from ClinicalTrials.gov (https://clinicaltrials.gov/ct2/about-studies/glossary, EMA, CDISC (https://www.cdisc.org/standards/glossary), WHO ICD-11. 

Full list of classification options of therapeutic area used during the coding process can be found in Supplementary Table 2B, Overview of which countries are part of each geographical region can be found in Supplementary Table 2C, one hospital-based trial had decentralised data collection (questionnaire packages) as part of standard of care, this trial was nonetheless considered as a hospital-based trial (NCT03927781). EMA, European Medicine’s Agency; CDISC, Clinical Data Interchange Standards Consortium; DSMC, Data Safety Monitoring Committee; WHO ICD-11, World Health Organization International Statistical Classification of Diseases.
| Disease area                              | Elaboration presented by ICD-11                                      |
|------------------------------------------|---------------------------------------------------------------------|
| Blood and blood forming organs diseases  | NA                                                                  |
| Codes for special purposes               | NA                                                                  |
| Conditions originating in the perinatal period | This chapter includes conditions that have their origin in the perinatal period even though death or morbidity occurs later. |
| Developmental anomalies                  | This chapter includes conditions caused by failure of a particular body site or body system to develop correctly during the antenatal period. |
| Diseases of the circulatory system       | This refers to diseases of the organ system that passes nutrients (such as amino acids, electrolytes and lymph), gases, hormones, blood cells, etc. to and from cells in the body to help fight diseases, stabilize body temperature and pH, and to maintain homeostasis. |
| Diseases of the digestive system         | NA                                                                  |
| Diseases of the ear or mastoid process   | NA                                                                  |
| Diseases of the genitourinary system     | Any disease characterised by pathological changes to the genitourinary system. |
| Diseases of the immune system            | NA                                                                  |
| Diseases of the musculoskeletal system or connective tissue | NA |
| Diseases of the nervous system           | Conditions characterised as being in or associated with the nervous system. |
| Diseases of the respiratory system       | NA                                                                  |
| Diseases of the skin                     | Diseases of the skin incorporate conditions affecting the epidermis, its appendages (hair, hair follicle, sebaceous glands, apocrine sweat gland apparatus, eccrine sweat gland apparatus and nails) and associated mucous membranes (conjunctival, oral and genital), the dermis, the cutaneous vasculature and the subcutaneous tissue (subcutis). |
| Diseases of the visual system            | This refers to any diseases of the visual system, which includes the eyes and adnexa, the visual pathways and brain areas, which initiate and control visual perception and visually guided behaviour. |
| Endocrine, nutritional or metabolic diseases | NA                                                              |
| Extension codes                          | NA                                                                  |
| Factors influencing health status or contact with health services | NA |
| Infectious and parasitic diseases        | Includes certain conditions caused by pathogenic organisms or microorganisms, such as bacteria, viruses, parasites or fungi. |
| Injury, poisoning or other consequences of external causes | In the ICD, injury means physical or physiological bodily harm resulting from interaction of the body with energy (mechanical, thermal, electrical, chemical or radiant, or due to extreme pressure) in an amount, or at a rate of transfer, that exceeds physical or physiological tolerance. Injury can also result from lack of vital elements, such as oxygen. Poisoning by and toxic effects of substances are included, as is damage of or due to implanted devices. Maltreatment syndromes are included even if physical or physiological bodily harm has not been reported. Otherwise, psychological effects are not included (e.g., injured feelings). |
| --- | --- |
| Mental, behavioral or neurodevelopmental disorders | Mental, behavioural and neurodevelopmental disorders are syndromes characterised by clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour that reflects a dysfunction in the psychological, biological, or developmental processes that underlie mental and behavioural functioning. These disturbances are usually associated with distress or impairment in personal, family, social, educational, occupational, or other important areas of functioning. |
| Neoplasms | An abnormal or uncontrolled cellular proliferation which is not coordinated with an organism's requirements for normal tissue growth, replacement or repair. |
| Pregnancy, childbirth or the puerperium | A group of conditions characterised as occurring during the period of time from conception to delivery (pregnancy), during labour and delivery (childbirth) or during the approximately six weeks after delivery during which the uterus returns to the original size (puerperium). |
| Symptoms, signs or clinical findings, not elsewhere classified | Diseases can manifest in many ways and in different body systems. Such specific manifestations may be a reason for treatment or encounter, with or without identifying or addressing the underlying condition. Categories in this chapter include the less well-defined conditions and symptoms that, without the necessary study of the case to establish a final diagnosis, could be designated 'not otherwise specified', 'unknown aetiology' or 'transient'. Clinical findings include those found using physical, laboratory and imaging techniques. |

NA, not applicable; ICD, WHO ICD-11, World Health Organization International Statistical Classification of Diseases.
**Supplementary Table 2C.** Overview of countries and regions per ClinicalTrials.gov.

| Geographical region | Countries included |
|---------------------|--------------------|
| Africa              | Algeria; Angola; Benin; Botswana; Burkina Faso; Burundi; Cameroon; Central African Republic; Chad; Congo; The Democratic Republic of Congo; Côte D'Ivoire; Djibouti; Egypt; Equatorial Guinea; Eritrea; Ethiopia; Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Kenya; Lesotho; Liberia; Libyan Arab Jamahiriya; Madagascar; Malawi; Mali; Mauritania; Morocco; Mozambique; Namibia; Niger; Nigeria; Rwanda; Senegal; Sierra Leone; Somalia; South Africa; Sudan; Swaziland; Tanzania; Togo; Tunisia; Uganda; Zambia; Zimbabwe |
| Central America     | Bahamas; Belize; Costa Rica; Cuba; Dominican Republic; El Salvador; Guatemala; Haiti; Honduras; Jamaica; Nicaragua; Panama; Puerto Rico; Trinidad; Tobago |
| East Asia           | China; Hong Kong; Democratic People's Republic of Korea; Republic of Korea; Mongolia; Taiwan; Japan |
| Europe              | Albania; Austria; Belgium; Bosnia and Herzegovina; Bulgaria; Croatia; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Hungary; Iceland; Ireland; Italy; Latvia; Lithuania; Luxembourg; The Former Yugoslav Republic of Macedonia; Montenegro; Netherlands; Norway; Poland; Portugal; Romania; Serbia; Slovakia; Slovenia; Spain; Sweden; Switzerland; United Kingdom |
| Middle East         | Cyprus; Islamic Republic of Iran; Iraq; Israel; Jordan; Kuwait; Lebanon; Oman; Qatar; Saudi Arabia; Syrian Arab Republic; Turkey; United Arab Emirates; Yemen |
| North America       | Canada, Greenland, Mexico, United States |
| North Asia          | Armenia; Azerbaijan; Belarus; Georgia; Kazakhstan; Kyrgyzstan; Republic of Moldova; Russian Federation; Tajikistan; Ukraine; Uzbekistan |
| Pacifica            | Australia; Fiji; New Caledonia; New Zealand; Papua New Guinea; Solomon Islands; Vanuatu |
| South America       | Argentina; Bolivia; Brazil; Chile; Colombia; Ecuador; French Guiana; Guyana; Paraguay; Peru; Suriname; Uruguay; Venezuela |
| South Asia          | Afghanistan; Bangladesh; Bhutan; India; Nepal; Pakistan; Sri Lanka |
| Southeast Asia      | Brunei Darussalam; Cambodia; Indonesia; Lao Peoples Democratic Republic; Malaysia; Myanmar; Philippines; Singapore; Thailand; Vietnam |
**Supplementary Table 3.** Rules to identify implicit reporting of decentralised and on-site conduct.

| Trial activity          | Rule of implicit reporting                                                                                                                                 |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Participant outreach    | If hospitalised patients are used as a study population, outreach was implicitly reported as on-site, unless explicitly stated otherwise.                   |
|                         | If protocols stated that “patients will be contacted”, and on-site visits can reasonably be ruled out based on the context of the protocol, this was implicitly reported as decentralised outreach (i.e., contact via e-mail or telephone). |
| (Pre-)screening         | If complex tests for (pre)screening requiring biological samples (e.g. haematology testing, uranology or serum pregnancy tests) or large medical devices (e.g. ECG or MRI) are performed and decentralised (pre-)screening is not explicitly mentioned, (pre-)screening was assumed to be conducted on-site. |
|                         | If hospitalised patients are used as a study population, (pre-)screening is implicitly reported as on-site, unless explicitly mentioned that (pre-)screening was conducted decentralised prior to hospitalization. |
|                         | If (pre-)screening is not explicitly mentioned to be conducted on-site and/or decentralised, but outreach and consenting take place on-site or decentralised, (pre-)screening was implicitly reported as on-site or decentralised respectively based on the context of the protocol. |
| Obtaining informed consent | If hospitalised patients are used as a study population and outreach as well as (pre)screening is conducted on-site, consenting was assumed to be conducted on-site during a (pre)screening visit. |
|                         | If informed was obtained by signing (a copy of) the informed consent form, and decentralised or electronic consenting methods were not detailed, it was assumed that this activity was performed on-site. |
|                         | If outreach and (pre-)screening were conducted on-site or decentralised and obtaining informed consent was mentioned, consenting was implicitly reported as on-site or decentralised respectively based on the context of the protocol. |
| Asynchronous communication with participants | NA                                                                                                                                 |
| Participant training    | If participants were supplied with study materials on-site (e.g. self-monitoring devices, (N)IMP) and the need for training on use of these materials is apparent based on protocol (e.g. use of study materials by participants is checked during follow-up on-site visits), but training method is not explicitly mentioned to be conducted decentralised (e.g. through videos on a website), this activity was implicitly reported as on-site. |
|                         | If participant training is mentioned in the protocol, but the mentioned time period in which the training should take place is not in line with the scheduled on-site visits, it was implicitly reported as decentralised participant training. |
### DtP IMP supply

If the use of self-administrable IMPs and recurrent use outside the hospital setting was apparent from the protocol, IMP supply was implicitly reported to be conducted on-site, provided that DtP IMP supply methods were not detailed in the protocol.

### IMP adherence monitoring

If pill counts were detailed in the protocol, these were implicitly reported as on-site, unless explicitly mentioned to be conducted via other (decentralised) means. In case participants are to receive reminders to take IMP in an at home setting, IMP adherence was implicitly reported as decentralised.

### CT monitoring

If the protocol states that “continuous CT monitoring” was conducted, this was implicitly reported as remote CT monitoring. If it is stated that source data are monitored during the trial and source data includes hardcopy paper data which is only available on-site, CT monitoring is implicitly reported as being conducted on-site.

### Investigator staff training

In case staff training is mentioned and all trial activities that require training are conducted on-site (e.g., data collection, IMP supply, adherence monitoring) and decentralised investigator staff training is not explicitly mentioned, then this activity is implicitly reported as being conducted on-site.

If the protocol mentions an on-site initiation visit, this was implicitly reported as on-site investigator staff training.

If specific techniques (e.g., taking respiratory swaps) required in-person training, this was implicitly reported as on-site investigator staff training.

**Nota bene:** the decentralised and on-site trial activities are not mutually exclusive. These rules were used to guide the implicit reporting on the trial activities. Implicit reporting was only performed when it was sufficiently clear from the protocol context that a trial activity was performed on-site or decentralised, based on the adjudication of the two researchers (A.J.d.J. and R.J.G). If the trial activities were not explicitly detailed in the protocol, both the decentralised and on-site trial activity were classified as “not reported”. DtP, direct-to-participant; ECG, electrocardiogram; MRI, magnetic resonance imaging; NA, not applicable; (N)IMP, (non) investigational medicinal product.
Supplementary Figure 1. Flowchart of the included protocols. a interventional phase 2, 3, 4 clinical trials with a start date in 2019 or 2020 registered in ClinicalTrials.gov, March 2021; b protocols categorised under two trial phases in ClinicalTrials.gov.
Supplementary Figure 2. Frequency of decentralised and on-site trial activities for publicly (n = 155) and privately (n = 99) sponsored protocols. The lighter parts of the bars display the fractions that were implicitly reported. Pre-screening through medical records (C) and asynchronous communication (I) do not have an on-site equivalent. IMP, investigational medicinal product.
Supplementary Figure 3. Frequency of decentralised and on-site trial activities reported in protocols for trials (to be) conducted in North America (n = 155), Europe (n = 66), and other regions (aggregated; n = 67). The lighter parts of the bars display the fractions that were implicitly reported. Pre-screening through medical records (C) and asynchronous communication (I) do not have an on-site equivalent. IMP, investigational medicinal product.
**Supplementary Figure 4.** Frequency of decentralised and on-site trial activities reported in phase 2 (n = 116), phase 3 (n = 72), and phase 4 (n = 66) protocols. The lighter parts of the bars display the fractions that were implicitly reported. Pre-screening through medical records (C) and asynchronous communication (I) do not have an on-site equivalent. IMP, investigational medicinal product.
Supplementary Figure 5. Frequency of decentralised and on-site trial activities reported in protocols over time (Q1&2 2019 n = 144, Q3&4 2019 n = 47, Q1&2 2020 n = 43, and Q3&4 2020 n = 20). The lighter parts of the bars display the fractions that were implicitly reported. Pre-screening through medical records (C) and asynchronous communication (I) do not have an on-site equivalent. IMP, investigational medicinal product.