831458 – Trials@Home

Center of Excellence – Remote Decentralised Clinical Trials

WP4 – EAGLE

D4.3 Overview of technical and regulatory implications of DCTs for efficient regulatory decision-making

Lead contributor	Yared Santa-Ana-Tellez (17 Utrecht University) Helga Gardarsdottir (17 Utrecht University)
Other contributors	Amos de Jong (17 Utrecht University) Hamidou Traore (31 UCB) Kate Huntley (28 Pfizer) Solange Corriol Rohou (20 AstraZeneca) Dinesh Mistry (23 Covance) Amy Rogers (8 University of Dundee) Olenka van Ardenne (3 Lygature) Martin Boeckhout (3 Lygature)

Document History

Version	Date	Description
V1.0	8 February 2023	Draft structure, first version sent for comments
V1.1	6 June 2023	Comments and corrections from the first revision round were addressed. Sent to WP4 for comments and suggestions
V1.2	23 June 2023	Comments and corrections from the second revision round were addressed.
V2.0	20 August 2023	Comments and corrections from ESP, PEP and ExBo were addressed.

Abstract

The Innovative Medicines Initiative (IMI) Trials@Home project, launched in 2019, represents a broad multinational private-public collaboration committed to examining the potential of decentralised clinical trials (DCTs). Work Package 4 (EAGLE) was charged with the task of scrutinising the technical and regulatory nuances of DCTs to streamline regulatory decision-making processes. This deliverable provides a tripartite analysis: First, it elucidates the language surrounding DCTs and evaluates their application in drug trials conducted in 2019-2020. Second, it offers an exhaustive examination of regulatory perspectives, incorporating diverse stakeholder experiences. Lastly, it explores the complex interplay of technical and regulatory dimensions of DCTs in diverse clinical areas. This integrated analysis aims to shed light on the current state and future trajectory of DCTs in clinical research.

List of abbreviations and acronyms

AMP	**Auxiliary medicinal product**
ATMP	**Advanced therapy medicinal product**
BfArM	**Federal Institute for Drugs and Medical Devices**
CIOMS	**Council for International Organizations of Medical Sciences**
CRO	**Contract research organisation**
COVID-19	**Coronavirus disease 2019**
CT	**Clinical trial**
CTA	**Clinical trial application**
CTFG	**Clinical trial facilitation group**
CTR	**Clinical trial regulation**
DCT	**Decentralised clinical trial**
DtP IMP	**direct-to-participant supply of the investigational medicinal product**
EMA	**European Medicines Agency**
EU	**European Union**
EC	**Ethics committee**
EWG	**Expert working group**
FDA	**Food and Drug Administration**
GCP	**Good clinical practice**
GDPR	**General Data Protection Regulation (EU) 2016/679**
HCP	**Healthcare provider**
HTA	**Health technology assessment**
HTAB	**Health technology assessment body**
ICH	**International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use**
IMI	**Innovative Medicines Initiative**
IMP	**Investigational medicinal product**
ITF	**Innovation Task Force**
MEDLINE	**National Library of Medicine's**
NCA	**National competent authority**
RADIAL	**Remote and Decentralised Innovative Approaches to Clinical Trials**
SAB	**Scientific advisory board**
VHP	**Voluntary harmonisation procedure**
WP	**Work package**
EAGLE	**Ethical regulatory, GCP and legal aspects.**

Link to the Trials@Home glossary: https://trialsathome.com/trialshome-glossary/

Table of Contents

Introduction

Decentralised clinical trial (DCT) approaches are transforming the landscape of clinical research, offering new opportunities for data collection and participant engagement. With advances in technology, DCTs are becoming increasingly popular because they allow people to participate in clinical trials from their home or other nearby location. DCTs leverage digital technologies to enable remote participation, reducing the need for physical visits to trial sites and potentially making clinical trials more accessible to participants. Potential benefits of DCTs include increased efficiency, reduced costs, and improved participant-centricity including participant inclusion and retention. However, DCTs also have important technical and regulatory implications that must be considered to ensure robust data generation and their successful integration into decision-making processes by health authorities (regulators and HTA bodies) and sponsors of DCT studies.

This deliverable provides an in-depth explanation of the importance of regulatory implications of DCTs in decision-making by exploring key issues and challenges as well as the experiences of various stakeholders. The report is divided into three main sections, each focusing on a specific aspect of DCTs. Each section also provides a summary of key points derived from various published scientific articles on the topic at hand (available in full in the supplementary material provided). The sections are as follows:

Section 1: Defining and Evaluating Decentralised Clinical Trials: Activities Reported in Clinical Trial Protocols
This section clarifies the various terms used to describe DCTs, such as remote, patient-centric, site-less, virtual and digital clinical trials, to establish a common understanding on the terminology used. Additionally, this section provides insights into the current situation by assessing the implementation of decentralised trial activities in drug trials initiated in 2019–2020.

Section 2: Regulatory Perspectives and Experiences in Decentralised Clinical Trials: A Comprehensive Analysis
This section describes the interaction between different DCT stakeholders, especially focusing on feedback from regulators for the RADIAL trial. Additionally, the section highlights the opportunities and challenges of DCTs from the perspectives of European regulators, health technology assessment (HTA) bodies, sponsors, site study staff and couriers involved in investigational medicinal product (IMP) supply.

Section 3. Exploring Technical and Regulatory Implications for Optimal Decision-Making in Key Clinical Areas

In this section, the technical and regulatory implications of DCTs for efficient decision-making are investigated in several clinical fields. This section includes a survey of the views of EFPIA (European Federation of Pharmaceutical Industries and Associations) partners and other stakeholders on the regulatory implications for these clinical areas.

By providing a comprehensive analysis of the current state of DCTs and their impact on various stakeholders, this report illuminates the potential benefits, challenges, and opportunities that DCTs bring to the clinical research landscape.

Section 1: Defining and Evaluating Decentralised Clinical Trials – Activities Reported in Clinical Trial Protocols and Published Trials

What are remote, decentralised, patient-centric, site-less, virtual, and digital clinical trials? From confusion to consensus.

Yared Santa-Ana-Tellez, Bart Lagerwaard, Amos J de Jong, Helga Gardarsdottir, Diederick E Grobbee, Kimberly Hawkins, Megan Heath, Mira GP Zuidgeest, Trials@Home Consortium. Drug Discov Today. 2023 Apr;28(4):103520.

Clinical trials are essential in evaluating the benefits and risks of new medicines, medical devices and non-pharmacological interventions. However, these trials involve numerous challenges, such as slow participant recruitment, low retention rates, burdensome trial-related visits, high costs and limited generalisability of trial results. The growing implementation of digital health technologies, including wearable devices, mobile applications and telemedicine, facilitates remote recruitment, assessment and monitoring of trial participants, reducing the time and effort required for travelling to investigator sites.

The COVID-19 pandemic, with its strict social distancing and travel restrictions, forced the clinical research community to adjust how they managed clinical trials, increasing the adoption of digital and innovative operational approaches. During this time, regulatory authorities like the FDA and EMA provided temporary flexibilities for various trials to ensure their continuation, remote consent guidelines, investigational medicinal product distribution and telemedicine visits. However, the lack of standardised terminology for describing these operational models in clinical trials, such as site-less trials, digital trials and decentralised clinical trials, has impeded discussions between stakeholders. Consequently, to provide an overview of this field's heterogeneous terminology, a scientific literature review was performed to map the terminology associated with clinical trials centred on participants using technology and innovative operational approaches.

The authors conducted a literature review using MEDLINE®, searching for terms like 'digital trials', 'virtual trials', 'site-less clinical trials', 'patient-centred trials', 'remote trials' and 'decentralized clinical trials'. They identified 211 articles and selected 26 after applying various inclusion and exclusion criteria. Next, the various extracted terms were divided into three groups: terms regarding the use of technology, terms involving the participant and terms concerning location. Clinical trial terms were grouped into three categories: technology-focused, participant-focused and location-focused terms.

Technology-focused terms:

Internet-based, online and web-based clinical trials are those conducted online, which have advantages such as reduced cost and improved conduct but also require attention to electronic data security.

Virtual clinical trials are characterised by limited in-person visits, rely on technology for interaction and data collection and are sometimes confused with ‘in-silico’ trials.

Digital clinical trials use technology to improve trial activities like recruitment, data collection and analysis.

Participant-focused terms:

Patient-centricity is a concept where all aspects of a clinical trial, including design and outcome measures, centre around the participant.

Location-focused terms:

Site-less trials involve health professionals to manage participants remotely, usually via phone or videoconferencing. Remote clinical trials are coordinated by a local investigative team but are based remotely and often use technology for activities such as enrolment and electronic consent. Decentralised clinical trials involve a single pivotal site managing patients in their usual environment using telemedicine and local care providers. For example, a doctor can remotely monitor a patient’s progress through telemedicine, local caregivers can administer treatments, and wearable devices can track real-time health data. These trials can be completely remote or hybrid, with some required on-site visits. Remote decentralised clinical trials and decentralised virtual clinical trials are recent terms that emphasise the use of digital innovations to make trials more accessible to participants by relocating trial activities to their homes or local settings.

This article discusses the need for a common terminology to describe clinical trials that centre trial activities around participants. Currently, multiple terms are used interchangeably in the literature, causing confusion among stakeholders, including patients, investigators, sponsors and regulators. In this study, the authors reviewed the existing literature and found that the most frequently used terms are ‘remote clinical trial’, ‘virtual clinical trial’ and ‘decentralised clinical trial’. However, each term has limitations and does not fully capture the benefits of the decentralised approaches for participants and the use of technology to ease trial conduct. Thus, the authors propose the use of the term ‘decentralised clinical trial’ (DCT) to refer to the operational model of clinical trials in which some or all the trial activities are designed to occur at or near the participant’s home rather than at a traditional clinical site. This process uses technologies and other innovative operational approaches to facilitate data collection. The

authors emphasise that DCT approaches do not necessarily decrease the number of clinical site visits and can be employed to meet other goals, such as enriching data sets or producing more continuous data collection in the ‘real world’. The authors recommend the use of the term DCT to ensure clear, effective communication among stakeholders and to facilitate productive discussions on the implementation, benefits and potential disadvantages of DCT approaches.

The scientific publication underpinning this summary appears in supplementary material S1, which contains the entire study.

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

Amos J de Jong, Renske J Grupstra, Yared Santa-Ana-Tellez, Mira GP Zuidgeest, Anthonius de Boer, Helga Gardarsdottir on behalf of the Trials@ Home Consortium.BMJ Open. 2022 Aug 29;12(8):e063236.

DCT activities involve organising operational trial activities around the trial participants and conducting these activities away from investigative sites. Examples of 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).

Implementing DCT activities in clinical trials (CTs) could address several issues with CT conduct, such as the heavy burden of participating in CTs and low recruitment and retention rates, and improve participant understanding, satisfaction, and protocol compliance. Decentralised consent, telemedicine visits, and DtP IMP supply could make CTs more participant-centred by reducing the number of required on-site visits. Additionally, data generated through wearables is less influenced by recall and observer bias caused by the change in behaviour (due to participants' awareness that they are being observed) and could produce more continuous data collection than in traditional clinical trials. Beyond this, wearables could introduce novel digital endpoints, which are particularly pertinent in diseases for which no objective biomarker currently exists, such as disease progression in Parkinson's disease.

Furthermore, the COVID-19 pandemic has affected the acceptance of decentralised trial activities and the attitudes of various stakeholders, including sponsors, investigators and regulators, regarding the incorporation of these activities into CT. Regulators overseeing CTs have published guidelines on decentralised trial activities for which no instructions or legislation were available before the pandemic, including DtP IMP shipment and telemedicine visits. Since then, the United States Food and Drug Administration, the Danish Medicines Agency, Swissmedic, and EMA, among other organisations, have published guidelines on implementing decentralised trial activities in clinical research.

In this vein, CT protocols from the ClinicalTrials.gov database with an (estimated) trial start date between January 1, 2019 and December 31, 2020 were analysed to investigate the occurrence of decentralised and on-site conduct of trial activities. As the World Health Organisation declared the COVID-19 outbreak a public health emergency of international concern (PHEIC) on 30 January 2020, this research importantly covers the time just before

and after the pandemic. This article discusses the increasing use of digital health technologies (DHTs) in clinical research and the potential benefits of decentralising clinical trial activities, such as reducing the burden on participants and improving recruitment and retention rates. The study collected data on CT characteristics such as trial location, type of sponsor, trial design, follow-up time, estimated sample size, type of participants involved and therapeutic area. The primary outcome of the study was the occurrence of decentralised, on-site conduct of predefined trial activities reported in CT protocols. The secondary outcome involved whether decentralisation was reported exclusively, complementarily or not at all.

The study demonstrated that on-site conduct was more frequently reported than decentralised conduct for all trial activities with an on-site equivalent. On-site data collection and consenting were the most frequently reported trial activities, whereas decentralised data collection was the most frequently reported decentralised activity, followed by CT monitoring and participant outreach. Furthermore, the authors noted that of the 254 protocols analysed, only 138 were suitable to implement ‘direct-to-participant IMP supply’ and ‘decentralized IMP adherence monitoring’ because at least one IMP was administered in an at-home setting in these protocols.

Additionally, the study revealed that the majority of decentralised data collection was used to complement on-site data collection (67.3%), and data collected exclusively by decentralised means was reported in only 1.6% of protocols. On the other hand, consent was exclusively on-site in 89.0% of protocols, whereas only 2.8% of protocols exclusively involved decentralised consenting.

The authors found that although on-site conduct was more frequently reported than decentralised conduct, decentralised conduct was still commonly reported, particularly for data collection (68.9%), especially 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. Additionally, trends in reporting over time were visible for several decentralised and on-site trial activities. For example, decentralised pre-screening increased by three percentage points, on average, per half a year, whereas on-site pre-screening was stable over time. 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.

Beyond this, the study identified several hiatuses in CT protocols, such as incomplete

reporting of training of staff and participants, CT monitoring and participant outreach. This incomplete reporting may affect the interpretation of CT results and the design of future CTs. Therefore, future protocols should clearly distinguish between on-site and decentralised conduct.

The study revealed that decentralised trial activities were implemented in a minority of CTs, and there is limited information about the extent to which activities were implemented in CTs. Therefore, further research on this topic is needed, to address the challenges associated with the implementation of decentralised trial activities to improve participant experience and outcomes. Despite the limitations of the study, such as the limited number of protocols available for 2020, the findings demonstrated that a broad set of operational trial activities can be executed in a decentralised fashion. Therefore, the authors suggest that sharing experiences on trial activities frequently and infrequently executed in a decentralised fashion could help progress future use and drive mutual learning among clinical research stakeholders to benefit trial participants.

The scientific publication underpinning this summary appears in supplementary material S2, which contains the entire study.

Section 2: Regulatory Perspectives and Experiences in Decentralised Clinical Trials: A Comprehensive Analysis

Decentralised Clinical Trials: Insights from meetings with the European Medicines Agency Innovation Task Force and requested Scientific Advice

Regulatory advice Task Force of Trials@Home

The Trials@Home consortium is exploring not only the opportunities and benefits offered by DCTs, but also the challenges and their potential solutions. Earlier in this project, the Trials@Home consortium sought the input of the Innovation Task Force (ITF) of the European Medicines Agency (EMA) and the scientific advice of a National Competent Authority (NCA) on various aspects of the consortium's proposed pan-European pilot study (RADIAL). The objective of the proof-of-concept RADIAL study is to compare the scientific and operational quality of fully decentralised and hybrid approaches to a conventional clinical trial approach and evaluate the feasibility of such approaches.
As part of the planning and preparations for RADIAL, the Trials@Home consortium realised that consultation with the ITF and a NCA would be highly beneficial.

This article outlines the discussions held during the EMA ITF meeting (27/05/2021) and with a NCA (24/09/2021) on the design and implementation of the RADIAL trial. We have separated the discussions based on the Trials@Home building block classification scheme developed by WP2 TECH (Technologies – Barriers, enablers, and data management) into the following phases:

- Set-up and design
- Conduct of the trial
- Safety oversight
- Data collection
- Closing phase of the clinical trial

In the setup and design phase, protocol development was underway when the meetings with the regulators took place, with the Consortium finalising aspects such as alerts for glycaemia measurements, and dose injections. The technology setup had yet to be completely defined, and the choice of devices such as wearables was still being made.
The ITF provided crucial advice on the regulatory compliance for these devices. The ITF highlighted ethical implications and legal concerns related to the investigators' roles and responsibilities. The NCA raised questions about data handling, patient-generated data, and the intended use of an eSource Direct Data Capture tool in the trial.

Moving onto the recruitment and enrolment phase, the NCA raised questions on participant outreach specifically on the potential bias in recruitment across different arms. The NCA commented on the selection bias that may arise from the use of social media platforms for recruitment. In terms of pre-screening, the ITF suggested that digital literacy should be measured during enrolment and factored into the analysis of results. The NCA had concerns about validating patient eligibility and assessing exclusion criteria via telemedicine, emphasizing the essential role of treating physicians within the trial. They also raised questions about pre-screening processes, informed consent, and data protection issues with electronic consent materials.

In the data acquisition there was focus on gathering and managing real-world data, such as that from wearables and glucose monitoring devices. The management of study-generated data has been discussed in terms of patient satisfaction and burden of data collection, with the ITF questioning how adverse events will be collected in the remote and hybrid arms.

Regarding safety oversight T@H consortium proposed four defence lines to ensure participant safety, leveraging technology for semi-automated safety monitoring, these include: i) automated guidance to participants on medication and event reporting, ii) notifications to the research team for potential safety signals, iii) escalation of serious issues to the Principal Investigator, iv) further escalation to the monitoring team if previous steps don't lead to appropriate action.
The ITF raised questions about the triggers used for the different defence lines proposed and expressed concern about potential bias in the comparison of recruitment across the different study arms.

Home health visits have been incorporated into the study plan and the laboratory setup and sampling process have been determined. Self-intervention and self-monitoring are emphasised, with the plan for participants to provide daily glucose readings and self-report safety events. There was also a focus on the investigator's role in ensuring participant medical safety and complying with ICH E6 guidelines.

Patient engagement

The ITF has emphasised the need for clear communication between investigators and participants, the Consortium has stressed the importance of direct messaging to participant, such as digital reminders for dose injections and alerts for glycaemia measurements. The participation of the patient panel in the study setup has been mentioned.

Closing Phase of the Clinical Trial

The ITF and the Consortium also discussed follow-up interactions and reporting procedures post-trial. The Consortium requested the ITF's feedback on selected KPIs/endpoints and on the use of novel technologies for safety monitoring. The ITF recommended considering the quality of interactions, possible selection, and digital literacy of the participants when assessing the results.

One significant challenge facing the implementation of DCTs is the diversity of country-specific regulations and requirements. The ITF recommended seeking scientific advice from NCAs and CHMP and exploring various options, such as parallel consultation or national scientific advice which was later done by consulting BfArM. This challenge highlights the importance of close collaboration between regulatory agencies, clinical investigators, and sponsors in navigating the complex regulatory landscape in which DCTs operate.

Conclusion

The willingness of the ITF and BfArM to provide support and expertise to Trials@Home suggests that collaboration between parties (sponsor/investigators and regulators) is possible and benefitable. Such collaboration can contribute to the successful implementation of DCTs and help shape the future of clinical research. By sharing the lessons learned from the pilot study and engaging in ongoing dialogue, Trials@Home, the EMA and NCAs can work together to refine existing guidelines, produce new guidelines, and develop best practises for DCTs.

In conclusion, close collaboration between regulatory agencies, clinical investigators, and sponsors is essential to overcome the challenges associated with DCTs and ensure the highest standards of participant safety and data quality. By working together and learning from pilot studies, such as the RADIAL study conducted by Trials@Home, the clinical research community can continue to advance and innovate, paving the way for a more efficient and accessible clinical-trial landscape.

The scientific publication underpinning this summary is currently being drafted and the authors aim to make the article publicly available through publication in a scientific journal.

Opportunities and Challenges for Decentralised Clinical Trials: European Regulators' Perspective

Amos J de Jong, Tessa I van Rijssel, Mira GP Zuidgeest, Ghislaine JMW van Thiel, Scott Askin, Jaime Fons-Martínez, Tim De Smedt, Anthonius de Boer, Yared Santa-Ana-Tellez, Helga Gardarsdottir, on behalf of the Trials@ Home Consortium Clin Pharmacol Ther. 2022 Aug;112(2):344-352.

Clinical trials are critical in determining the efficacy and safety of therapeutic interventions. However, the processes involved in conducting clinical trials, including participant recruitment, data collection and preventing loss to follow-up, can be suboptimal and can hinder the clinical development of new interventions. Frequently, these processes are burdensome for participants, leading to low participation and retention rates.

The COVID-19 pandemic has catalysed the use of decentralised elements to ensure participant safety and maintain data integrity. Since the pandemic, investigators and sponsors have been interested in incorporating decentralised trial elements, and regulators have expressed interest in DCTs by issuing guidance and monitoring DCT pilot studies. However, relatively few full DCTs have been conducted in Europe thus far, regulatory requirements and a perceived low degree of acceptance by national competent authorities and ethics committees limit their implementation.

To identify the opportunities and challenges for DCTs from a regulatory perspective, this study employed in-depth, semi-structured interviews with 20 European regulators involved in assessing the application, implementation, and interpretation of clinical trials. The interviews revealed five major themes: justification of decentralised elements, sponsor and investigator responsibilities, trial participants' interests, data quality and future directions. Both opportunities and challenges applicable to DCTs and conventional clinical trials were identified.

The respondents indicated that decentralised elements should suit the research question and be clearly described and justified on a case-by-case basis within the clinical trial protocol. Additionally, risks associated with implementing decentralised elements should be anticipated and mitigated. Late-phase confirmatory clinical trials were considered more suitable for DCTs than early-phase trials. Opportunities to conduct DCTs for chronic diseases, low-risk diseases and rare diseases were recognised by several respondents because of the ability to self-manage chronic diseases and the wider geographic reach for recruiting participants with rare diseases. However, therapeutic areas that require careful assessment or observation —such as Parkinson's disease and oncology— were considered less appropriate for DCTs.

The regulators further believe that DCTs can be considered for various types of trials but that decentralised elements must be justified using the research question and trial characteristics. The benefits of DCTs include reducing the participation burden, allowing underserved groups to participate in clinical trials, and capturing data from the ‘real world’. However, reducing face-to-face contact, maintaining investigator oversight when involving third parties and the possible impact of decentralisation on data quality are considered challenges to implementing DCTs.

The article identifies six aspects related to data quality that are important in DCTs: generalisability, participant preference, big data, data completeness, variability and validation. Challenges associated with validating digital technologies have hindered these technologies’ adoption. Involving third parties, such as home nurse services, may be necessary to manage DCTs, but investigators may be hesitant to delegate specific tasks, and training third parties can create additional challenges.

Finally, this article concludes that regulators are open to DCT proposals, but their experience with full DCTs is limited. Harmonising guidance and regulations on decentralised elements at European level could facilitate the uptake of DCTs and overcome the need for country-specific adjustments. Consequently, future studies are recommended to determine whether decentralised elements and recruitment approaches permit the inclusion of a more representative and diverse trial population. Additionally, further work could develop a regulatory framework for DCT assessment and educational activities.

The scientific publication underpinning this summary appears in supplementary material S3, which contains the entire study.

Evaluating the European Health Technology Assessors' Perspective on Decentralised Clinical Trials

Amos J. de Jong, Nadi Shahid, Mira G.P. Zuidgeest, Yared Santa-Ana-Tellez, Milou Hogervorst, Wim Goettsch, Hamidou Traore, Anthonius de Boer, Helga Gardarsdottir, on behalf of the Trials@Home Consortium

Health technology assessment (HTA) is a multidisciplinary process that determines the value of health technology at various stages of this technology's lifecycle to promote a high-quality, efficient and equitable health system. In this process, HTA bodies (HTABs) conduct assessments to inform decisions, such as medication reimbursement. With the advent of digital health technologies (DHTs), decentralised clinical trials (DCTs) have emerged, enabling clinical trials to be conducted around the participant's homes.

The perspective of HTABs on DCTs have not been formally evaluated. Therefore, this study investigated the opportunities and challenges for DCTs in supporting HTA decision-making from a European perspective.

This study used semi-structured, in-depth interviews with representatives of European HTABs. The authors conducted 24 interviews with 25 respondents to assess perceptions and experiences with DCTs. The study's findings were categorised under two main themes: "Acceptability and relevance of DCT data" and "DCTs in HTA decision-making".

Acceptability and relevance of DCT data

Participants noted concerns about missing data, variability and validating data collection methods in DCTs. Although DCTs were expected to reduce missing data due to their convenience and continuous data collection, they could also cause more missing data due to connectivity issues or reduced willingness to fill out recurring patient-reported outcomes (PRO). Furthermore, the participants mentioned the potential for both increased and decreased biases with DCTs. Although DCTs could reduce recall bias and the 'Hawthorne effect', they could also increase the risk of unblinding when participants can see their own outcomes. From an economic perspective, DCTs could offer informative quality of life (QoL) data, by reducing recall bias and administration in a real-life setting. Additionally, the respondents in this study noted that DCTs could potentially attract more diverse participants, including individuals who are unable or unwilling to frequently visit the trial sites. However, DCTs could select participating groups based on digital literacy, willingness to use technology and access to technology.

Decentralised Clinical Trials in Health Technology Assessment decision-making

Although most of the respondents had no experience with full DCTs, many had experience with individual DCT elements, including remote data collection, wearables and telemedicine visits. The respondents believed that simple measures and outcomes that require frequent monitoring are suitable to be evaluated utilizing DCT approaches. However, endpoints requiring physical examinations or complex measurements and interventions necessitating close monitoring or complex administration were considered inappropriate for DCTs. Additionally, the respondents discussed the role of DCTs in the evidence framework and its relation to real-world, observational studies and pragmatic trial approaches. In this regard, the respondents mentioned that DCT approaches should be employed to generate evidence in addition to conventional randomized controlled trials.

This study identified potential benefits and concerns regarding data generated utilising a DCT approach and its value for HTA decision-making. Stakeholder views reflect cautious optimism toward DCTs but the views also emphasise the need to consider potential risks.

The scientific publication underpinning this summary is currently being drafted and the authors aim to make the article publicly available through publication in a scientific journal.

Direct-to-Participant Investigational Medicinal Product Supply in Clinical Trials in Europe – Exploring the Experiences of Sponsors, Site Study Staff, and Couriers

Amos J. de Jong, Yared Santa-Ana-Tellez, Mira G.P. Zuidgeest, Renske J. Grupstra, Fatemeh Jami, Anthonius de Boer, Helga Gardarsdottir, on behalf of the Trials@Home Consortium

Implementing direct-to-patient (DtP) solutions for investigational medical product (IMP) supply in Europe is hindered by the lack of harmonised regulatory guidance and the varying perspectives of national competent authorities (NCAs).

To support the development of harmonised regulatory guidance, this study explored how the DtP IMP supply was employed in trials executed in Europe before and during the COVID-19 pandemic. Data were collected through online, semi-structured interviews with representatives from pharmaceutical companies, courier services and investigative sites. The participants were selected based on their involvement in IMP handling and their experience with DtP IMP supply in Europe. Maximum variation and snowball sampling were employed to capture diverse perspectives.

Several DtP IMP supply models employed in Europe were identified, including the site-to-participant model, local and central pharmacy-to-participant models. The respondents discussed experience with the delivery of IMP by home nurses, postal mail and courier services and collection at local pharmacies.

Additionally, the researchers identified the drivers of DtP supply implementation, including the need to improve patient access and convenience, reduce costs and burden on sites and mitigate risks associated with COVID-19. Beyond this, the study identified the barriers and facilitators of implementing DtP solutions in Europe. The main barriers identified were the lack of harmonised regulatory guidance and the varying perspectives of NCAs. Furthermore, the respondents highlighted the need for infrastructure and technology to support DtP solutions and the importance of patient and site engagement.

The first model discussed was the site-to-participant supply model, which was noted as relatively easy to implement but had logistical burden associated with the shipment of IMPs to participants. This method may also be challenging when IMPs have stringent stability requirements. In contrast, shipment from a central location was considered most efficient because only IMPs which have been ordered by interactive response technology (IRT) are dispensed, reducing spillage and reducing costs of establishing sites' pharmacies. However, for central shipment, services provided by a nurse or pharmacist, such as answering

participants' questions, were expected to be limited.

The study noted that not all DtP supply models are suitable for all types of IMPs. In this regard, IMP characteristics such as safety profile, phase of development, stability, need for complex preparations and route of administration must be considered when selecting a DtP supply solution. Marketed drugs are particularly suitable for DtP supply through local pharmacies because participants may obtain them with a prescription.

The article discussed the advantages and disadvantages of different delivery methods for DTP supply. Shipment via postal mail was considered financially attractive but may not be suitable for certain IMPs, such as controlled analgesics, where the identity of the recipient cannot be ascertained. Dedicated courier services were noted to be advantageous since they could deliver the IMP to locations other than the participant's homes, such as campsites or workplaces.

Moreover, the study discussed the drivers for DtP supply implementation. The COVID-19 pandemic was noted as a significant motivator for exploring DtP approaches because it ensured clinical trial continuation during the pandemic. Additionally, DtP approaches were perceived to make clinical trials more patient-centric by reducing the need for on-site visits, reducing travel expenses and facilitating participation for those individuals who live far from investigative sites, and for those with mobility challenges or people experiencing distress during visits. However, certain barriers to implementation remain, such as unharmonized regulations and privacy and data protection considerations.

Overall, investigators are responsible for the IMP-dispensing process, IMP-adherence monitoring and participant safety, but they may delegate tasks to third parties such as courier services or central or local pharmacies. Some investigators were hesitant to delegate tasks to third parties, but it was suggested that this could be solved by engaging site staff in the setup and execution of DtP processes and providing an opt-in/opt-out possibility for the site.

The study distinguished four models of DtP IMP supply: (i) investigative site-to-participant, (ii) central pharmacy-to-participant, (iii) local pharmacy-to-participant and (iv) sponsor-to-participant. The article explained that the investigative site-to-participant model is currently the most frequently employed model in Europe because there are no regulatory barriers to its implementation, and it is seen as the closest model to the traditional pathway in a non-DCT setting. However, this model can potentially impact the quality of the medicinal product and cause additional burdens for site study staff and participants.

Beyond this, the article discussed the regulatory barriers that hamper the local and central pharmacy-to-participant models, such as a lack of harmonised regulations and acceptability, restricted access to personally identifiable data and the willingness of investigators to delegate tasks regarding IMP-dispensing and accountability. The study revealed that the local pharmacy-to-participant model was considered most suitable for investigating IMPs with market authorisations and should be explored for low-intervention clinical trials under the EU Clinical Trials Regulation.

Additionally, the article advocated for more explicit definitions in guidance documents and case study reports to share best practices while acknowledging different combinations of models and means of IMP delivery. The study also suggested that future research should focus on patient and investigator acceptability of these approaches and investigate the impact of DtP IMP supply on IMP adherence and accountability.

The scientific publication underpinning this summary appears in supplementary material S4, which contains the entire study.

Section 3. Exploring Technical and Regulatory Implications for Optimal Decision-Making in Key Clinical Areas

Survey EFPIA partners on their views of regulatory implications for different clinical areas.

Yared Santa-Ana-Tellez, Amos J de Jong, Tessa I van Rijssel, Kate Huntley, Olenka van Ardenne, Hamidou Traore, Helga Gardarsdottir, on behalf of the Trials@ Home Consortium

The trend in implementing DCT approaches is reshaping the clinical research landscape, making it crucial to fully understand its technical and regulatory intricacies. In this search for clarity, we sought insights of representatives of the European Federation of Pharmaceutical Industries and Associations (EFPIA) through a survey. The objective of the survey was to gather experiences and insights on the operational, regulatory, and decision-making aspects of conducting DCTs in different clinical areas. The survey was conducted between March and May of 2023. The learning derived from this exercise revealed a complex landscape with challenges and opportunities.

Among the respondents, a broad spectrum of roles within pharmaceutical companies (27 out of 30) was represented, from clinical compliance officers, regulatory directors, and associate directors to statisticians. The geographical distribution of these respondents was equally extensive, with the majority from the United States (10 out of 30), Switzerland (6 out of 30), and the United Kingdom (4 out of 30). Their collective expertise covered various stages of drug development and various diseases, including, but not limited to, cancer, cardiovascular disease, and immunological disorders.

Many of these professionals indicated high levels of competence in drug development (17 out of 30 rated 5 out of 5). Furthermore, while their experience with DCTs varied, most reported significant experience. As a result, they were able to provide unique insights into the perceived benefits of DCT, such as enhanced patient participation and higher recruitment and retention rates, particularly in cancer research.

Regarding DCT approaches, data quality and security, remote monitoring strategies, and regulatory compliance were among the key study design concerns expressed by the respondents. Furthermore, they emphasised technical difficulties related to data integration and remote participant monitoring. Despite these concerns, the respondents proposed many potential solutions, including, but not limited to, investment in staff training, standardisation of remote monitoring procedures, and enhancement of patient engagement strategies. In addition, they emphasised the need for robust data management software, stringent data

security protocols, and the greater acceptance of digital endpoints by regulatory bodies.

Another important aspect that came to the forefront was regulatory implications, particularly those related to side effect management and reporting. The promise of technology-enabled real-time monitoring and reporting, together with increased collaboration among contract research organisations (CROs), pharmaceutical companies, and healthcare providers, was viewed as a compelling strategy.

However, despite the enthusiasm for DCTs, regulatory challenges still need to be addressed. Compliance with data protection regulations, and local regulations were identified as the primary obstacles. The respondents expressed concerns about varying regulations in the different EU member states, specifically those related to the delivery of IMP direct-to-participant and data protection laws like the GDPR. They highlighted the potential risk of exclusion of specific demographics due to technological competence requirements.

The respondents emphasised the urgent need for clear guidelines for compliance with good clinical practice and greater harmonisation of regulatory requirements. Proposing avenues for improvement, they stressed enhancing data protection measures, creating robust data-sharing agreements, and increasing the oversight of ethics boards. The respondents advocated for more support and guidance from health authorities, particularly with respect to the use of technology for remote assessment of adverse events.

In navigating the complex path toward broader adoption of DCTs, the respondents emphasised the need to focus on cost efficiency, user friendliness for both sites and participants. Interestingly, feedback from the survey indicated that a more detailed examination of patient engagement could significantly benefit the ongoing conversation about DCTs, thus underlining the criticality of these elements.
In conclusion, this survey reveals that while DCTs present unique technical and regulatory challenges, the industry is poised and ready to embrace DCT approaches more broadly. The insights from our survey underscore that with better guidelines, strategic planning, and a collaborative approach, we can effectively navigate the complexities and maximise the benefits of DCTs.

The scientific publication underpinning this summary is currently being drafted and the authors aim to make the article publicly available through publication in a scientific journal.

Overall discussion conclusion

This multifaceted analysis under the Trials@Home project provides a comprehensive picture of the potential, as well as the limitations associated with DCTs. The implications of these findings span both operational and regulatory perspectives in the field of clinical research.

The ambiguity of terms within the literature was an initial challenge that we addressed, one that could lead to confusion among stakeholders. We concluded that the term decentralised clinical trial is most appropriate to encapsulate “the operational model of clinical trials in which trial activities are designed to take place at, or in the vicinity of, the participan''s home, rather than at a traditional clinical site. This approach can make use of technologies and other innovative operational approaches to facilitate data collection.” This terminology consensus is vital to facilitate effective communication among stakeholders and foster a better understanding of the potential benefits and l disadvantages of DCT approaches.

We further examined the implementation of DCTs in clinical trials initiated in 2019-2020. Our cross-sectional analysis of ClinicalTrials.gov demonstrated the emerging stage of integration of DCTs, with a minority of trials incorporating decentralised activities. This illustrates the underuse of DCTs, prompting the need for additional research. Sharing experiences and fostering an environment for mutual learning among clinical research stakeholders could be key to accelerating the adoption of DCTs.

In evaluating regulatory perspectives and experiences, we observed a notable willingness to collaborate and support DCTs from regulatory entities such as the EMA ITF and BfArM. These positive interactions between regulators and initiatives such as Trials@Home suggest that DCTs can become a well-supported operational approach within clinical research. In this cooperative atmosphere, the lessons learnt from pilot studies such as the RADIAL study can help refine guidelines and develop best practises, leading to successful implementation and helping to shape the future of clinical research.

However, we also identified possible challenges that come with the implementation of DCTs. Data concerns, such as generalisability, participant preference, big data management, data completeness, variability, and validation, pose hurdles. In addition, engaging third parties to manage DCTs, validating digital technologies, and training these parties brings additional complexities.

The industry's eagerness to adopt DCTs is apparent, but navigating the complexities and maximising the benefits of DCTs requires strategic planning, better guidelines, and a collaborative approach among all stakeholders. For example, the DtP IMP supply analysis presented the different models and their limitations, demonstrating the need for more detailed guidelines and robust regulatory frameworks.

Lastly, the lack of harmonised guidance and regulations, particularly on a European level, was seen as a significant roadblock for DCT'' widespread adoption. Overcoming this would necessitate concerted efforts towards aligning regulations and guidance across countries, facilitating the smooth conduct of DCTs, and alleviating the need for country-specific adjustments.

The discussions presented in this report underscore the necessity of creating an inclusive, collaborative and forward-thinking culture within the clinical research community. This would help overcome technical and regulatory challenges, accelerate the adoption of DCTs, and ultimately lead to more efficient and accessible clinical trials.

The potential benefits of DCTs for clinical research will be evaluated in the RADIAL trial, such as accessibility and participant experience. Furthermore, translating these benefits into widespread reality requires addressing a series of significant challenges. More research is needed to understand the acceptability of participants and investigators of different decentralised approaches and to explore the impact of DtP IMP supply on adherence and accountability. Such research will help create a robust framework that ensures both participant safety and data integrity, two cornerstones of successful clinical trials.
Our analysis underscores the need for unified terminology, robust support for DCT implementation, comprehensive guidance, strategic planning, and collaboration among all key stakeholders.

Similarly, establishing best practises and sharing lessons learnt from different models can further provide invaluable information to those planning to use DCTs.

An additional area that demands attention is the integration of technology. Given the heavy reliance of DCTs on digital tools for data collection and management, validating these technologies is critical to maintaining the reliability of the results. Concerns about data completeness, variability, and validation must be addressed effectively to ensure the credibility and validity of the data collected in DCTs.

The role of third-party services in the management of DCTs is another dimension that requires careful consideration. Although engaging third parties can enhance the efficiency of DCTs, it also raises questions about task delegation and data privacy, which must be handled with care.

In summary, our findings suggest that while DCTs hold significant promise for the future of clinical research, the realisation of their potential requires addressing a complex matrix of technical, operational, and regulatory challenges. Collaboration between stakeholders is of utmost importance, as it allows mutual learning and shared problem-solving.

As the clinical research community continues to learn from pilot studies and refine practises and guidelines, we suggest that widespread adoption of DCTs could potentially lead to a more efficient and participant-centric clinical trial landscape. This change will reflect a paradigm shift from traditional site-focused trials, thereby revolutionising the way clinical research is conducted.

Supplementary material 1

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

Yared Santa-Ana-Tellez, Bart Lagerwaard, Amos J de Jong, Helga Gardarsdottir, Diederick E Grobbee, Kimberly Hawkins, Megan Heath, Mira GP Zuidgeest, Trials@ Home Consortium. Drug Discov Today. 2023 Apr;28(4):103520.

POST-SCREEN (GREY)

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

Yared Santa-Ana-Tellez [1], Bart Lagerwaard [2], Amos J. de Jong [1], Helga Gardarsdottir [1,3,4], Diederick E. Grobbee [2], Kimberly Hawkins [5], Megan Heath [6], Mira G.P. Zuidgeest [2,*], on behalf of the Trials@Home Consortium[7]

[1] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands
[2] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
[3] Department of Clinical Pharmacy, Division Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, the Netherlands
[4] Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland
[5] Global Clinical Project Operations & Dossiers Delivery, Sanofi, United States
[6] Clinical Studies Unit Europe, Sanofi, United Kingdom

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

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

Introduction

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

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

* *Corresponding author: Zuidgeest, M.G.P. (m.g.p.zuidgeest@umcutrecht.nl)*
[1] Website: https://www.trialsathome.com.

1359-6446/© 2023 The Authors. Published by Elsevier Ltd.
https://doi.org/10.1016/j.drudis.2023.103520This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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

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

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

Literature review of terms used to describe clinical trials

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

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

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

Terms focusing on the use of technology

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

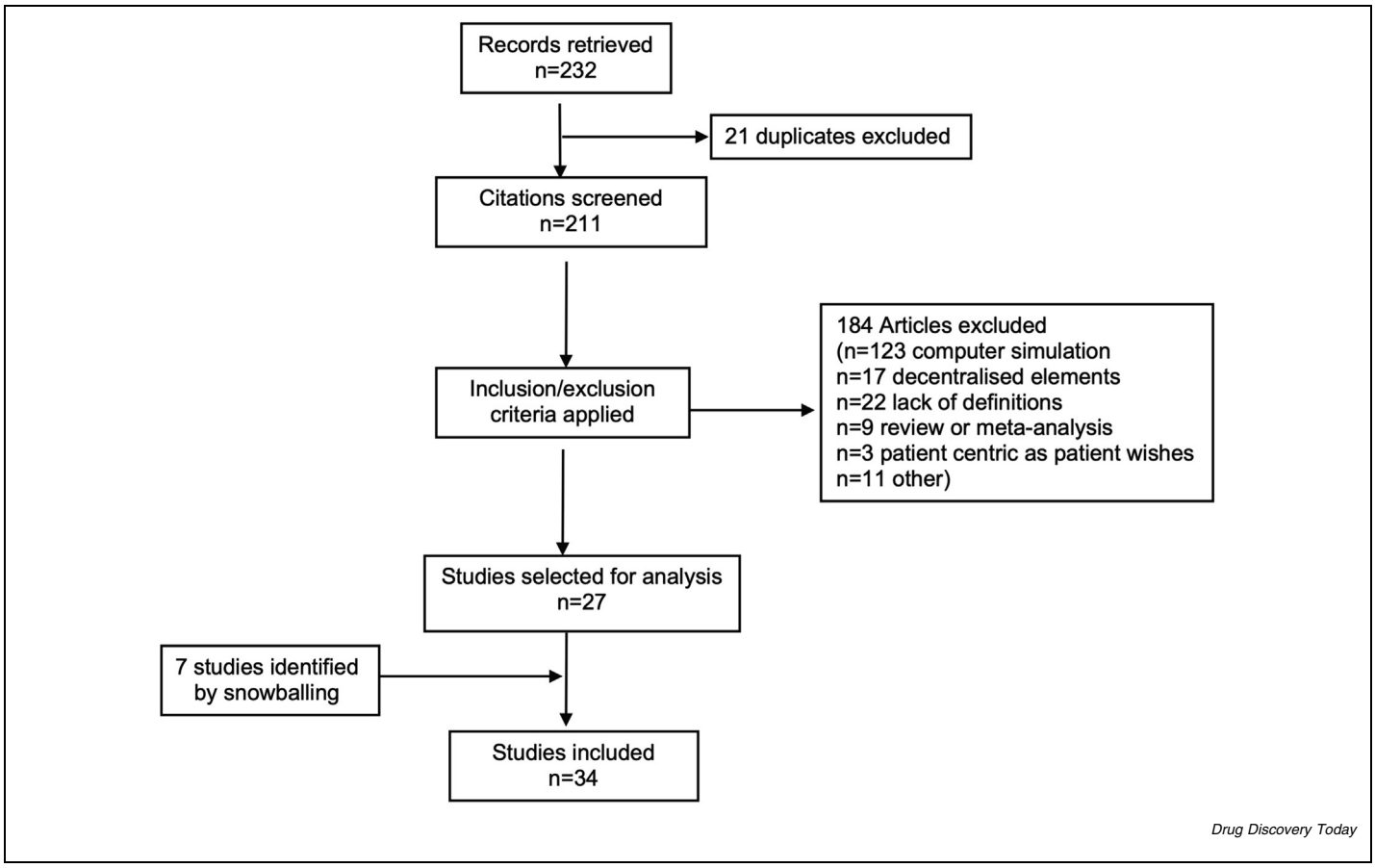

FIGURE 1
Literature search and review strategy.

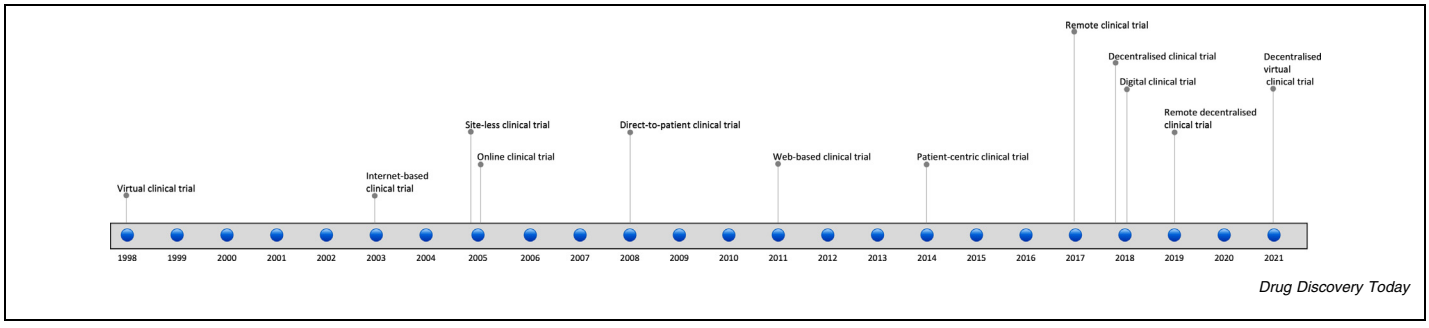

FIGURE 2
Chronological order of terms identified on their first appearance in the scientific literature.

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

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

TABLE 1

Terms and definitions, as described in the literature.

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

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

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

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

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

Terms focusing on the participant

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

Terms focusing on the location of trial conduct

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

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

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

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

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

Need for common terminology

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

Commonly used terms and their (dis)advantages

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

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

Toward a consensus definition

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

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

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

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

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

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

Concluding remarks

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

Authors' contributions.

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

Data availability

Literature review; data is already available

Acknowledgments

The Trials@Home project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement n° 831458. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and EFPIA. The Innovative Medicines Initiative website can be accessed through the following link: www.imi.europa.eu. The research leading to these results was conducted as part of the Trials@Home consortium. This paper only reflects the personal views of the stated authors. Patients or the public were not involved in the design, or conduct, or reporting of this manuscript.

Declaration of interests

The authors declare no conflict of interest.

Appendix A. Supplementary material

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

References

[1]. Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: a review. *Contemp. Clin. Trials Commun.*. 2018;11:156–164.
[2]. Briel M et al.. A systematic review of discontinued trials suggested that most reasons for recruitment failure were preventable. *J. Clin. Epidemiol.*. 2016;80:8–15.
[3]. Dorsey ER et al.. Novel methods and technologies for 21st-century clinical trials: a review. *JAMA Neurol.*. 2015;72:582–588.
[4]. Bagiella E et al.. The consequences of the COVID-19 pandemic on non-COVID-19 clinical trials. *J. Am. Coll. Cardiol.*. 2020;76:342–345.
[5]. McDermott MM, Newman AB. Preserving clinical trial integrity during the coronavirus pandemic. *J. Am. Med. Assoc.*. 2020;323:2135–2136.
[6]. Upadhaya S et al.. Impact of COVID-19 on oncology clinical trials. *Nat. Rev. Drug Discov.*. 2020;19:376–377.
[7]. FDA. *Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards*. Silver Spring: FDA; 2020.
[8]. EMA. *Guidance on the Management of Clinical Trials During the Covid-19 (Coronavirus) Pandemic*. Brussels: EMA; 2020.
[9]. de Jong AJ et al.. COVID-19 and the Emerging Regulatory Guidance for Ongoing Clinical Trials in the European Union. *Clin. Pharmacol. Ther.*. 2021;109:1517–1527.
[10]. Yu H, Singh Badhan RK. The pharmacokinetics of gefitinib in a Chinese cancer population group: a virtual clinical trials population study. *J. Pharm. Sci.*. 2021;110:3507–3519.
[11]. Wang H et al.. Conducting a virtual clinical trial in HER2-negative breast cancer using a quantitative systems pharmacology model with an epigenetic modulator and immune checkpoint inhibitors. *Front. Bioeng. Biotechnol.*. 2020;8:1–16.
[12]. Abadi E et al.. Virtual clinical trials in medical imaging: a review. *J. Med. Imaging*. 2020;7:42805.
[13]. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J. Clin. Epidemiol.*. 2009;62:499–505.
[14]. Zuidgeest MGP et al.. Series: Pragmatic trials and real world evidence: Paper 1. Introduction. *J. Clin. Epidemiol.*. 2017;88:7–13.
[15]. Coravos A et al.. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. *NPJ Digit. Med.*. 2019;2:1–5.
[16]. Mcalindon T et al.. Conducting clinical trials over the internet: feasibility study. *Br. Med. J.*. 2003;327:484–487.
[17]. Paul J et al.. The internet and clinical trials: background, online resources, examples and issues. *J. Med. Internet Res.*. 2005;7:e5.
[18]. Ledford, H. 'Virtual' trial brings clinical research home. *Nat Blogs*. https://blogs.nature.com/news/2011/06/virtual_clinical_trial_could_h_1.html. [Accessed 1 February 2023].
[19]. Orri M et al.. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial. *Contemp. Clin. Trials*. 2014;38:190–197.
[20]. Andrews L et al.. Virtual clinical trials: one step forward, two steps back. *J. Health Care Law Policy*. 2017;19:2.
[21]. Persky S. A virtual home for the virtual clinical trial. *J. Med. Internet Res.*. 2020;22:e15582.
[22]. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Health Sciences Policy, Forum on Drug Discovery, Development, and Translation, Shore C, Khandekar E, Alper J, eds. *Virtual Clinical Trials: Challenges and Opportunities: Proceedings of a Workshop*. Washington (DC): National Academies Press; 2019.
[23]. Coert RMH et al.. Stakeholder perspectives on barriers and facilitators for the adoption of virtual clinical trials: qualitative study. *J. Med. Internet Res.*. 2021;23:e26813.
[24]. Nissen J. Do digital clinical trials offer hope for patients? *Popul. Health Manag.*. 2020;23:273–275.
[25]. Erridge, S. *et al.* (2020) Virtual trials: looking beyond covid-19. Published online February 9, 2020.
[26]. Pappalardo F et al.. In silico clinical trials: concepts and early adoptions. *Brief. Bioinform.*. 2019;20:1699–1708.
[27]. Carlier A et al.. In silico clinical trials for pediatric orphan diseases. *Sci. Rep.*. 2018;8:2465.
[28]. Inan OT et al.. Digitizing clinical trials. *NPJ Digit. Med.*. 2020;3:101.
[29]. Hall CL et al.. Opportunities and challenges of delivering digital clinical trials: lessons learned from a randomised controlled trial of an online behavioural intervention for children and young people. *Trials*. 2020;21:1011.
[30]. Robbins DA et al.. Defining patient-centricity: opportunities, challenges, and implications for clinical care and research. *Ther. Innov. Regul. Sci.*. 2013;47:349–355.
[31]. Covington, D. (2014) The remote patient-centered study approach in clinical research. www.appliedclinicaltrialsonline.com/view/remote-patient-centered-study-approach-clinical-research [Accessed 1 February 2023].
[32]. Hirsch IB et al.. Incorporating site-less clinical trials into drug development: a framework for action. *Clin. Ther.*. 2017;39:1064–1076.
[33]. Cummings SR. Clinical trials without clinical sites. *JAMA Intern. Med.*. 2021;181:680–684.
[34]. Arean PA et al.. The use and effectiveness of mobile apps for depression: Results from a fully remote clinical trial. *J. Med. Internet Res.*. 2016;18:e330.
[35]. Donnelly S et al.. The burden of a remote trial in a nursing home setting: qualitative study. *J. Med. Internet Res.*. 2018;20:1–14.
[36]. Dahne J et al.. Remote methods for conducting tobacco-focused clinical trials. *Nicotine Tob. Res.*. 2020;22:2134–2140.
[37]. Danish Medicines Agency. *The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products v2.0 2021*. Copenhagen: Danish Medicines Agency; 2021.
[38]. SwissEthics. *SwissMedic. Decentralised clinical trials (DCTs) with medicinal products in Switzerland 2021*. Bern: SwissMedic; 2021.
[39]. Sommer C et al.. Building clinical trials around patients: evaluation and comparison of decentralized and conventional site models in patients with low back pain. *Contemp. Clin. Trials Commun.*. 2018;11:120–126.
[40]. Clinical Trials Transformation Initiative. *CTTI Recommendations: Decentralized Clinical Trials*. Durham: Clinical Trials Transformation Initiative; 2018.

[41]. Apostolaros M et al.. Legal, regulatory, and practical issues to consider when adopting decentralized clinical trials: recommendations from the Clinical Trials Transformation Initiative. *Ther. Innov. Regul. Sci.*. 2020;54:779–787.
[42]. Ali Z, Joergensen KM, et al.. Remote rating of atopic dermatitis severity using photo-based assessments: proof-of-concept and reliability evaluation. *JMIR Form. Res.*. 2021;5:1–8.
[43]. Allison M. Reinventing clinical trials. *Nat. Biotechnol.*. 2012;30:41–49.
[44]. FDA. *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations*. Silver Spring: FDA; 2022.
[45]. Ethics, D.N.C.F. (2022) Guidance on decentralised clinical trials (DCT). Published online February 3, 2022, 1–29.
[46]. EMA. *EMA Regulatory Science to 2025: Strategic Reflection*. Brussels: EMA; 2020.
[47]. EMA. *Guideline for Good Clinical Practice ICH E6(R2)*. Brussels: EMA; 2016.
[48]. Baumfeld Andre E et al.. Trial designs using real-world data: the changing landscape of the regulatory approval process. *Pharmacoepidemiol. Drug Saf.*. 2020;29:1201–1212.

POST-SCREEN (GREY)

Supplementary material 2

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

Amos J de Jong, Renske J Grupstra, Yared Santa-Ana-Tellez, Mira GP Zuidgeest, Anthonius de Boer, Helga Gardarsdottir on behalf of the Trials@ Home Consortium.BMJ Open. 2022 Aug 29;12(8):e063236..

BMJ Open

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

Amos J de Jong ,[1] Renske J Grupstra,[1] Yared Santa-Ana-Tellez,[1] Mira G P Zuidgeest,[2] Anthonius de Boer,[1,3] Helga Gardarsdottir ,[1,4,5] On behalf of Trials@Home consortium

To cite: de Jong AJ, Grupstra RJ, Santa-Ana-Tellez Y, *et al*. Which decentralised trial activities are reported in clinical trial protocols of drug trials initiated in 2019–2020? A cross-sectional study in ClinicalTrials.gov. *BMJ Open* 2022;**12**:e063236. doi:10.1136/bmjopen-2022-063236

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-063236).

Received 26 March 2022
Accepted 03 August 2022

Check for updates

© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Helga Gardarsdottir;
h.gardarsdottir@uu.nl

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

BMJ Open: first published as 10.1136/bmjopen-2022-063236 on 29 August 2022. Downloaded from http://bmjopen.bmj.com/ on June 6, 2023 by guest. Protected by copyright.

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

BMJ Open: first published as 10.1136/bmjopen-2022-063236 on 29 August 2022. Downloaded from http://bmjopen.bmj.com/ on June 6, 2023 by guest. Protected by copyright.

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

BMJ Open: first published as 10.1136/bmjopen-2022-063236 on 29 August 2022. Downloaded from http://bmjopen.bmj.com/ on June 6, 2023 by guest. Protected by copyright.

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

BMJ Open: first published as 10.1136/bmjopen-2022-063236 on 29 August 2022. Downloaded from http://bmjopen.bmj.com/ on June 6, 2023 by guest. Protected by copyright.

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%).

BMJ Open: first published as 10.1136/bmjopen-2022-063236 on 29 August 2022. Downloaded from http://bmjopen.bmj.com/ on June 6, 2023 by guest. Protected by copyright.

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

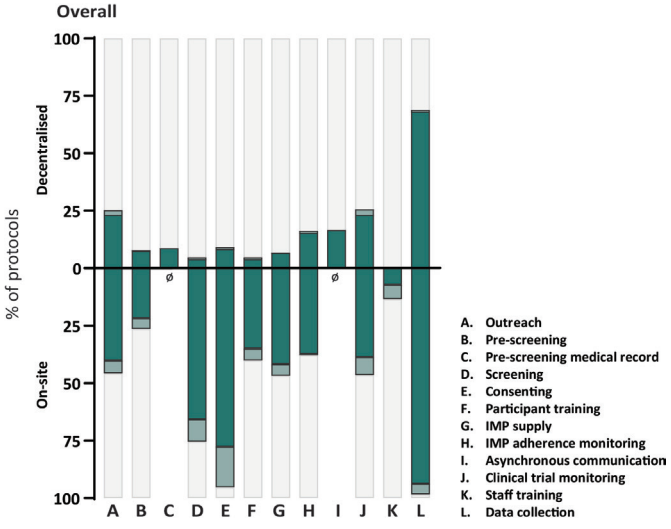

Figure 1 Frequency of decentralised and on-site trial activities reported in the protocols (n=254). The lighter green parts of the bars display the proportions that were implicitly reported. Prescreening through medical records (C) and asynchronous communication (I) do not have an on-site equivalent.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

BMJ Open: first published as 10.1136/bmjopen-2022-063236 on 29 August 2022. Downloaded from http://bmjopen.bmj.com/ on June 6, 2023 by guest. Protected by copyright.

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.

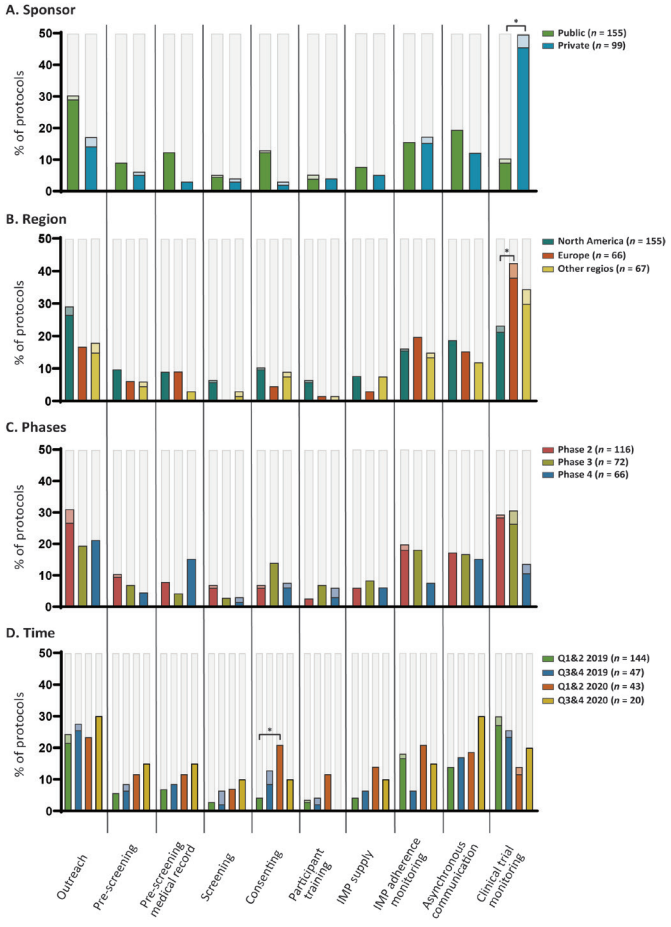

Figure 2 Frequency of decentralised trial activities reported in different strata. The lighter parts of the bars display the proportions that were implicitly reported. IMP, investigational medicinal product; Q1&2, first and second quarter; Q3&4, third and fourth quarter.

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

BMJ Open: first published as 10.1136/bmjopen-2022-063236 on 29 August 2022. Downloaded from http://bmjopen.bmj.com/ on June 6, 2023 by guest. Protected by copyright.

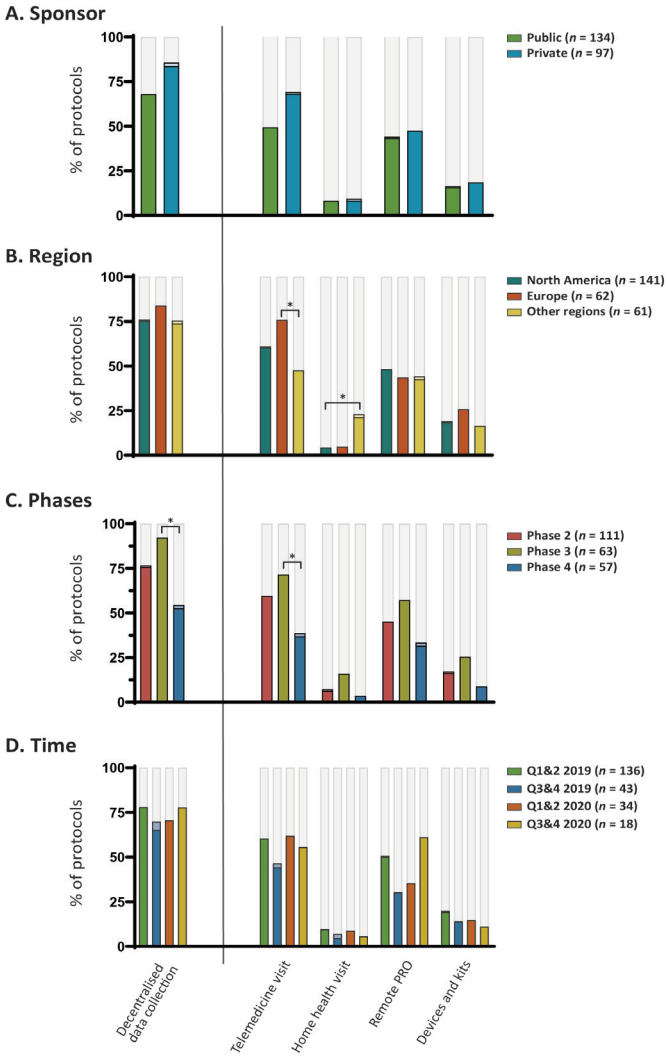

Figure 3 Data collection by decentralised means reported in the different strata. Data are presented for non-hospital-based trials (n=231). The lighter parts of the bars display the proportions that were implicitly reported. PRO, participant-reported outcome; Q1&2, first and second quarter; Q3&4, third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

BMJ Open: first published as 10.1136/bmjopen-2022-063236 on 29 August 2022. Downloaded from http://bmjopen.bmj.com/ on June 6, 2023 by guest. Protected by copyright.

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

BMJ Open: first published as 10.1136/bmjopen-2022-063236 on 29 August 2022. Downloaded from http://bmjopen.bmj.com/ on June 6, 2023 by guest. Protected by copyright.

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.

Author affiliations
[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
[2]Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands
[3]Dutch Medicines Evaluation Board, Utrecht, The Netherlands
[4]Department of Clinical Pharmacy, Division Laboratory and Pharmacy, University Medical Centre Utrecht, Utrecht, The Netherlands
[5]Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland

Contributors AJdJ, RJG, YS-A-T, MGPZ, and HG designed the research. AJdJ and RJG collected the data and analysed the data. HG is responsible for the overall content as a guarantor. All authors wrote the manuscript.

Funding The Trials@Home project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement n° 831458. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and EFPIA. The Innovative Medicines Initiative website can be accessed through the following link: www.imi.europa.eu.

Disclaimer The research leading to these results was conducted as part of the Trials@Home consortium. This paper only reflects the personal views of the stated authors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. The data file has been made freely available and is accessible via doi.org/10.17632/9ns6gmtz3j.1.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Amos J de Jong http://orcid.org/0000-0002-6860-9213
Helga Gardarsdottir http://orcid.org/0000-0001-5623-9684

REFERENCES

1 Marra C, Chen JL, Coravos A, *et al*. Quantifying the use of connected digital products in clinical research. *NPJ Digit Med* 2020;3:50.
2 Perry B, Herrington W, Goldsack JC, *et al*. Use of mobile devices to measure outcomes in clinical research, 2010–2016: a systematic literature review. *Digit Biomark* 2018;2:11–30.
3 Noah B, Keller MS, Mosadeghi S, *et al*. Impact of remote patient monitoring on clinical outcomes: an updated meta-analysis of randomized controlled trials. *NPJ Digit Med* 2018;1:20172.
4 Rosa C, Campbell ANC, Miele GM, *et al*. Using e-technologies in clinical trials. *Contemp Clin Trials* 2015;45:41–54.
5 Wilkinson M, Young R, Harper B, *et al*. Baseline assessment of the evolving 2017 eClinical landscape. *Ther Innov Regul Sci* 2019;53:71–80.
6 Dahne J, Tomko RL, McClure EA, *et al*. Remote methods for conducting Tobacco-Focused clinical trials. *Nicotine Tob Res* 2020;22:2134–40.
7 Amstutz A, Schandelmaier S, Frei R, *et al*. Discontinuation and non-publication of randomised clinical trials supported by the main public funding body in Switzerland: a retrospective cohort study. *BMJ Open* 2017;7:e016216.
8 Walters SJ, Bonacho Dos Anjos Henriques-Cadby I, Bortolami O, *et al*. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom health technology assessment programme. *BMJ Open* 2017;7:e015276.
9 Barnett AG, Glasziou P. Target and actual sample sizes for studies from two trial registries from 1999 to 2020: an observational study. *BMJ Open* 2021;11:e053377.

BMJ Open: first published as 10.1136/bmjopen-2022-063236 on 29 August 2022. Downloaded from http://bmjopen.bmj.com/ on June 6, 2023 by guest. Protected by copyright.

10 Moseson H, Kumar S, Juusola JL. Comparison of study samples recruited with virtual versus traditional recruitment methods. *Contemp Clin Trials Commun* 2020;19:100590.
11 Brøgger-Mikkelsen M, Ali Z, Zibert JR, *et al*. Online patient recruitment in clinical trials: systematic review and meta-analysis. *J Med Internet Res* 2020;22:e22179.
12 Rothwell E, Wong B, Rose NC, *et al*. A randomized controlled trial of an electronic informed consent process. *J Empir Res Hum Res Ethics* 2014;9:1–7.
13 Skelton E, Drey N, Rutherford M, *et al*. Electronic consenting for conducting research remotely: a review of current practice and key recommendations for using e-consenting. *Int J Med Inform* 2020;143:104271.
14 Rowbotham MC, Astin J, Greene K, *et al*. Interactive informed consent: randomized comparison with paper consents. *PLoS One* 2013;8:e58603.
15 Lentz J, Kennett M, Perlmutter J, *et al*. Paving the way to a more effective informed consent process: recommendations from the clinical trials transformation initiative. *Contemp Clin Trials* 2016;49:65–9.
16 Trials@Home WP1 - BEST. D1.1 First set of recommendations for RDCTs, 2020. Available: https://trialsathome.com/wp-content/uploads/2020/09/Trials@Home_D1.1-First-set-of-recommendations-for-RDCTs-to-be-implemented-in-the-pan-EU-pilot-RDCT.pdf [Accessed 18 Feb 2022].
17 Cox SM, Lane A, Volchenboum SL. Use of wearable, mobile, and sensor technology in cancer clinical trials. *JCO Clin Cancer Inform* 2018;2:1–11.
18 Coravos A, Goldsack JC, Karlin DR, *et al*. Digital medicine: a primer on measurement. *Digit Biomark* 2019;3:31–71.
19 Stephenson D, Badawy R, Mathur S, *et al*. Digital progression biomarkers as novel endpoints in clinical trials: a Multistakeholder perspective. *J Parkinsons Dis* 2021;11:S103–9.
20 Trials@Home. Centre of excellence for remote and decentralised clinical trials. Available: https://trialsathome.com/ [Accessed 18 Feb 2022].
21 Clinical Trials Transformation Initiative. Supporting decentralized trial approaches. Available: https://ctti-clinicaltrials.org/our-work/digital-health-trials/running-a-decentralized-trial/ [Accessed 18 Feb 2022].
22 TransCelerate Biopharma Inc. Modernizing clinical trial conduct. Available: https://www.transceleratebiopharmainc.com/initiatives/modernizing-clinical-trial-conduct/ [Accessed 18 Feb 2022].
23 de Jong AJ, Santa-Ana-Tellez Y, van Thiel GJMW, *et al*. COVID-19 and the emerging regulatory guidance for ongoing clinical trials in the European Union. *Clin Pharmacol Ther* 2021;109:1517–27.
24 Waterhouse DM, Harvey RD, Hurley P, *et al*. Early impact of COVID-19 on the conduct of oncology clinical trials and long-term opportunities for transformation: findings from an American Society of clinical oncology survey. *JCO Oncol Pract* 2020;16:417–21.
25 US FDA. Digital health technologies for remote data acquisition in clinical investigations, 2021. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/digital-health-technologies-remote-data-acquisition-clinical-investigations [Accessed 18 Feb 2022].
26 Danish Medicines Agency. The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products v2.0, 2021. Available: https://laegemiddelstyrelsen.dk/en/news/2021/guidance-on-the-implementation-of-decentralised-elements-in-clinical-trials-with-medicinal-products-is-now-available/~/media/5A96356760ED408CBFA9F85784543B53.ashx [Accessed 18 Feb 2022].
27 SwissMedic, SwissEthics. Decentralised clinical trials (DCTs) with medicinal products Switzerland v1.1, 2021. Available: https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/clinical-trials/clinical-trials-on-medicinal-products/publikationen.html [Accessed 18 Feb 2022].
28 Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. *JAMA* 2020;323:844–53.
29 Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. *Biostatistics* 2019;20:273–86.
30 Trials@Home Work Package 1 (BEST). D1.1 First set of recommendations for RDCTs (to be implemented in the pan-EU pilot RDCT), 2020. Available: https://trialsathome.com/wp-content/uploads/2020/09/Trials@Home_D1.1-First-set-of-recommendations-for-RDCTs-to-be-implemented-in-the-pan-EU-pilot-RDCT.pdf [Accessed 18 Feb 2022].
31 Trials@Home Work Package 2 (TECH). D2.3 – Technology scan, 2020. Available: https://trialsathome.com/wp-content/uploads/2020/10/D2.3-Scanning-results_Master.pdf
32 de Jong AJ, Grupstra RJ, Santa-Ana-Tellez Y, *et al*. Data from: which decentralised trial activities are reported in clinical trial protocols of drug trials initiated in 2019-2020? A cross-sectional study in ClinicalTrials.gov. *Mendeley Data* 2022.
33 Polhemus AM, Kadhim H, Barnes S, *et al*. Accelerating adoption of Patient-Facing technologies in clinical trials: a pharmaceutical industry perspective on opportunities and challenges. *Ther Innov Regul Sci* 2019;53:8–24.
34 Marra C, Gordon WJ, Stern AD. Use of connected digital products in clinical research following the COVID-19 pandemic: a comprehensive analysis of clinical trials. *BMJ Open* 2021;11:e047341.
35 Gerke S, Shachar C, Chai PR, *et al*. Regulatory, safety, and privacy concerns of home monitoring technologies during COVID-19. *Nat Med* 2020;26:1176–82.
36 Li G, Yin C, Zhou Y, *et al*. Digitalized adaptation of oncology trials during and after COVID-19. *Cancer Cell* 2020;38:148–9.
37 McDermott MM, Newman AB. Preserving clinical trial integrity during the coronavirus pandemic. *JAMA* 2020;323:2135–6.
38 World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020 [Accessed 18 Feb 2022].
39 Lasch F, Psarelli E-E, Herold R, *et al*. The impact of COVID-19 on the initiation of clinical trials in Europe and the United States. *Clin Pharmacol Ther* 2022;111:1093–102.
40 Bharucha AE, Rhodes CT, Boos CM, *et al*. Increased utilization of virtual visits and electronic approaches in clinical research during the COVID-19 pandemic and Thereafter. *Mayo Clin Proc* 2021;96:2332–41.
41 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Guideline for Good Clinical Practice ICH E6(R2), 2016. Available: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf [Accessed 18 Feb 2022].
42 Chan A-W, Tetzlaff JM, Altman DG, *et al*. Spirit 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
43 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
44 Tse T, Fain KM, Zarin DA. How to avoid common problems when using ClinicalTrials.gov in research: 10 issues to consider. *BMJ* 2018;361:k1452.
45 National Institutes of Health (Department of Health and Human Services). 42 CFR 11 § 11.48(A)(5)— Protocol and Statistical Analysis Plan, 2016. Available: https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission [Accessed 18 Feb 2022].
46 DeVito NJ, Bacon S, Goldacre B. Compliance with legal requirement to report clinical trial results on ClinicalTrials.gov: a cohort study. *Lancet* 2020;395:361–9.
47 Clinicaltrials.Gov background. Available: https://clinicaltrials.gov/ct2/about-site/background [Accessed 18 Feb 2022].

BMJ Open: first published as 10.1136/bmjopen-2022-063236 on 29 August 2022. Downloaded from http://bmjopen.bmj.com/ on June 6, 2023 by guest. Protected by copyright.

Supplementary material 3

Opportunities and Challenges for Decentralised Clinical Trials: European Regulators' Perspective

Amos J de Jong, Tessa I van Rijssel, Mira GP Zuidgeest, Ghislaine JMW van Thiel, Scott Askin, Jaime Fons-Martínez, Tim De Smedt, Anthonius de Boer, Yared Santa-Ana-Tellez, Helga Gardarsdottir, on behalf of the Trials@ Home Consortium Clin Pharmacol Ther. 2022 Aug;112(2):344-352.

Check for updates

Opportunities and Challenges for Decentralized Clinical Trials: European Regulators' Perspective

Amos J. de Jong[1], Tessa I. van Rijssel[2], Mira G. P. Zuidgeest[2], Ghislaine J. M. W. van Thiel[2], Scott Askin[3], Jaime Fons-Martínez[4], Tim De Smedt[5], Anthonius de Boer[1,6], Yared Santa-Ana-Tellez[1] and Helga Gardarsdottir[1,7,8,*] on behalf of the Trials@Home Consortium

Decentralized clinical trials (DCTs) have the potential to improve accessibility, diversity, and retention in clinical trials by moving trial activities to participants' homes and local surroundings. In this study, we conducted semi-structured interviews with 20 European regulators to identify regulatory challenges and opportunities for the implementation of DCTs in the European Union. The key opportunities for DCTs that were recognized by regulators include a reduced participation burden, which could facilitate the participation of underserved patients. In addition, regulators indicated that data collected in DCTs are expected to be more representative of the real world. Key challenges recognized by regulators for DCTs include concerns regarding investigator oversight and participants' safety when physical examinations and face-to-face contact are limited. To facilitate future learning, hybrid clinical trials with both on-site and decentralized elements are proposed by the respondents.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THIS TOPIC?

☑ Decentralized clinical trials (DCTs) have the possibility to improve clinical trial conduct. However, regulatory requirements and perceived low degree of regulatory acceptance may impact the implementation of DCTs.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ What are the opportunities and challenges for the authorization and implementation of DCTs in Europe from a regulators' perspective?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Regulators expect that DCTs will facilitate the recruitment of underserved patients. Data collected in DCTs are furthermore expected to be more representative of the real-world. However, concerns regarding investigator oversight and safety monitoring may challenge DCT implementation. Regulators suggested that further experience with DCTs can be exerted through hybrid clinical trials, combining decentralized and on-site activities.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This research helps progress the implementation of DCTs by providing insights into the opportunities and challenges for its implementation from a European regulator's perspective. The themes described in this research should be considered when designing a DCT and could help to educate regulators on DCTs.

Clinical trials (CTs) are essential for determining the efficacy and safety of therapeutic interventions. However, several CT processes related to operations, data collection, participant recruitment, and prevention of loss to follow-up are suboptimal and hamper the clinical development of new interventions.[1,2] Current processes for participant identification, recruitment, and follow-up are expensive and often burdensome for participants,[1] which may lead to low participation and retention.[3] Furthermore, meeting recruitment targets is challenging,[4,5] and this can lead to underpowered CTs, and CT discontinuation.[6,7] Together, these factors have scientific, ethical, and financial implications that can hinder timely access to new therapeutic interventions.

The implementation of digital technologies and other novel approaches may help to improve overall CT conduct and could enable a new operational approach known as "decentralized clinical trials" (DCTs). DCTs are CTs in which trial activities are performed at

[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Regulatory Affairs Innovation, Novartis Pharma AG, Basel, Switzerland; [4]The Foundation for the Promotion of Health and Biomedical Research of Valencia Region, Valencia, Spain; [5]Global Regulatory Affairs, UCB Pharma, Brussels, Belgium; [6]Dutch Medicines Evaluation Board, Utrecht, The Netherlands; [7]Department of Clinical Pharmacy, Division Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands; [8]Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland. *Correspondence: Helga Gardarsdottir (h.gardarsdottir@uu.nl)

Received February 4, 2022; accepted March 20, 2022. doi:10.1002/cpt.2628

participants' homes and/or at local health care facilities.[8] In addition to the full DCT approach, where participants do not visit the trial site at all during the trial, hybrid CTs incorporate both decentralized and site-based elements.[8] For conceptual clarity, we use "DCTs" to refer to both full DCTs and hybrid DCTs. Examples of decentralized trial elements (also referred to as "remote elements") include recruitment via social media, shipping study drugs directly to participants, data collection through wearables, and telemedicine visits to integrate trial participation into participants' daily lives by reducing the need to physically attend on-site visits. As a result, DCTs may be less disruptive to the participants' lives, whereas allowing the recruitment of a more diverse participant population[9] and enriching datasets through more frequent or even continuous data collection in a real-world setting.[10]

The healthcare restrictions resulting from the coronavirus disease 2019 (COVID-19) pandemic catalyzed the use of decentralized elements to ensure participant safety (by reducing the risk of infection and continuing the investigational medicinal product (IMP) treatment) and maintain data integrity.[11,12] Surveys have found that, post-COVID-19, investigators are interested in incorporating decentralized trial elements,[13,14] and previous initiatives have underlined the willingness of sponsors to implement DCTs.[15,16] Furthermore, the pandemic has compelled regulators to take a position on the implementation of decentralized elements in clinical trials,[17] and several European national competent authorities (NCAs) have recently expressed interest in DCTs, issuing guidance and conducting DCT pilot studies.[18–21] Nonetheless, relatively few full DCTs have been conducted in Europe thus far. Recent work has suggested that, among other factors, regulatory requirements and a perceived low degree of acceptance by NCAs and ethics committees may be limiting their implementation.[22–24] Hence, identifying the opportunities and challenges for DCTs from a regulatory bodies' perspective could help enable progress. At present, these have not been formally evaluated in the European context. Therefore, this study involves interviews with European regulators—who work within different roles overseeing the authorization, conduct, or data generated in a CT—to identify those opportunities and challenges from a regulatory perspective that affect the authorization and implementation of DCTs.

METHODOLOGY

Study design and study population

Data were collected through in-depth semi-structured interviews with European regulators. The Consolidated Criteria for Reporting Qualitative Research (COREQ) were used to report on the methodology.[25] Representatives from 37 European Economic Area (EEA) NCAs, covering all EEA member states, were identified from the NCA and European Medicines Agency (EMA) websites and the research team's network. Participant eligibility was restricted to regulators involved in assessing the application, implementation, and interpretation of CTs (e.g., clinical assessors and statisticians) who worked for an NCA in the EEA during the study period. Experience with assessing DCTs was not required. The respondents were asked for their personal perspectives and did not participate on behalf of their NCA. This work did not include patients and was therefore exempt from ethics review.

Outcomes and interview guide development

The interview guide was designed to collect information about regulatory opportunities and challenges for DCTs (**Table S1**). To that end, it included five topics, open interview questions, and detailed probes. The interview guide topics were identified via the Trials@Home "decentralized trial process" framework[26] and using the authors' experience, and they were as follows: (i) CT authorization of DCTs; (ii) decentralized recruitment and enrollment of participants; (iii) direct-to-participant (DtP) IMP supply; (iv) the acceptance of the evidence generated by decentralized means; and (v) the impact of COVID-19 on CTs. The content of the interview guide was validated by a discussion of the preliminary guide with a clinical assessor from an NCA, expert reviews by six Trials@Home consortium members with DCT regulatory expertise, and three pilot interviews.

Data collection

Semi-structured interviews of ~1 hour each were conducted online by a trained researcher (A.J.d.J.), with 1 to 3 respondents at a time, between May and October 2021. Data collection continued until no new themes were being identified from new data according to the saturation criterion.[27] Before the interviews, the interview guide and informed consent form were shared with the respondents. Because the interviews were conducted online, verbal consent was obtained from each participant before their interview. All topics and open interview questions detailed in **Table S1** were discussed with the respondents, and the respondents were free to elaborate on the topics that suited their expertise. A summary of each interview was drafted based on field notes and shared with the respective respondent for additional clarification or correction if necessary. The respondents' current areas of expertise were classified by the following categories: (i) CT assessors—who are involved in the assessment of CT application dossiers before trial commencement, (ii) GCP inspectors, (iii) and clinical data assessors. The geographic region in which the interviewee's NCA operates was determined using the geographic regions from the "standard country or area codes for statistical use (M49)."[28] The participant's years of experience as regulator were collected from the transcripts or curricula vitae.

Data analysis

The interviews were audio-recorded, transcribed verbatim, and pseudonymized for further analysis. Transcripts from the three pilot interviews were included in the data analysis because no changes were made to the interview guide topics based on these pilot interviews. The interview transcripts were qualitatively analyzed by thematic analysis[29] using NVivo 12 Pro, QSR International (Burlington, MA). First, two interview transcripts were independently coded by two authors (A.J.d.J. and T.I.v.R.). In the next stage, the codes were iteratively reviewed, aggregated, and categorized into (sub-)themes to draft a codebook and a preliminary thematic map. Six of the 13 subsequent transcripts were coded in duplicate and discussed by three researchers (A.J.d.J., T.I.v.R., and Y.S.A.T.) to refine the initially identified (sub-)themes, thus allowing for triangulation between the authors. We then classified opportunities and challenges for the identified themes.

RESULTS

Respondents' characteristics and experience

In total, 124 representatives from all European regions[28] were invited to participate, 53 of whom responded. Twenty regulators from 11 European NCAs participated in one of the 15 interviews (**Table 1**). All European regions except Eastern Europe were represented in the interview series. The reasons for non-participation were lack of prior experience with DCTs ($n = 12$), time constraints ($n = 8$), the project not being within the remit of the invitee or department ($n = 4$), or other reasons ($n = 9$).

All respondents had experience with individual decentralized elements, such as DtP IMP supply, electronic data collection

15326535, 2022, 2, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2628 by Cochrane Netherlands, Wiley Online Library on [06/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1 Characteristics of the respondents (*n* = 20)

Characteristic	Category	Frequency (%)
Years of experience[a]	0–4 years	4 (20)
	5–9 years	5 (25)
	>10 years	11 (55)
Expertise/role	Clinical trial assessor	8 (40)
	GCP inspector	5 (25)
	Clinical data assessor	6 (30)
	Other[b]	1 (5)
European region	Northern Europe	6 (30)
	Southern Europe	5 (25)
	Western Europe	9 (45)
	Eastern Europe	0 (0)

GCP, good clinical practice.
[a]Experience as a clinical regulator.
[b]Ethicist. The European region where the interviewees' national competent authority operates was determined using the Geographic Regions from the "standard country or area codes for statistical use (M49)."[28]

tools, and home nurse visits. In addition, most respondents had experience of providing scientific advice for DCTs or had been involved in European-level discussions regarding DCTs, for example, through the EMA Innovation Task Force (ITF), Good Clinical Practice Inspectors Working Group (GCP IWG), and/or Clinical Trials Facilitation and Coordination Group (CTFG). None of the respondents had assessed a full DCT.

Five major themes were identified from the interview data: (i) justification of decentralized elements, (ii) sponsor and investigator responsibilities; (iii) trial participants' interests; (iv) data quality; and (v) future directions (**Figure 1**). In relation to these themes, both opportunities and challenges applicable to DCTs and conventional CTs were identified (**Table S2**). The key opportunities and challenges are presented in **Table 2**.

Justification of decentralized elements

The respondents indicated that decentralized elements should suit the research question and be clearly described and justified on a case-by-case basis within the clinical trial protocol, owing to the novelty of these approaches. It was stated that a decrease of trial costs would not be considered sufficient justification for implementing decentralized elements. Risks associated with the implementation of decentralized elements should be anticipated and mitigated.

Late-phase confirmatory CTs were considered more suitable for DCTs than early-phase CTs, as the safety-risk profile of the IMP should be sufficiently elucidated. However, the respondents indicated that they were open to all proposals from trial sponsors:

> It is up to the sponsor to push the envelope and convince us that it is safe, that it is actually a good way of conducting a clinical trial. I think as a regulator you should not hinder the progress, but you are not the person who does the interventions either. And one way of hindering progress is to state certain things like 'this would never go' and 'this is never acceptable,' when in fact you don't have the expertise to think through every scenario and what is actually acceptable (clinical trial assessor).

Opportunities to conduct DCTs for chronic diseases, low-risk diseases (such as allergic rhinitis or smoking cessation), and rare diseases were recognized by several respondents, due to the ability to self-manage chronic diseases; and the opportunity to recruit more participants in a CT for rare diseases due to the wider geographic reach. On the contrary, therapeutic areas (TAs) that require careful assessment or observation—such as Parkinson's disease or those requiring more intensive care, such as oncology—were considered by several respondents to be less appropriate. It was acknowledged, however, that, in certain instances, oncology and palliative care trials could and should be conducted close to the participants' direct surroundings

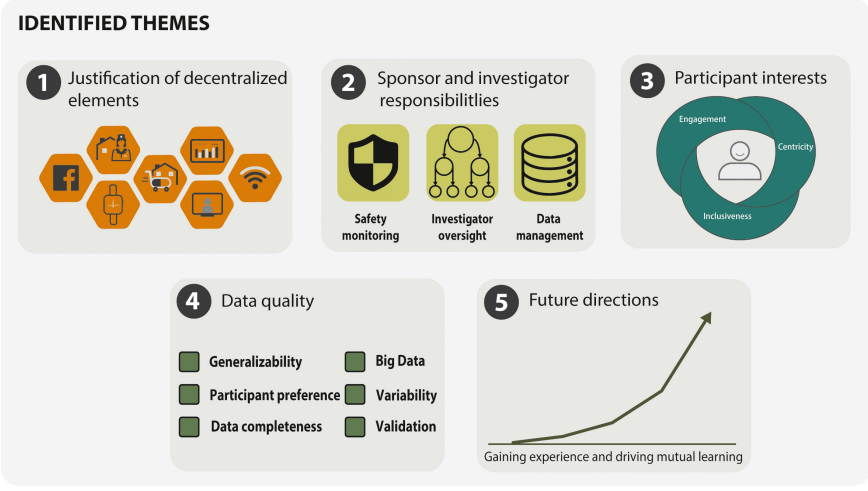

Figure 1 Graphical representation of the five identified themes. [Colour figure can be viewed at wileyonlinelibrary.com]

15326535, 2022, 2, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2628 by Cochrane Netherlands, Wiley Online Library on [06/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2 Key opportunities and challenges for the implementation of decentralized clinical trials as stated by the interviewees

Theme	Opportunities	Challenges
Justification of decentralized elements	• DCT approaches can be particularly suitable for trials with chronic diseases, rare diseases, immobile participants, self-administrable IMP, lower safety risk profile, and confirmatory CTs	• Insufficiently detailed description and justification of decentralized elements in the protocol
Sponsor and investigator responsibilities	• Home health visits to ensure proper oversight and detection of safety events	• Participants becoming responsible for communicating safety information • Inappropriate delegation of tasks
Trial participants' interests	• Less (travel) burden • Larger geographical reach • Improved accessibility by recruiting participants that would not normally participate in a conventional CT	• Insufficient relationship building with participant • Inability to assess participant's ability and eligibility to participate • Increased workload for participants and investigators
Data quality	• Collection of continuous data closer to the real-world setting • More complete data by enabling home/telemedicine visits, and by reducing the data collection burden	• Recruitment of a skewed (tech-savvy, younger) population • Difficulty interpreting large datasets • Limited validation of novel digital outcome measures
Future directions	• Facilitate 'learning-by-doing' through hybrid CTs • More harmonized evaluation of DCTs under the CTR	• Limited information on the effectiveness of decentralized elements and its comparability to conventional CTs • Heterogenicity in the acceptance of decentralized elements

CT, clinical trial; CTR, Clinical Trials Regulation EU 536/2014; DCT, decentralized clinical trial; EU, European Union; IMP, investigational medicinal product.

to benefit the participant (**Supplementary Information Quote S1**).

Sponsor and investigator responsibilities

Investigator oversight. Several challenges regarding the use of third parties in DCTs were recognized, including the training of third parties and the hesitancy of NCAs, ethics committees, and investigators to delegate tasks to third parties. This is because of a lack of clarity regarding qualifications and the overall responsibility of the investigator, under the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP guideline. One respondent explained this as follows:

> The most difficult issue we have experienced is the acceptance of external staff so, home visits by home nurses, and home doctors. They are not very well accepted, either by ethics committees but, even more, by the PI (clinical data assessor).

As a solution, one respondent proposed that home visits should ideally be organized via a site's existing infrastructure. Furthermore, there was a need for clear lines of communication among the investigator staff, local healthcare professionals, and vendors, as participants should not be responsible for communicating safety information.

Safety monitoring. Many respondents indicated that proper safety monitoring typically requires in-person (on-site) visits to perform physical examinations and reported challenges regarding fully decentralized safety monitoring. Namely, timely and uninterrupted access to interpretable safety data is vital, and safety data should be synchronized to the electronic medical record to ensure continuity of care. In addition, safety data should be reviewed regularly by site study staff. Opportunities to ensure timely review of safety data include (i) monitoring the investigator staff's data review, (ii) provision of a stable data transfer connection, (iii) provision of mobile internet to trial participants if needed, and (iv) use of algorithms to assist manual review.

Data management and privacy. One potential challenge mentioned by the interviewees is that the participants' personally identifiable data should not be available to the sponsor during a DCT. Therefore, several respondents indicated that activities during which personal data is obtained or required—including screening procedures and shipment of IMP—should be performed under the responsibility of the investigator. In addition, the data flow—including the data transfer and (temporary) data storage—should be clearly described.

Trial participants' interests

Many respondents highlighted reducing the burden of trial participation as one of the main opportunities for DCTs. The DCTs could also enable the inclusion of patients with reduced or challenged mobility, as well as patients from larger geographic areas. However, multiple interviewees indicated that the inclusion of digitally illiterate patients (e.g., elderly people) in DCTs may be a challenge, although others indicated that elderly patients may be able to participate (**Supplementary Information Quote S2**).

The limited in-person interaction in a DCT was considered a challenge. The respondents highlighted the importance of in-person visits for engaging participants and building rapport, which was considered particularly helpful for recruiting and retaining

15326535, 2022, 2, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2628 by Cochrane Netherlands, Wiley Online Library on [06/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

participants. Furthermore, in-person visits may be important for assessing whether patients are suitable for a CT and could help participants decide whether to participate. One respondent explained this as follows:

> If you are face-to-face, you see the whole patient; there's a direct contact and you can get attention to a medical health condition or characteristics which you would not have seen if you just have a video. You could miss something that may lead to exclusion or maybe an additional risk (clinical trial assessor).

It was recognized that there is an opportunity to introduce a "personal contact moment" in DCTs with the incorporation of home visits, which could also facilitate certain study activities, such as complex IMP administration.

Data quality

A recurrent theme in the interviews was the regulatory acceptance of data generated by decentralized means. Six aspects were identified relating to this theme (**Figure 2**).

Generalizability. There was a diversity of views regarding generalizability in the context of a DCT. Several respondents were concerned about enrolling a "skewed population," as both online recruitment and digital illiteracy in relation to the digital tools were considered potential challenges. However, other respondents indicated that conventional CTs are subject to similar challenges and remarked that DCTs may attract populations who are not included in conventional CTs, making them more generalizable. Furthermore, respondents mentioned that DCTs offer the possibility to test IMP closer to a real-world setting (**Supplementary Information Quote S3**).

Participant preference. The option to introduce decentralized or on-site activities according to a participant's preference or need, was considered an opportunity for DCTs. However, other respondents were concerned about these optional approaches, as different methods of data collection could differently affect the outcomes (**Supplementary Information Quote S4**). As a solution, one clinical data assessor indicated that the optional approach should be incorporated in both the interventional and control arms, and proper randomization should be ensured.

Big data. Incorporating digital technologies in DCTs may provide further opportunities for continuous data collection, thereby generating large data sets. However, the respondents indicated that the generation of "Big Data" through digital technology could unnecessarily burden participants and the dataset could be challenging to interpret (**Supplementary Information Quote S5**).

Data completeness. Missing data and the reasons for these gaps could create challenges for data interpretation and were considered by several respondents to be a challenge for DCTs:

> If, remotely, something is missing, it may be very unclear what is happening. [...] If, for instance, you think about a diary where the patient enters a score every day. If you do this for a year and let's say 50% of the entries are missing, it will be very difficult to interpret because you cannot just simply assume that he forgot to answer or that it's not related to the outcome (clinical data assessor).

However, other respondents argued that DCTs provide the opportunity to reduce missing data by improving protocol compliance, training stakeholders, passively collecting data, implementing monitoring and reminder systems, considering device practicalities, and enabling visits through the use of home nurses.

Variability. Interviewees also mentioned that variability of measurements may increase in DCTs, due to self-measurement, the inclusion of local healthcare professionals and laboratories, and more diverse populations. This potential increase in variability was considered a challenge by the respondents, as it could hinder the inference of drug effects. Therefore, it was suggested that DCTs may need to enroll larger samples and must limit the amount of missing data. It should also be ensured that the participant-reported data are entered and generated by the trial participants themselves—for example, using adequate identification systems.

Validation. The respondents indicated that the validation of novel digital outcome measures might be challenging because sponsors may not know what is expected of them when validating a new outcome and may be unwilling to invest in novel outcome measures when conventional and accepted alternatives are available. The respondents agreed that accepted outcome measures could be adopted for at-home situations, albeit dependent on the context of the CT, as one interviewee explained:

> [Adopting an accepted measurement to an at-home situation] would be acceptable, but what we would like to know is: how do you do it? And if you do, what study population do you have? Are they used to taking their blood pressure at home? Does everyone in the study population have the same wearables? Are they trained? Is there a helpdesk they can call if they have issues? (clinical trial assessor).

In the context of digital data-collection technologies, CT assessors in particular highlighted that the devices used to collect the data should have a *Conformité Européenne* marking to show they are used in line with their intended use.

Future directions

According to the respondents, the COVID-19 pandemic and associated restrictions have been a catalyst for the implementation of decentralized elements in CTs. To ensure further mutual learning, the respondents emphasized that DCT approaches

15326535, 2022, 2, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2628 by Cochrane Netherlands, Wiley Online Library on [06/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

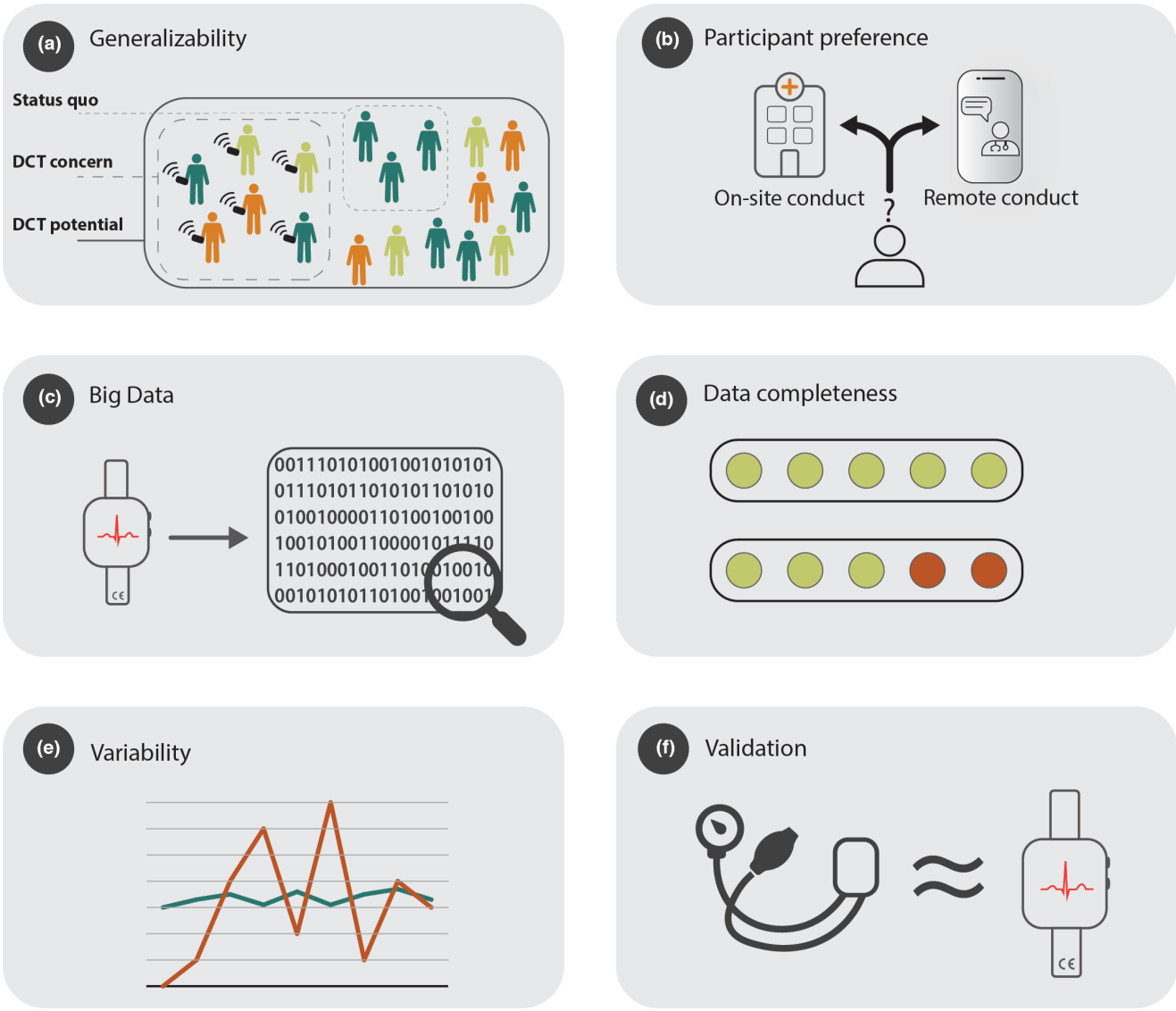

Figure 2 Graphical representation of the data quality sub-themes identified from the interview data. (**a**) Generalizability; the current inability to recruit a diverse and representative trial population for a clinical trial, the concern that DCT recruitment is limited to participants with digital skills, and the potential of DCTs to recruit a representative sample generalizable to the target population. (**b**) Participant preference; the opportunity to incorporate participant preferences and the potential impact of different data collection methods on the outcomes. (**c**) Big Data; the challenge to interpret large datasets generated through, for example, wearables. (**d**) Data completeness; the opportunity to generate more complete data through passive data collection, and the challenge of more missing data because of poor technology adherence. (**e**) variability; the potential increase in variability in DCTs, because more data collection methods are utilized. (**f**) Validation; the challenge to validate novel digital outcomes. DCT, decentralized clinical trial. [Colour figure can be viewed at wileyonlinelibrary.com]

should be discussed with regulators—for example, through scientific advice. In addition, the use of hybrid CTs was advocated by the respondents to gain more experience with a combination of decentralized elements, whereas allowing for the incorporation of on-site visits.

Currently, the acceptance of individual decentralized elements—such as electronic consent and DtP IMP supply—differs between NCAs, due to variation in national legislation. In addition, the respondents explained that ethics committees may have different views regarding the implementation of decentralized elements. To harmonize the evaluation of DCTs, the respondents described the need for a consolidated opinion on DCTs, which is being drafted by the CTFG is (at the time of the interviews). The application of the 536/2014 EU Clinical Trials Regulation (CTR) could further lead to a more harmonized evaluation of DCTs. One respondent explained this as follows:

> When it comes to an individual clinical trial under the CTR, there will be this common assessment as well. So, I suppose that that will facilitate the discussion as well, and hopefully, at some point, we will have a common view in Europe (clinical trial assessor).

15326535, 2022, 2, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2628 by Cochrane Netherlands, Wiley Online Library on [06/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

DISCUSSION

In this study, we investigated the perspectives of European regulators regarding the implementation of DCTs for benefit-risk assessments. Opportunities and challenges for implementing DCTs were identified. Of note, several identified challenges may also be relevant for conventional CTs, such as challenges related to the validation of data collection tools, investigator oversight, and generalizability of trial results—although some may be more evident for DCTs.

Justification of decentralized elements

In this study, we found that DCT approaches may be considered for a diverse set of TAs and target populations, as was also illustrated by a pilot project conducted in Sweden in which DCTs were used for all phases throughout clinical development, covering a diverse set of TAs (including diabetes, COVID-19, and breast cancer).[19] Clinical development for rare diseases may, however, especially benefit from a DCT approach, as participant recruitment may be difficult, requiring continued evidence generation after marketing authorization has been granted.[30]

Data quality of data generated by decentralized means

It has been suggested that digital technologies could lead to more clinically meaningful end points than conventional end points, as data could be collected more frequently, and more objectively due to the reduced impact of observer and recall bias.[31,32] Although the opportunity to collect richer data via digital technologies was recognized by the regulators, they were cautious about the impact of large data sets on end points. In addition, missing data due to technical defects or poor technology adherence were found to be a potential challenge. Solutions to limit missing data are context-specific but could include training, sending reminders, minimizing participation burden, making user support available (e.g., helpdesks), backing-up operating systems, and validating the technology.[33,34]

Challenges associated with the validation of digital technologies have been said to impede their uptake.[35,36] In agreement with our findings, a recent study found that the main concerns of the Committee for Medicinal Products for Human Use of the EMA regarding digital data collection technologies include the relevance and validation of the novel technology.[37] A discussion of the requirements for the qualification of digital technology is beyond the scope of this paper, but these have been previously described.[38,39]

Investigator oversight

Although the involvement of third parties, such as home nurse services, may be necessary to manage DCTs, the respondents suggested that investigators may be hesitant to delegate specific tasks, as they may be held responsible for any noncompliance by third parties, as stated in ICH E6 R2 4.2.5 and 4.2.6.[40] Furthermore, previous research has found that training third parties, obtaining data from third parties, and obtaining ethics approval can all create additional challenges for the involvement of third parties in a DCT.[41] Home nursing services provided through a site's existing infrastructure can address these issues. The use of external home nurse services could also be considered, provided the qualifications are clear.

Participants' interests and generalizability

The reduction in the burden on participants was considered by the regulators to be a key opportunity for DCTs. However, there is also a need to avoid overburdening participants with digital technology.[42] In addition, the (perceived) need for in-person visits—for physical examinations and to build a relationship—could limit the implementation of full DCTs. A trusting relationship between the investigator and (potential) trial participants has been shown in trials to aid the recruitment and retention of trial participants.[43] However, other studies have shown that recruiting participants through online means can accelerate and improve recruitment rates, compared with traditional on-site participant recruitment.[44,45] In DCTs, safety of participants and relationships with investigator staff should be ensured and maintained through regular contact via decentralized means or home visits.

The risk of excluding digitally illiterate participants was considered a potential challenge for DCTs, with elderly participants considered to be more often digitally illiterate. Whereas digital recruitment strategies have recruited younger participants in some studies,[44,46] another study found no differences between traditional and digital recruitment strategies in terms of age.[47] In addition, DCTs can use recruitment strategies similar to conventional CTs, such as physicians' networks and registries. Although recruitment of demographically skewed samples may limit the generalizability of trial results, it should be noted that conventional CTs suffer from similar issues because of strict eligibility criteria or sampling in specific clinical settings.[48]

Future directions

In this study, regulators said they were open to DCT proposals but indicated that their experiences with full DCTs were limited. The Danish Medicines Agency's and Swissmedic/Swissethics DCT guidance emphasize that experience is needed "to identify the weaknesses and strengths [...], including the impact of the reduced face-to-face visits"[18] and to show if "new standards are needed to approve DCTs".[20] The respondents in this study suggested that regulators should be approached with proposals for (hybrid) DCTs, for example, through EMA scientific advice. This process of learning-by-doing can be supplemented by providing training for regulators to support the evaluation of DCTs, complex datasets, and novel end points through initiatives such as Trials@Home (https://trialsathome.com/), Mobilise-D (https://www.mobilise-d.eu/), RADAR-AD (https://www.radar-ad.org/), and the United States-based Clinical Trials Transformation Initiative (https://ctti-clinicaltrials.org/). In addition, changes in CT conduct engendered by the COVID-19 pandemic provide the opportunity to identify learnings relevant for DCTs. For example, the US Food and Drug Administration Oncology Center of Excellence has launched an initiative to evaluate the effect of decentralized assessments on data quality and to identify mitigation strategies from trial data affected by the COVID-19 pandemic.[49]

Endeavors to harmonize guidance and regulations regarding decentralized elements on a European level may further facilitate the uptake of DCTs and could overcome the need for country-specific adjustments. For example, there is currently no consensus in the European Union regarding the acceptability and validity of using

15326535, 2022, 2, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2628 by Cochrane Netherlands, Wiley Online Library on [06/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

decentralized elements, such as electronic signatures to obtain informed consent via decentralized means, and the shipment of IMPs directly to trial participants.[50]

Strengths, limitations, and suggestions for future research

This study provides a list of important opportunities and challenges for the implementation of DCTs in Europe from a regulatory perspective. This study incorporated complementary perspectives of regulators from different European regions involved in assessing the authorization, conduct, and clinical data of CTs. However, their representativeness may be restricted, as the perspectives of regulators who are less familiar with—or more critical of—DCT approaches may have been limited. Although no prior experience with DCTs was required to participate in this project, we found that some potential interviewees chose not to participate in this research due to lack of experience. As such, the perspective of regulators who are less supportive of DCTs may not have been fully captured in this research. Furthermore, the individual perspectives captured in this research may not fully reflect the NCAs' standpoints.

Currently, it is not clear whether decentralized elements and recruitment approaches allow for the inclusion of a more representative and diverse trial population. In addition, data on the comparability of DCTs and conventional CTs are needed. Finally, the development of a regulatory framework for DCT assessment and educational activities could facilitate mutual learning by sponsors and regulators. Future studies on these topics are therefore recommended.

CONCLUSION

Regulators agree that DCT approaches can be considered for various types of trials, provided that the decentralized elements are justified considering the research question and trial characteristics. The key opportunities of DCTs recognized by European regulators include exerting a lower participation burden, allowing underserved groups to participate in CTs, and capturing data from the "real world." However, from a regulatory perspective, reducing face-to-face contact, and the maintenance of investigator oversight when involving third parties are considered challenges to implementation of DCTs. The possible impact of decentralization on data quality should also be addressed when designing a DCT. The factors identified in this study indicate that the EU regulatory network is ready to gain experience with DCTs to ensure participant-centered trials.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

The authors thank the respondents for their time and willingness to participate in this research project.

FUNDING

This work has received support from the EU/EFPA Innovative Medicines Initiative Joint Undertaking Trials@Home (grant No. 831458). The Innovative Medicines Initiative (IMI) website can be accessed through the following link: www.imi.europa.eu.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.J.d.J., T.I.v.R., M.G.P.Z., G.J.M.W.v.T., S.A., J.F.M., T.D.S., A.d.B., Y.S.A.T., and H.G wrote the manuscript. A.J.d.J., Y.S.A.T., M.G.P.Z., and H.G. designed the research. A.J.d.J. performed the research. A.J.d.J, T.I.v.R., and Y.S.A.T. analyzed the data.

DISCLAIMER

This paper reflects the views of the Trials@Home consortium and neither IMI nor the European Union and EFPIA are liable for any use that may be made of the information contained herein.

DATA AVAILABILITY STATEMENT

Interview transcript data was used in this study. Participants did not consent to make the transcripts publicly available. Supporting quotes are available in the results section of this paper. Excerpts from anonymized transcripts can be made available upon request. Please contact the corresponding author for more information.

© 2022 The Authors. *Clinical Pharmacology & Therapeutics* published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

1. Fogel, D.B. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: a review. *Contemp. Clin. Trials Commun.* **11**, 156–164 (2018).
2. Gross, D. & Fogg, L. Clinical trials in the 21st century: the case for participant-centered research. *Res. Nurs. Health* **24**, 530–539 (2001).
3. Gul, R.B. & Ali, P.A. Clinical trials: the challenge of recruitment and retention of participants. *J. Clin. Nurs.* **19**, 227–233 (2010).
4. Walters, S.J. *et al*. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. *BMJ Open* **7**, e015276 (2017).
5. Carlisle, B., Kimmelman, J., Ramsay, T. & MacKinnon, N. Unsuccessful trial accrual and human subjects protections: an empirical analysis of recently closed trials. *Clin. Trials* **12**, 77–83 (2015).
6. Amstutz, A. *et al*. Discontinuation and non-publication of randomised clinical trials supported by the main public funding body in Switzerland: a retrospective cohort study. *BMJ Open* **7**, e016216 (2017).
7. Kasenda, B. *et al*. Prevalence, characteristics, and publication of discontinued randomized trials. *JAMA* **311**, 1045–1051 (2014).
8. Trials@Home. Trials@Home glossary <https://trialsathome.com/trialshome-glossary/> (2020). Accessed January 18, 2022.
9. Khozin, S. & Coravos, A. Decentralized trials in the age of real-world evidence and inclusivity in clinical investigations. *Clin. Pharmacol. Ther.* **106**, 25–27 (2019).
10. Izmailova, E.S., Wagner, J.A. & Perakslis, E.D. Wearable devices in clinical trials: hype and hypothesis. *Clin. Pharmacol. Ther.* **104**, 42–52 (2018).
11. Li, G. *et al*. Digitalized adaptation of oncology trials during and after COVID-19. *Cancer Cell* **38**, 148–149 (2020).
12. Gaba, P. & Bhatt, D.L. The COVID-19 pandemic: a catalyst to improve clinical trials. *Nat. Rev. Cardiol.* **17**, 673–675 (2020).
13. Xue, J.Z. *et al*. Clinical trial recovery from COVID-19 disruption. *Nat. Rev. Drug Discov.* **19**, 662–663 (2020).
14. Waterhouse, D.M. *et al*. Early impact of COVID-19 on the conduct of oncology clinical trials and long-term opportunities for transformation: findings from an American Society of Clinical Oncology Survey. *JCO Oncol. Pract.* **16**, 417–421 (2020).
15. TransCelerate Biopharma Inc. Beyond COVID-19: modernizing clinical trial conduct <https://www.transceleratebiopharmainc.

15326535, 2022, 2, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2628 by Cochrane Netherlands, Wiley Online Library on [06/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

com/wp-content/uploads/2020/07/TransCelerate_Beyond-COVID19_Modernizing-Clinical-Trial-Conduct_July-2020.pdf> (2020). Accessed January 18, 2022.
16. National Academies of Sciences, Engineering, and Medicine. *Virtual Clinical Trials: Challenges and Opportunities: Proceedings of a Workshop* (The National Academies Press, Washington, DC, 2019).
17. de Jong, A.J. *et al*. COVID-19 and the emerging regulatory guidance for ongoing clinical trials in the European Union. *Clin. Pharmacol. Ther.* **109**, 1517–1527 (2021).
18. Danish Medicines Agency. The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products <https://laegemiddelstyrelsen.dk/en/news/2021/guidance-on-the-implementation-of-decentralised-elements-in-clinical-trials-with-medicinal-products-is-now-available/~/media/5A96356760ED408CBFA9F85784543B53.ashx> (2021). Accessed October 20, 2021.
19. Swedish Medical Products Agency. Decentralised and virtual interventional clinical trials <https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/medicinal-products-for-human-use/decentralised-and-virtual-interventional-clinical-trials> (2021). Accessed November 26, 2021.
20. Swissmedic and Swissethics. Position paper by Swissmedic and swissethics on decentralized clinical trials (DCTs) with medicinal products <https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/clinical-trials/clinical-trials-on-medicinal-products/publikationen.html> (2021). Accessed March 9, 2021.
21. BfArM. BfArM im dialog: decentralised clinical trials (DCT) <https://www.bfarm.de/DE/Aktuelles/Veranstaltungen/Termine/2021-06-30-dezentrale_klinische_pruefungen.html> (2021). Accessed October 27, 2021.
22. Coert, R.M.H., Timmis, J.K., Boorsma, A. & Pasman, W.J. Stakeholder perspectives on barriers and facilitators for the adoption of virtual clinical trials: qualitative study. *J. Med. Internet Res.* **23**, e26813 (2021).
23. Polhemus, A.M. *et al*. Accelerating adoption of patient-facing technologies in clinical trials: a pharmaceutical industry perspective on opportunities and challenges. *Ther. Innov. Regul. Sci.* **53**, 8–24 (2019).
24. Cox, S.M., Lane, A. & Volchenboum, S.L. Use of wearable, mobile, and sensor technology in cancer clinical trials. *JCO Clin. Cancer Informatics* **2**, 1–11 (2018).
25. Tong, A., Sainsbury, P. & Craig, J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int. J. Qual. Health Care* **19**, 349–357 (2007).
26. Trials@Home (Work Package 2 – TECH). Deliverable 2.3 – technology scan <https://trialsathome.com/wp-content/uploads/2020/10/D2.3-Scanning-results_Master.pdf> (2020). Accessed March 1, 2021.
27. Saunders, B. *et al*. Saturation in qualitative research: exploring its conceptualization and operationalization. *Qual. Quant.* **52**, 1893–1907 (2018).
28. United Nations (Statistics Division). Geographic regions <https://unstats.un.org/unsd/methodology/m49/> (2021). Accessed July 13, 2021.
29. Braun, V. & Clarke, V. Using thematic analysis in psychology. *Qual. Res. Psychol.* **3**, 77–101 (2006).
30. Pontes, C. *et al*. Evidence supporting regulatory-decision making on orphan medicinal products authorisation in Europe: methodological uncertainties. *Orphanet J. Rare Dis.* **13**, 206 (2018).
31. Boehme, P. *et al*. How soon will digital endpoints become a cornerstone for future drug development? *Drug Discov. Today* **24**, 16–19 (2019).
32. Stephenson, D., Badawy, R., Mathur, S., Tome, M. & Rochester, L. Digital progression biomarkers as novel endpoints in clinical trials: a multistakeholder perspective. *J. Parkinsons Dis.* **11**, S103–S109 (2021).
33. Marquis-Gravel, G. *et al*. Technology-enabled clinical trials: transforming medical evidence generation. *Circulation* **140**, 14261436 (2019).
34. European Medicines Agency. Guideline on computerised systems and electronic data in clinical trials (draft) <https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-guideline-computerised-systems-electronic-data-clinical-trials_en.pdf> (2021). Accessed October 27, 2021.
35. Coravos, A. *et al*. Modernizing and designing evaluation frameworks for connected sensor technologies in medicine. *NPJ Digit. Med.* **3**, 37 (2020).
36. Mantua, V., Arango, C., Balabanov, P. & Butlen-Ducuing, F. Digital health technologies in clinical trials for central nervous system drugs: an EU regulatory perspective. *Nat. Rev. Drug Discov.* **20**, 83–84 (2021).
37. Dekker, M.J.H.J., Stolk, P. & Pasmooij, A.M.G. The use of remote monitoring technologies: a review of recent regulatory scientific advices, qualification opinions, and qualification advices issued by the European Medicines agency. *Front. Med.* **8**, 619513 (2021).
38. Goldsack, J.C. *et al*. Verification, analytical validation, and clinical validation (V3): the foundation of determining fit-for-purpose for Biometric Monitoring Technologies (BioMeTs). *NPJ Digit. Med.* **3**, 55 (2020).
39. European Medicines Agency. Questions and answers: qualification of digital technology-based methodologies to support approval of medicinal products <https://www.ema.europa.eu/en/documents/other/questions-answers-qualification-digital-technology-based-methodologies-support-approval-medicinal_en.pdf> (2020). Accessed December 21, 2021.
40. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Guideline for good clinical practice ICH E6 (R2) <https://www.ich.org/page/efficacy-guidelines> (2016).
41. Apostolaros, M. *et al*. Legal, regulatory, and practical issues to consider when adopting decentralized clinical trials: recommendations from the clinical trials transformation initiative. *Ther. Innov. Regul. Sci.* **54**, 779–787 (2020).
42. Coyle, J. *et al*. Learning from remote decentralised clinical trial experiences: A qualitative analysis of interviews with trial personnel, patient representatives and other stakeholders. *Br. J. Pharmacol.* **88**, 1031–1042 (2022).
43. Chhatre, S. *et al*. Patient-centered recruitment and retention for a randomized controlled study. *Trials* **19**, 205 (2018).
44. Moseson, H., Kumar, S. & Juusola, J.L. Comparison of study samples recruited with virtual versus traditional recruitment methods. *Contemp. Clin. Trials Commun.* **19**, 100590 (2020).
45. Brøgger-Mikkelsen, M., Ali, Z., Zibert, J.R., Andersen, A.D. & Thomsen, S.F. Online patient recruitment in clinical trials: systematic review and meta analysis. *J. Med. Internet Res.* **22**, e22179 (2020).
46. Frandsen, M., Thow, M. & Ferguson, S.G. The effectiveness of social media (Facebook) compared with more traditional advertising methods for recruiting eligible participants to health research studies: a randomized, Controlled Clinical Trial. *JMIR Res. Protoc.* **5**, e161 (2016).
47. Reuter, K., Liu, C., Le, N., Angyan, P. & Finley, J.M. General practice and digital methods to recruit stroke survivors to a clinical mobility study: comparative analysis. *J. Med. Internet Res.* **23**, e28923 (2021).
48. Kennedy-Martin, T., Curtis, S., Faries, D., Robinson, S. & Johnston, J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials* **16**, 495 (2015).
49. FDA Oncology Center of Excellence. Advancing oncology decentralized trials <https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials> (2021). Accessed March 9, 2021.
50. Trials@Home work package 4 (EAGLE). Deliverable 4.1: mapping and analysis of the EU legislation on remote decentralised clinical trials including legal, regulatory, ethical and stakeholder recommendations for the conduct of the pan-EU pilot <https://trialsathome.com/mapping-and-analysis-of-the-eu-legislation-on-remote-decentralised-clinical-trials-d4-1/> (2021). Accessed March 9, 2021.

15326535, 2022, 2, Downloaded from https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2628 by Cochrane Netherlands, Wiley Online Library on [06/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Supplementary material 4

Direct-to-Participant Investigational Medicinal Product Supply in Clinical Trials in Europe – Exploring the Experiences of Sponsors, Site Study Staff, and Couriers

Amos J. de Jong, Yared Santa-Ana-Tellez, Mira G.P. Zuidgeest, Renske J. Grupstra, Fatemeh Jami, Anthonius de Boer, Helga Gardarsdottir, on behalf of the Trials@Home Consortium Br J Clin Pharmacol. 2023 Jul 12..

Received: 25 October 2022 | Revised: 21 June 2023 | Accepted: 4 July 2023

DOI: 10.1111/bcp.15850

ORIGINAL ARTICLE

Direct-to-participant investigational medicinal product supply in clinical trials in Europe: Exploring the experiences of sponsors, site staff and couriers

Amos J. de Jong[1] | Yared Santa-Ana-Tellez[1] | Mira G. P. Zuidgeest[2] | Renske J. Grupstra[1] | Fatemeh Jami[3] | Anthonius de Boer[1,4] | Helga Gardarsdottir[1,5,6] | on behalf of the Trials@Home Consortium

[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

[2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

[3]Strategic Advice R&D Quality Assurance, AstraZeneca, Cambridge, UK

[4]Dutch Medicines Evaluation Board, Utrecht, The Netherlands

[5]Department of Clinical Pharmacy, Division Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands

[6]Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland

Correspondence
Helga Gardarsdottir, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Science, Faculty of Science, Utrecht University, PO Box 80 082, 3508 TB Utrecht, the Netherlands.
Email: h.gardarsdottir@uu.nl

Funding information
This work has received support from the EU/EFPA Innovative Medicines Initiative Joint Undertaking Trials@Home (grant No 831458). The Innovative Medicines Initiative (IMI) website can be accessed through the following link: www.imi.europa.eu. The research leading to these results was conducted as part of the Trials@Home consortium. This paper only reflects the personal view of the stated authors and neither IMI nor the European Union, EFPIA or any Associated Partners are responsible for any use that may be made of the information contained herein.

Abstract

Aims: Insights into the current practice of direct-to-participant (DtP) supply of investigational medicinal product (IMP) in the context of clinical trials conducted in Europe are needed, as regulations are unharmonized. This study is set out to explore how DtP IMP supply has been employed in Europe and what the advantages and disadvantages and barriers and facilitators of its implementation are.

Methods: We conducted semi-structured interviews with representatives from sponsor companies, courier services and site study staff involved in the IMP dispensing and delivery process in Europe. Interviews were conducted between May and November 2021, and data were analysed following thematic analysis.

Results: Sixteen respondents participated in one of the 12 interviews. Respondents had experience with different models of DtP IMP supply including shipment from the investigative site, a central pharmacy (a depot under the control of a pharmacist) and a local pharmacy—aiming to reduce trial participation burden. The respondents indicated that investigative site-to-participant shipment is not affected by regulatory barriers, but could burden site staff. Shipment from central locations was considered most efficient, but possible regulatory barriers related to maintaining participants' privacy and investigator oversight were identified. The respondents indicated that the involvement of local pharmacies to dispense IMP can be considered when the IMP is authorized.

Conclusions: Several DtP IMP supply models are implemented in clinical trials conducted in Europe. In this study, three main DtP IMP models were identified, which can be referenced when describing these approaches for regulatory approval.

KEYWORDS
decentralized clinical trial, direct-to-participant, direct-to-patient, DtP, home delivery, patient-centric

trialsathome.com.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2023 The Authors. *British Journal of Clinical Pharmacology* published by John Wiley & Sons Ltd on behalf of British Pharmacological Society.

1 | INTRODUCTION

Clinical trials are essential for the development of medicinal products. The increasing availability of digital technologies and the implementation of these technologies into clinical trials offer the possibility of conducting clinical trials in a decentralized fashion. Decentralized clinical trials (DCTs) are trials in which activities are conducted in participants' homes and local settings, rather than at investigative sites,[1] potentially improving accessibility and reducing the burden on participants.[2] One trial activity enabling DCTs is the provision of the investigational medicinal product (IMP, "a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial")[3] directly to the trial participants, thereby reducing the need for travel to the investigative site.

In the European Union (EU), EU laws (Regulation EU 536/2014) and national laws govern the assessment of clinical trials, including the direct-to-participant (DtP) supply of IMPs. While EU laws do not prohibit at-home dispensing or administration of IMPs, the Good Clinical Practice (GCP) Inspectors Working Group of the European Medicines Agency (EMA) has previously highlighted that national legislation may prohibit such practices.[4] Previous research has found that national provisions regarding DtP IMP supply are often lacking and unharmonized,[5,6] necessitating case-by-case decisions by national competent authorities (NCAs) and ethics committees, which ensure that investigator oversight and accountability are maintained per the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 guideline throughout the DtP process.[7] The research by Malone et al found that, pre-Covid-19, DtP IMP supply was not widely accepted by NCAs.[6] During the Covid-19 pandemic, when access to healthcare was limited and travel restrictions were in place, more detailed guidance regarding the shipment of IMPs was provided by international and national regulatory bodies.[8–10] These guidelines state that IMPs normally dispensed at a trial site could be provided from the site, or in certain cases and countries from the sponsor, via a courier service.[8] However, national differences were apparent, and it is unclear whether and how such guidance will be translated into regulation in the future.[10] These factors, taken together, may engender a risk-averse approach to the implementation of DtP solutions.

Given that regulations and NCA perspectives regarding DtP IMP supply are unharmonized, insight into current practice is needed to support the development of harmonized regulatory guidance and the implementation of supply approaches. The current project therefore explores how DtP IMP supply has been employed in trials executed in Europe before and during the Covid-19 pandemic, seeking to identify the advantages and disadvantages of such approaches and to identify the barriers to and facilitators of their implementation in Europe.

What is already known about this subject

- Regulations regarding clinical trial operations, including the shipment of drugs directly to the trial participants, are not harmonized across Europe.
- Dispensing of investigational medicinal products (IMPs) in clinical trials typically requires on-site visits.
- Direct-to-participant (DtP) supply of IMP could enable decentralization of drug trials.

What this study adds

- DtP IMP supply from the investigative site, central pharmacy and local pharmacy is conducted in Europe.
- The need to lower the burden of trial participants drives the implementation of DtP IMP supply.
- The disease demographic, IMP characteristics, unharmonized regulations and participant privacy should be considered when implementing DtP approaches.

2 | METHODS

2.1 | Study design

This paper explored the experiences of pharmaceutical company representatives, courier-service representatives and investigative site staff operational in Europe. These experiences were collected between May and November 2021 through online, 1-h, semistructured interviews that allowed for tailoring of the discussions to the respondents' expertise, while discussing predefined topics. The consolidated criteria for reporting qualitative research were used to report on the methodology.[11]

2.2 | Eligibility and recruitment

Participant eligibility was restricted to clinical trial sponsor representatives, courier-service representatives and site study staff who were involved in IMP handling and had experience with, or planned to implement, DtP IMP supply in the EU/European Economic Area (EEA) before or during the Covid-19 pandemic. To capture diverse perspectives, maximum variation and snowball sampling were employed,[12] that is, representatives were invited to participate on the basis of the type of sponsor, size of their company and previous (known)

13652125, 0, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15850 by Cochrane Netherlands, Wiley Online Library on [28/08/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

experience with DtP IMP supply. Eight experts were initially approached via the Trials@Home network and asked to identify potential respondents within their networks. Subsequent respondents were identified through snowballing.

2.3 | Interview guide development

Based on the aim of this study and other important concepts from the literature,[6,8,13] four topics for the interview guide were drafted. First, where possible, case study examples of DtP IMP supply put forward by the respondents were discussed. Second, their experiences of barriers to and facilitators of DtP IMP supply were solicited. Third, the advantages and disadvantages of different DtP IMP supply models were discussed. Fourth, recommendations from the respondents were collected. A preliminary interview guide was discussed with an industry expert on DtP IMP solutions. The interview guide was adapted to include questions on (i) sponsors' strategies for supporting hospital pharmacies with the implementation of DtP IMP solutions and (ii) experiences with importing IMP. The interview guide was subsequently piloted, with three interviews. The guide was not adapted based on the findings, and the data were included in the analysis. The concise interview guide can be found in Table 1.

TABLE 1 Concise interview guide.

Topic	Questions
Case study examples	• Can you tell me about a specific trial (conducted in Europe) in which you were involved, where DtP IMP supply was implemented? a. Why was DtP IMP supply chosen to be implemented in this trial? b. What type of DtP IMP supply model was chosen for this trial (eg, from investigative site-to-participant, sponsor-to-participant)?
Experienced facilitators and barriers	• What made the execution of this DtP IMP supply model possible (in terms of ethical, regulatory, practical and legislative matters)? • What barriers did you experience when implementing DtP IMP supply? • Do you know of any clinical trials within your company which were intended to implement DtP IMP supply, but this was ultimately not done? If so, why was this?
Perceived advantages and disadvantages	• What do you consider the (dis)advantages of the different DtP IMP supply approaches you previously described, as compared to on-site supply?
Recommendations and advice	• What advice would you give to sponsors that want to implement DtP IMP solutions?

Abbreviations: DtP, direct-to-participant; IMP, investigational medicinal product.

2.4 | Data collection

Semistructured interviews with one to three interviewees at a time were conducted by R.J.G. and/or A.J.d.J. between May and November 2021 via an online videoconference service (WebEx™). Each interview lasted approximately 1 h. Verbal informed consent was obtained from the trial participants before the interviews. As the research did not include patients, it was exempt from ethics review. Summaries of the interviews were shared with the respondents to ensure correct interpretation and to allow for the provision of additional feedback if deemed necessary.

2.5 | Data analysis

The interviews were audio-recorded, transcribed verbatim and inductively coded following thematic analysis[14] using NVivo 12 Pro, QSR International (Burlington, MA, USA). All the transcripts were coded in duplicate by A.J.d.J. and R.J.G. The identified codes were categorized, discussed and reviewed iteratively within the research team and aggregated into (sub)themes.

3 | RESULTS

3.1 | Respondents' characteristics

In total, 27 potential respondents were approached, of whom 16 (59%) participated in one of the 12 interviews. Eleven invitees did not reply or confirm their participation. The participants were representatives from courier-service providers (n = 8), pharmaceutical companies (n = 5), hospital pharmacists (n = 2) and one academic researcher. The characteristics of the respondents, including their experiences with DtP IMP in Europe, are displayed in Table 2.

3.2 | Themes identified from the data

Three main themes were identified from the transcript data: (i) DtP models employed in Europe, (ii) drivers of DtP supply implementation and (iii) impact of regulations.

3.2.1 | Direct-to-participant models employed in Europe

Experience

Several DtP IMP supply models were identified from the respondents' experiences (Figure 1). The respondents indicated that they had predominantly implemented the investigative site-to-participant model in Europe, as there are few barriers to its implementation, as one respondent explained:

13652125, 0, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15850 by Cochrane Netherlands, Wiley Online Library on [28/08/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

> You can almost think of the site-to-patient paradigm as the extended arm of a study nurse. There is no change in any of the processes, and therefore there are little or no barriers really.
>
> (Pharmaceutical company representative)

In addition, the respondents had experience with delivering IMPs from local and central pharmacies to participants, although this was less common. We observed a lack of standardized terminology to distinguish DtP models from one another, with the terms "central pharmacies", "sponsor depots" and "courier depots" all used. The respondents indicated that, in Europe, the dispensing of an IMP to a participant is performed by a pharmacist following a single or consecutive prescription, without the sponsor having access to personally identifiable information. Therefore, references to "central pharmacy to participant" or "pharmacy depot to participant" denote those models in which IMP is dispensed from a pharmacy depot under the control of a pharmacist who is then able to distribute to other locations away from the clinical setting (Table 3). The respondents did not have any experience with the sponsor-to-participant model, in which IMP is shipped from a private company sponsor or distributor depot, in Europe, whereas some had implemented this model in trials conducted elsewhere.

Additionally, the respondents had implemented several means of delivery, including the delivery and potentially the administration of IMPs to the participant by home nurses (Box 1), the shipment of IMPs via postal mail (Box 2), delivery by courier services (Box 3) and collection at a local pharmacy (Box 4).

TABLE 2 Respondents' characteristics (n = 16).

Characteristic		Number of interviewees (%)
Stakeholder group	Industry sponsor	5 (31)
	Site study staff[a]	3 (19)
	Courier-service providers	8 (50)
Years of experience[b]	0-5 years	3 (19)
	6-10 years	4 (25)
	≥10 years	9 (56)
Experience with DtP IMP supply in Europe[c]	Investigative site-to-participant	13 (81)
	Central pharmacy-to-participant	7 (44)
	Local pharmacy-to-participant	2 (13)

Abbreviations: DtP, direct-to-participant; IMP, investigational medicinal product.
[a]Research staff, hospital pharmacists.
[b]Experience with clinical trial logistics based on information shared during the interview or online curricula vitae.
[c]As discussed during the interviews (unprompted).

Advantages and disadvantages of the different models

Despite the investigative site-to-participant supply model being reported as relatively easy to implement, it was indicated that the logistics associated with the shipment may be burdensome for sites and that easy-to-use interfaces and processes may facilitate this model. Furthermore, industry and site study staff representatives mentioned that shipment from a central location is most efficient, in other words, only interactive response technology (IRT)-ordered IMP is dispensed, provided this can be accommodated by the central location and no excess IMP is dispensed due to inflexibility in quantity contents, thereby reducing IMP spillage and saving costs associated with setting up the sites' pharmacies. Additionally, one respondent indicated that shipment from central pharmacies facilitates DtP supply for IMP with stringent stability requirements. However, when IMPs are shipped from a central location, the services provided by a nurse or pharmacist (eg, answering participants' questions) were expected to be limited.

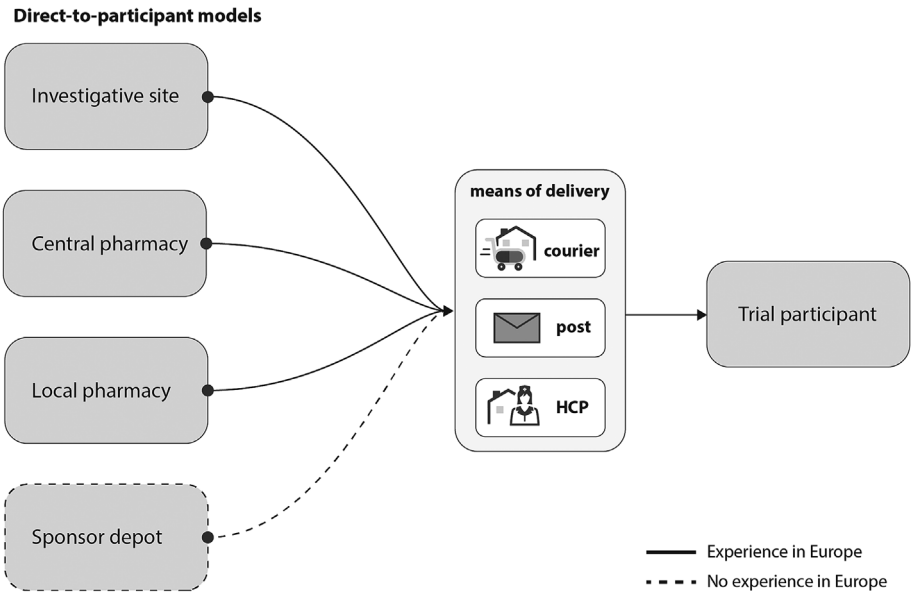

FIGURE 1 Direct-to-participant models and means of investigational medicinal product delivery based on the interviews.

13652125, 0, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15850 by Cochrane Netherlands, Wiley Online Library on [28/08/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 Definitions of the different models and the potential advantages and disadvantages.

Model	Definition[a]	(Potential) advantages and disadvantages	Example
Investigative site-to-participant	Model in which the IMP is shipped from the investigative site or site's pharmacy to the participant's home or other address.	• Few regulatory barriers • Increased burden for site staff	Box 1, Box 3
Central pharmacy/ pharmacy depot-to-participant	Model in which the IMP is shipped from a central (or remote) pharmacy depot with distribution facilities under the control of a pharmacist, and not the investigative site's pharmacy. In a multicenter clinical trial, one site's pharmacy could act as a central pharmacy, shipping the IMP to the trial participants. This can also include cross-border shipments.	• Reduced costs and IMP spillage • Enabling direct-to-participant delivery of IMP with stringent stability requirements • Increased distance between site study staff/ pharmacist and the participant • Not accepted by regulators in all EU countries	Box 2
Local pharmacy-to-participant	Model in which the IMP is picked up by the participant or legal authorized representative at, or shipped from, a local pharmacy. A local pharmacy is a community or hospital pharmacy that is not the investigative site's pharmacy.	• Enabling low-intervention trials with authorized IMP • Increased burden for local pharmacists (eg, training)	Box 2, Box 4
Sponsor-to-participant	Model in which the IMP is shipped from a private company sponsor depot, or a contracted manufacturing site, wholesaler depot or distributor location without the involvement of a pharmacist, to the participant.	• Respondents had no experience with this model in Europe	

Abbreviations: EU, European Union; IMP, investigative medicinal product.
[a]Based on interpretation of the respondents' comments.

Box 1 Investigative site-to-participant IMP supply involving home nurses

A courier-service representative supported phase 2 and 3 trials investigating monoclonal antibody infusions in oncology patients. The trials were conducted in several European and north American countries. IMP was shipped from the investigative sites to the patient via couriers, and patients were administered intravenous infusions at home by home nurses. For a patient residing near the site, the home nurse was given the possibility to collect the IMP before visiting the patient.

Box 2 Central and local pharmacy-to-participant supply using postal mail

Respondents involved in a postauthorization safety trial discussed this trial of urate-lowering therapies in patients with gout, which was conducted in the UK, Denmark and Sweden. In this clinical trial, the IMP was authorized and supplied directly by post from the central pharmacy to participants in the UK and Denmark. In Sweden, participants were supplied with the IMP from the central pharmacy via local pharmacies. The relatively low costs of the DtP IMP model enabled this clinical trial.[15]

Not all models were considered suitable for all types of IMP, and the IMP characteristics, such as safety profile (and phase of development), stability, need for complex preparations and route of administration, should all be taken into account when considering DtP IMP supply solutions. Drugs with a marketing authorization are particularly suitable, as indicated by one respondent:

> With the upcoming legislation, the ECTR [regulation EU 536/2014], if a medicine is investigated conform to the SmPc [summary of product characteristics], then it does not have to be labelled as an investigational product. Thus, a participant could pick up this medicinal product with a prescription at a local pharmacy.
>
> (Hospital pharmacist)

Advantages and disadvantages of the different delivery methods

Although shipment via postal mail was considered financially attractive, this method does not allow for ascertaining the identity of the recipient, which may be a problem for certain IMPs (eg, strong painkillers). Another concern with postal mail involves

13652125, 0, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15850 by Cochrane Netherlands, Wiley Online Library on [28/08/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Box 3 Investigative site-to-participant model using a courier service

A representative from a large pharmaceutical company discussed a phase 2 clinical trial designed to investigate temperature-controlled tablets for psoriasis and which used a site-to-participant model. This trial was conducted in France, Germany, Poland, Spain and the UK. Each country had an investigative site from which couriers collected the drug for delivery to the participants' homes. However, the relatively large IMP packaging and the need for temperature control (ie, the IMP had to be stored in a refrigerator) impeded at-home storage and required multiple IMP shipments.

Box 4 Local pharmacy-to-participant model

A hospital trial pharmacist discussed an investigator-initiated clinical trial in which a "local model" was employed. In this study, a registered injectable antibiotic was investigated for an indication other than the authorized indication. Local healthcare professionals were involved in the clinical trial and trained in GCP. General practitioners were involved in the recruitment of study participants and community pharmacists were responsible for dispensing the IMP. According to the respondent, the use of an authorized IMP enabled the use of this DtP IMP supply model.

the lack of control over the IMP shipment, which may result in participants having to report nonreceipt of the IMP. Courier-service representatives indicated that they allow for flexible IMP deliveries (eg, to workplaces), which may support participants to continue their daily lives. However, the use of courier services may be more expensive and organizationally complex, as mentioned by several respondents.

Direct from participants

Unused products and biological samples can be shipped back direct from participants for reconciliation purposes and analysis. The respondents indicated that unused and empty IMP packages are typically returned to site pharmacies for reconciliation and destruction purposes. Processes similar to DtP can be implemented, such as postal mail or courier collection, although a pharmacist involved in postal mail deliveries indicated that participants may be less diligent regarding the return of unused IMPs through postal mail, which may influence adherence monitoring.

3.2.2 | Drivers of direct-to-participant supply implementation

Covid-19

Some respondents indicated that they had no experience with DtP IMP supply before the Covid-19 pandemic. The interviewees explained that the pandemic was an important motivation to explore DtP approaches, as it could ensure clinical trial continuation. Moreover, courier-service and industry representatives suggested that the Covid-19 pandemic could provide an opportunity to change future clinical trial conduct. However, one hospital pharmacist reported that, after the initial Covid-19 outbreaks, IMP was no longer shipped directly to participants but once again had to be collected at the investigative site.

Patient-centricity and engagement

Most respondents indicated that the implementation of DtP IMP supply, alongside other decentralized trial activities such as remote data collection, contributes to making clinical trials more patient-centric by reducing the need for on-site visits. Additionally, travel expenses are reduced and the participation of those who live further from investigative sites, have mobility challenges or experience distress during visits is facilitated. Furthermore, respondents from all categories of interviewees said that recruitment and retention of participants could improve because interest to participate (eg, from participants living in more remote areas) may increase when the need for on-site visits is reduced through, amongst others, the implementation of DtP IMP supply. This was considered to be of particular importance for clinical trials with long follow-up and limited on-site procedures. It was suggested that, although they may be more challenging to organize, trials could employ an opt-in/opt-out approach in which participants can choose between DtP IMP shipment or collection of the IMP at the investigative site. Industry representatives, based on their interactions with participants, mentioned that participants generally react positively to the implementation of DtP approaches, although personal and cultural differences exist. The interviewees explained that it is important to incorporate the patient voice when designing a trial:

> Does it fit the patient's needs? Things cannot just be like, Okay, let us just simply move this over to the home. Other things are going to have to be looked at, so we are looking at the patient's perspective and the hurdles they might see: do they like it, do they not like it? [...] We are trying to learn from them as well. What challenges do they see and where do roadblocks come up?
>
> (Pharmaceutical company representative)

3.2.3 | Impact of regulations

Unharmonized regulations

A lack of specific or harmonized regulations was reported to be a barrier to the implementation of DtP IMP supply. Regulations concerning

13652125, 0, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15850 by Cochrane Netherlands, Wiley Online Library on [28/08/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the DtP IMP supply models, home health visits, and the import and dispensing licences were reported to differ within Europe and globally. Although not experienced as a barrier in the EU/EEA, cross-border shipping was considered by several respondents to be an important barrier to DtP shipments more generally, as it typically requires a lot of time. Due to an absence of regulation, the implementation of DtP IMP supply must be assessed on a case-by-case basis:

> Based on our experience, we can provide information to clients, but that does not necessarily mean […] that they will allow the same for your study, because they might think that for this specific project there is an additional risk, meaning that they will not allow it. We have no general answer about whether something is allowed or not, because there might be differences across the [clinical trial] protocols and depending on the product.
>
> (Courier-service representative)

Others explained, however, that a lack of regulation, or a lack of clarity in existing regulation, could be regarded as a facilitator, as this allows for the integration of DtP solutions on a case-by-case basis. To allow for country-specific adjustments, one sponsor representative suggested the use of "flexible protocols" regarding IMP provision (ie, not detailing the specifics per country). However, others emphasized that specificity in the protocol or dispensing plan is needed to obtain regulatory and ethics approval.

Additionally, the requirements for DtP supply models were not considered consistent with conventional dispensing practices. For example, one respondent indicated that IMP storage requirements are not considered when participants collect their IMP on-site, whereas additional requirements, such as temperature monitoring, are imposed when courier services are used.

Privacy

Compliance with data privacy regulations was discussed frequently in the interviews. It was indicated that the data privacy considerations of the investigative site-to-participant model are not fundamentally different from those of the conventional clinical trial conduct. Privacy considerations, which are particularly evident for the sponsor- and central pharmacy-to-participant models, are principally related to shielding personal data from trial sponsors and contract manufacturing/research organizations. The respondents indicated that no personal data should be accessible to the trial sponsor per the ICH E6 guideline and that personal data should be solely used for the delivery of the IMP. To that end, couriers should have the minimal data needed to deliver the IMP parcel and confirm the authorized recipient's identity. For example, the respondents indicated that the protocol numbers and the participants' full names and dates of birth should be left off the parcel label. In addition, informed consent forms should contain sufficient information regarding the DtP IMP supply processes. Therefore, the success of the DtP model is dependent on the set-up and design of appropriate privacy controls to ensure access to data is granted per the needs of the trial. Courier-service representatives indicated that it is appropriate to hand the IMP only to the participant or authorized representative, reach out to the participants prior to the delivery to agree on a specific delivery time window and to return the IMP shipment to the sending party when the participant is not there to receive the delivery.

Investigator oversight

It was reiterated by most respondents that, per ICH E6, the overall responsibility for the IMP-dispensing process, IMP return, IMP-adherence monitoring and participant safety rest with the investigator, who may delegate tasks to third parties (eg, courier services, central or local pharmacies). Although the respondents indicated that investigators are generally willing to participate in DtP solutions, several respondents had experienced investigators who were hesitant about delegating, or unwilling to delegate, tasks to third parties. This hesitation may occur because the investigator is ultimately responsible and may not be confident with the offered DtP solution or vendor, or may want to use their own infrastructure. Engaging site staff in the set-up and execution of the DtP processes and the provision of an opt-in/opt-out possibility for the site may enable DtP IMP supply by fostering investigator confidence in their oversight.

4 | DISCUSSION

This study explored the experiences with DtP processes in the context of a clinical trial in Europe. Investigative site-to-participant, local and central pharmacy-to-participant supply models are employed across Europe. The respondents suggested that the most important drivers of the implementation of DtP IMP supply solutions were the Covid-19 pandemic and the need to centre clinical trials around participants. A lack of harmonized regulatory perspectives was experienced as a barrier to implementation, but may allow for DtP approaches on a case-by-case basis.

4.1 | Experience with the direct-to-participant investigational medicinal product supply models

DtP supply has been used previously in a diverse set of clinical trials,[15–23] including trials to evaluate drugs for Alzheimer's disease[16] and antithrombotic therapies in patients with Covid-19[17] and to investigate drug adherence.[18] In line with the results of the current study, DtP IMP solutions are reported to be advantageous in clinical trials because of a "geographically dispersed rare population", as well as being more convenient for participants' daily lives,[16] enabling more pragmatic[19,20] and decentralized[21] trial approaches, limiting in-person interactions and thus allowing participants to quarantine during the Covid-19 pandemic,[17] facilitating the inclusion of a large number of physicians and patients,[22] decreasing the workload of the site study staff and minimizing potential interruptions in the

13652125, 0, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15850 by Cochrane Netherlands, Wiley Online Library on [28/08/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

treatment course.[23] Although DtP IMP supply has been reported throughout different phases of clinical development,[24] not all types of IMP may be suitable for DtP shipment, such as products with an unknown safety profile, complex route of administration or strict cold chain requirement. As an example, a systematic review investigating decentralized methods in clinical trials found that DtP shipment was mostly employed for authorized oral IMPs.[25] Furthermore, the infrastructure, such as courier services and central pharmacies, that is available in the specific country of interest should allow for DtP IMP supply.

We found that the investigative site-to-participant model is currently the most frequently employed model in Europe because there are few regulatory barriers to its implementation. It is also seen to be the closest model to the traditional pathway in a non-DCT setting, which may also support investigator willingness and uptake. Furthermore, the investigator should remain responsible for IMP dispensing and administration per ICH E6, although they may delegate these tasks to contracted external services per the EMA GCP inspector working group questions and answers (Q10 and Q11).[4] This can, however, cause additional barriers as the investigator would be expected to oversee trial-related activities delegated to individuals who are outside of the jurisdiction of the site, which may lead to unwillingness to delegate tasks associated with IMP shipment.

The respondents indicated to have no experience with the sponsor-to-participant model in the EU, owing to privacy issues (ie, shielding personally identifiable data from commercial trial sponsors) and the need for pharmacy controls required in the dispensing of the IMPs. While sponsor depots could involve pharmacists dispensing the drugs, this model was not explicitly mentioned by the respondents, and privacy and investigator oversight concerns may remain with such a model. However, a set-up comparable to source data verification, during which a monitor has access to personally identifiable information,[7] could be envisioned for IMP-dispensing by sponsor pharmacists. Additionally, models could be employed in which participants visit the investigative site for the initial dispensation, with resupplies then provided by a DtP IMP supply model. Other options may also include the addition of a home health nurse to the DtP service who is the responsible healthcare professional and may receive the IMP, and administer and observe the patient as needed per the requirements of the clinical trial protocol. Although such an approach would cost more and may not be as efficient as planned, it allows for generating more experience by trial sponsors and investigators.

4.2 | Toward more explicit definitions of the models

Based on the findings of the study, we conclude that the various DtP IMP supply models are currently not well-defined. Furthermore, it is not clearly defined which tasks may be delegated by the investigator while maintaining oversight per ICH E6 requirements in the various DtP models. The main changes in responsibilities when implementing DtP models may include (i) the sponsor selecting the pharmacy and process for distribution instead of the investigator using the site's pharmacy, (ii) the courier obtaining a more patient facing role and (iii) the patient obtaining a more substantial role in IMP accountability. Thus, we advocate the use of more explicit definitions in guidance documents and case study reports to share best practices, while acknowledging a panoply of variants and combinations of models and means of delivery. We distinguish four models of DtP IMP supply: (i) investigative site-to-participant, (ii) central pharmacy-to-participant, (iii) local pharmacy-to-participant and (iv) sponsor-to-participant. Our results show that essential elements of the description of an IMP supply model include the location from which the IMP is shipped and whether or not a pharmacist is involved in dispensing the IMP, the method of shipment and data privacy implications (ie, who has access to the personally identifiable data). When implementing DtP IMP supply solutions, at least these elements should be described in protocols or IMP-dispensing plans for regulatory and ethics review.

4.3 | Regulations and direct-to-participant investigational medicinal product supply

In Europe, different dispensing models may be implemented dependent on the risk profile and stability of the IMP, provided it is in accordance with national legislation,[26] which is known to be lacking or unharmonized.[5,6] In turn, lacking or unclear legislation may lead to careful selection of countries by the sponsor to ensure trial timelines are not unnecessarily delayed by rejection of the DCT element. Nonetheless, the impact of the Covid-19 pandemic on clinical trial conduct has been a driver of DtP IMP supply approaches and influenced the regulatory perspectives of DCT elements.[10,27] The guidance provided and experience gained during the pandemic can now become a starting point for the development of durable guidance regarding DtP IMP supply. Nonetheless, a hospital pharmacist mentioned a return to on-site dispensing post-Covid-19, which may reflect a perceived limited benefit or need for DtP shipment, particularly for trials that were initially set-up without DtP IMP supply and only moved to this model out of necessity during the Covid-19 pandemic. Recently, a European recommendation paper and national guidance documents on the implementation of decentralized elements, including DtP IMP supply, have been published (Supporting Information, Data S1).[28–31] Common themes in these guidelines include the responsibility of the investigator to dispense the IMP, the provision of sufficient information (including privacy implications) to participants and the suitability of IMPs, including the safety profile of the IMP and organizational aspects (eg, temperature control, accountability processes, compliance with GxP). Additionally, the European recommendation paper contains an annex with national requirements regarding DtP IMP delivery to trial participants.[31] According to this national overview, most EU countries allow for IMP delivery from the investigative site or pharmacy associated with the investigative site. Several EU countries further allow for IMP delivery from any delegated pharmacy or

13652125, 0, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15850 by Cochrane Netherlands, Wiley Online Library on [28/08/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

dispensing by a local pharmacy, and only a few countries allow for delivery directly from the manufacturer or sponsor or are currently developing their respective regulatory framework. The recommendation paper does, however, not extensively discuss the conditions under which different means of delivery (eg, through postal mail or courier service) could be considered. Regulatory considerations on this aspect could be included in future recommendations.

Under the Clinical Trials Regulation (EU 536/2014), low-intervention clinical trials which investigate authorized IMPs following the terms of the marketing authorization are subject to less stringent rules regarding the labelling and traceability of the IMP,[3] potentially facilitating the local pharmacy-to-participant model. Nevertheless, the interviewees in this study cited the training of local pharmacists in GCP as a challenge for the local pharmacy-to-participant model. The Salford Lung Studies, which involved 130 community pharmacies and over 2500 pharmacy staff being trained to dispense the study drug, have shown that the training of local pharmacists is feasible.[32] The challenges encountered included the involvement of locums and independent pharmacies, turnover in pharmacy staff and additional standard operating procedures.[32] Furthermore, the need for additional GCP training of local pharmacists in the context of a clinical trial investigating drugs with a marketing authorization is disputable, as pharmacist training may suffice and be compliant with ICH E6, which states that, "each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)".[7]

4.4 | Strengths, limitations and suggestions for future research

In this article, we explored case study examples of DtP IMP supply in the context of clinical trials conducted in Europe. We were able to interview a diverse set of respondents, including hospital pharmacists and representatives of courier services and pharmaceutical companies with experience in Europe and globally, thereby ensuring the applicability of the results. Nonetheless, the number of site study staff respondents, including investigators, was limited, which may have led to a skewed representation of their views. This research has shown that it is feasible to employ DtP IMP supply models in Europe, and the findings of this study could be used when discussing these supply models with regulatory bodies and ethics committees. The models and associated definitions described here could furthermore be used to identify best practices regarding DtP IMP supply.

This exploratory research primarily focused on the operational feasibility and acceptability of different DtP IMP supply approaches, whereas other perspectives should also be taken into account when considering the implementation of such activities in clinical trials. For example, the participant and ethical perspectives regarding the intrusiveness of DtP IMP supply are essential and may differ across patient populations and cultures. This study was further limited by the lack of information in some of the case study examples, which was potentially engendered by participants' hesitancy about sharing detailed information, therefore case studies should be shared and described in both scientific publications and grey literature to show the circumstances under which DtP IMP supply is feasible and acceptable. Furthermore, more empirical evidence is needed to support the use of the different models. For example, studies could investigate the impact of DtP IMP supply on IMP adherence and accountability. Additionally, further studies should focus on patient and investigator acceptability of these approaches.

5 | CONCLUSION

In Europe, investigative site-to-participant IMP supply can be implemented, provided the IMP characteristics including the safety profile allow for it, as there are few regulatory barriers to its use. However, this model could engender an increased burden for site study staff. Regulatory aspects that may influence the local and central pharmacy-to-participant models include a lack of harmonized regulations and acceptability, and the responsibility of investigators to oversee IMP handling and accountability, which may influence their willingness to delegate IMP-related tasks. The local pharmacy-to-participant model was considered most suitable for investigating IMPs with marketing authorizations, and this should be explored for low-intervention clinical trials under the EU Clinical Trials Regulation.

AUTHOR CONTRIBUTIONS

Amos J. de Jong: Conceptualization; methodology; formal analysis; investigation; writing. **Yared Santa-Ana-Tellez**: Conceptualization; methodology; formal analysis; writing; supervision. **Mira G. P. Zuidgeest**: Conceptualization; methodology; writing; supervision.**Renske J. Grupstra**: Conceptualization; methodology; formal analysis; investigation. **Fatemeh Jami**: Writing. **Anthonius de Boer**: Conceptualization; methodology; supervision. **Helga Gardarsdottir**: Conceptualization; methodology; writing; supervision.

ACKNOWLEDGEMENTS

The authors thank the respondents for their time and willingness to participate in this research project. We are also grateful to Hamidou Traore for useful comments on the manuscript.

CONFLICT OF INTEREST STATEMENT

F.J. is employed by and holds stocks in AstraZeneca. No competing interests were disclosed for this work by the other authors.

DATA AVAILABILITY STATEMENT

Interview transcript data was used in this study. Participants did not consent to make the transcripts publicly available. Supporting quotes are available in the results section of this paper. Excerpts from anonymized transcripts can be made available upon request. Please contact the corresponding author for more information.

13652125, 0, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15850 by Cochrane Netherlands, Wiley Online Library on [28/08/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

ORCID

Amos J. de Jong https://orcid.org/0000-0002-6860-9213
Anthonius de Boer https://orcid.org/0000-0002-9485-8037
Helga Gardarsdottir https://orcid.org/0000-0001-5623-9684

REFERENCES

1. Trials@Home. Trials@Home Glossary. 2020 (accessed 29 June 2022). https://trialsathome.com/trialshome-glossary/
2. Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: a review. *Contemp Clin Trials Commun*. 2018;11:156-164. doi:10.1016/j.conctc.2018.08.001
3. European Parliament and the Council. Regulation (EU) No 536/2014. 2014 (accessed 29 June 2022). https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
4. Good Clinical Practices Inspectors Working Group. Q&A: Good clinical practice (GCP). (accessed 29 June 2022). https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp
5. Trials@Home Work Package 4 (EAGLE). Deliverable 4.1: Mapping and analysis of the EU legislation on Remote Decentralised Clinical Trials including legal, regulatory, ethical and stakeholder recommendations for the conduct of the pan-EU pilot. 2021 (accessed 29 June 2022). https://trialsathome.com/mapping-and-analysis-of-the-eu-legislation-on-remote-decentralised-clinical-trials-d4-1/
6. Malone M, Ferguson P, Rogers A, Mackenzie IS, Rorie DA, MacDonald TM. When innovation out-paces regulations: the legal challenges for direct-to-patient supply of investigational medicinal products. *Br J Clin Pharmacol*. 2021;88(3):1115-1142. doi:10.1111/bcp.15040
7. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Guideline for Good Clinical Practice ICH E6(R2), 2016.
8. European Commission, European Medicines Agency, Heads of Medicines Agencies. Guidance on the Management of Clinical Trials during the Covid-19 (Coronavirus) Pandemic: Version 5. 2022 (accessed 29 June 2022). https://ec.europa.eu/health/system/files/2022-02/guidanceclinicaltrials_covid19_en_1.pdf
9. United States Food and Drug Administration. Clinical Trial Conduct During the COVID-19 Pandemic. 2020 (accessed 29 June 2022). https://www.fda.gov/drugs/coronavirus-covid-19-drugs/clinical-trial-conduct-during-covid-19-pandemic
10. de Jong AJ, Santa-Ana-Tellez Y, van Thiel GJMW, et al. COVID-19 and the emerging regulatory guidance for ongoing clinical trials in the European Union. *Clin Pharmacol Ther*. 2021;109(6):1517-1527. doi:10.1002/cpt.2225
11. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International J Qual Health Care*. 2007;19(6):349-357. doi:10.1093/intqhc/mzm042
12. Green J, Thorogood N. *Qualitative methods for Health Research*. 4th ed. SAGE Publications Ltd; 2018:75-78.
13. Eli M, Hall C, Oth M, Peskett A, Sadler-Williams E. Establishing and managing processes enabling delivery and returns of investigational medicinal products (IMPs) to Patient's homes. *Pharm Eng*. 2014;34:1-7. (accessed 29 June 2022). https://www.ispe.gr.jp/ISPE/02_katsudou/pdf/201512_en.pdf
14. Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol*. 2006;3(2):77-101. doi:10.1191/1478088706qp063oa
15. Mackenzie IS, Ford I, Nuki G, et al. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. *Lancet*. 2020;396:1745-1757. doi:10.1016/S0140-6736(20)32234-0
16. Mills SM, Mallmann J, Santacruz AM, et al. Preclinical trials in autosomal dominant AD: implementation of the DIAN-TU trial. *Rev Neurol*. 2013;169(10):737-743. doi:10.1016/j.neurol.2013.07.017
17. Connors JM, Brooks MM, Sciurba FC, et al. Effect of antithrombotic therapy on clinical outcomes in outpatients with clinically stable symptomatic COVID-19 the ACTIV-4B randomized clinical trial. *JAMA*. 2021;327(17):1703-1712. doi:10.1001/jama.2021.17272
18. Warren SR, Raisch DW, Campbell HM, et al. Medication adherence assessment in a clinical trial with centralized follow-up and direct-to-patient drug shipments. *Clin Trials*. 2013;10(3):441-448. doi:10.1177/1740774511410331
19. Zawertailo L, Mansoursadeghi-Gilan T, Zhang H, Hussain S, Le Foll B, Selby P. Varenicline and bupropion for long-term smoking cessation (the MATCH study): protocol for a real-world, pragmatic, randomized controlled trial. *JMIR Res Protoc*. 2018;7(10):e10826. doi:10.2196/10826
20. Selby P, Hussain S, Voci S, Zawertailo L. Empowering smokers with a web-assisted tobacco intervention to use prescription smoking cessation medications: a feasibility trial. *Implement Sci*. 2015;10(1):139. doi:10.1186/s13012-015-0329-7
21. Orri M, Lipset CH, Jacobs BP, Costello AJ, Cummings SR. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial, Contemp. *Clin Trials*. 2014;38(2):190-197. doi:10.1016/j.cct.2014.04.009
22. Symons JP, Ibara M, Kraemer DF, Luscombe FA. Tacrine hydrochloride treatment IND: methods for rapid physician and patient enrolment and data retrieval. *Pharmacoepidemiol Drug Saf*. 1997;6(6):409-416. doi:10.1002/(SICI)1099-1557(199711/12)6:6%3C409::AID-PDS278%3E3.0.CO;2-H
23. Jawitz OK, Wang TY, Lopes RD, et al. Rationale and design of PROACT Xa: a randomized, multicenter, open-label, clinical trial to evaluate the efficacy and safety of apixaban versus warfarin in patients with a mechanical on-X aortic heart valve. *Am Heart J*. 2020;227:91-99. doi:10.1016/j.ahj.2020.06.014
24. de Jong AJ, Grupstra RJ, Santa-Ana-Tellez Y, Zuidgeest MGP, de Boer A, Gardarsdottir H. Which decentralised trial activities are reported in clinical trial protocols of drug trials initiated in 2019-2020? A cross-sectional study in ClinicalTrials.Gov. *BMJ Open*. 2022;12(8):e063236. doi:10.1136/bmjopen-2022-063236
25. Rogers A, De Paoli G, Subbarayan S, et al. A systematic review of methods used to conduct decentralised clinical trials. *Br J Clin Pharmacol*. 2021;8(6):2843-2862. doi:10.1111/bcp.15205
26. Expert Group on Clinical Trials, Risk proportionate approaches in clinical trials. 2017 (accessed 29 June 2022). https://ec.europa.eu/health/system/files/2017-08/2017_04_25_risk_proportionate_approaches_in_ct_0.pdf
27. de Jong AJ, van Rijssel TI, Zuidgeest MGP, et al. Opportunities and challenges for decentralized clinical trials: European Regulators' perspective. *Clin Pharmacol Ther*. 2022;112(2):344-352. doi:10.1002/cpt.2628
28. Danish Medicines Agency, The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products version 2.0. 2021 (accessed 29 June 2022). https://laegemiddelstyrelsen.dk/en/news/2021/guidance-on-the-implementation-of-decentralised-elements-in-clinical-trials-with-medicinal-products-is-now-available/~/media/5A96356760ED408CBFA9F85784543B53.ashx
29. Swissmedic, Swissethics, Decentralised clinical trials (DCTs) with medicinal products in Switzerland version 1.1. 2021 (accessed 29 June 2022). https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/clinical-trials/clinical-trials-on-medicinal-products/publikationen.html

13652125, 0, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15850 by Cochrane Netherlands, Wiley Online Library on [28/08/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

30. Swedish Medical Products Agency, Decentralised and virtual interventional clinical trials. 2021 (accessed 29 June 2022). https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/medicinal-products-for-human-use/decentralised-and-virtual-interventional-clinical-trials
31. Recommendation paper on decentralised elements in clinical trials. 2022 (accessed 7 June 2023). https://health.ec.europa.eu/latest-updates/recommendation-paper-decentralised-elements-clinical-trials-2022-12-14_en
32. Leather DA, Howard S, Haydock G, Stephens L. Community pharmacy: a crucial enabler in creating the effectiveness study environment in the Salford lung studies. *Int J Pharm Pract*. 2020;28(5):529-533. doi:10.1111/ijpp.12647

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: de Jong AJ, Santa-Ana-Tellez Y, Zuidgeest MGP, et al. Direct-to-participant investigational medicinal product supply in clinical trials in Europe: Exploring the experiences of sponsors, site staff and couriers. *Br J Clin Pharmacol*. 2023;1-11. doi:10.1111/bcp.15850

13652125, 0, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15850 by Cochrane Netherlands, Wiley Online Library on [28/08/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License