**831458 – Trials@Home**

**Centre of Excellence – Remote Decentralised Clinical Trials**

**WP4 – EAGLE**

# D4.4 Overview of innovative scenarios for a responsible and sustainable DCT ecosystem


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## Document History

| Version | Date | Description |
|---|---|---|
| V1 | 06 February 2023 | First draft |
| V2 | 23 March 2023 | Revisions after review by WP4 members and other Work Packages |
| V3 | 15 May 2023 | Revisions after second round of review |
| V4 | 1 June 2023 | Revisions after EAGLE review |
| V5 | 20 June 2023 | For ExBo, ESP and PEP review |
| V6 | 22 August 2023 | Final version |

## Abstract

The IMI Trials@Home consortium aims to reshape clinical trial design, conduct and operations, by developing and piloting standards, recommendations and tools for the definition and operationalisation of decentralised clinical trials (DCTs) in Europe. Decentralised clinical trials aim to optimise the conduct of clinical research by moving most or all trial activities to participants' usual surroundings. This aims to provide solutions for some of the current challenges in conducting clinical trials. Specifically, DCTs aim to improve participant-centricity, generate data in a more real-world setting, make the conduct of clinical trials more efficient, and include a more diverse population. In this deliverable, we present four scenarios based on the most important aims of DCTs.

DCTs also bring forth several potential ethical and regulatory concerns and challenges. The four scenarios are analysed considering the relevant ethical and regulatory challenges. These challenges relate to the uncertainties of the precise effects of DCTs, resulting from to the use of multiple digital technologies and lack of in-person contact, and to the lack of sufficient regulations and guidance. Challenges include ensuring participants' safety and participant-researcher relationships, ensuring accessibility for less digitally skilled participants, maintaining data quality, privacy issues and difficulties with collecting and analysing large amounts of data.

We present potential solutions and proposals for overcoming these challenges. These include both advice for researchers – such as ways of mitigating challenges – and proposals for adjustments of the regulatory framework. Finally, we also identify areas that require further research. These findings inform what is needed from an ethical and regulatory perspective to achieve the aims of DCTs optimally and can guide a responsible implementation and sustainable conduct of DCTs. We emphasise the importance of considering the different aims of DCTs and prioritise, as different aims require a different approach.

## Contents

## List of abbreviations and acronyms

| | |
|---|---|
| **AI** | Artificial intelligence |
| **BYOD** | Bring your own device |
| **CT** | Clinical trial |
| **CTR** | Clinical trial regulation |
| **DCT** | Decentralised Clinical Trial |
| **EAGLE** | **E**thical regul**a**tory, **G**CP and **le**gal aspects |
| **EMA** | European Medicines Agency |
| **EU** | European Union |
| **GCP** | Good clinical practice |
| **GDPR** | General Data Protection Regulation (EU) 2016/679 |
| **HCP** | Healthcare provider |
| **IMI** | Innovative Medicines Initiative |
| **IMP** | Investigational medicinal product |
| **MS** | Member state |
| **NCA** | National competent authority |
| **REC** | Research ethics committee |
| **(S)AE** | (Serious) adverse event |
| **USA** | United States of America |
| **WP** | Work Package |

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

## Introduction

Decentralised Clinical Trials (DCTs) aim to offer a solution for some of the current inefficiencies and obstacles in the conduct of clinical trials, such as low recruitment and retention rates and high burden on both participants and researchers.[1,2] In DCTs, most (or sometimes all) of the trial-related activities are moved to participants' own surroundings, instead of research sites, using digital technologies and other innovative operational approaches.[3] Clinical trials can also combine traditional site-based approaches with decentralised approaches, which is referred to as a 'hybrid' decentralised trial.[3]

DCTs may reduce some of the burden for participants in clinical trials, as participants do not have to travel to research sites (as often), and because DCTs can integrate trial participation more easily into the overall daily lives of participants. This has the potential to make clinical trial participation accessible to larger and more diverse populations.[2,4,5] In turn, this could contribute to more efficient, and, in some cases, more cost-effective trials. Moreover, the ability of digital tools to capture more continuous and objective data has advantages for data quality and participants' safety monitoring during a trial.[2,4,6,7] Depending on the exact setup, participation in a DCT could offer participants more flexibility, empowerment, knowledge and insight into their medical condition and disease, as they have more control over the trial process and can receive information through various digital tools or platforms.[8-10]

Incorporation of decentralised approaches into clinical trials has accelerated over the last few years,[11] including publication by the European Commission and European Medicines Agency of EU-wide recommendations to facilitate the conduct of DCTs.[12] Acceptance of full DCTs, or the harmonisation of acceptable decentralised approaches, is however quite new to the system of ethics review and regulatory assessment, which have largely been established with site-based trials in mind. The identification of potential ethical and regulatory barriers in the implementation of DCTs and possible resolutions will help towards establishing a consistent view on the acceptability of especially full DCT studies or studies with decentralised approaches within a multi-regional study. Additionally, DCTs could have a profound impact on the

practice of clinical research in general. They could change the way many trial activities are conducted and how researchers and participants communicate. Therefore, the impact of DCTs on current ethical and regulatory requirements for research needs to be evaluated as these remote approaches to clinical trial conduct are being increasingly used.[11]

The IMI Trials@Home consortium aims to reshape clinical trial design, conduct and operations, by developing and piloting standards, recommendations and tools for the definition and operationalisation of decentralised clinical trials (DCTs) in Europe (www.trialsathome.com). Within Work Package (WP) 4 (EAGLE), the ethical, regulatory, Good Clinical Practice (GCP), and legal aspects of DCTs are being assessed. As a part of this Work Package, **deliverable 4.4 aims to develop an overview of innovative scenarios for a responsible and sustainable DCT ecosystem**. These scenarios aim to examine what is needed from an ethical and regulatory perspective to achieve and foster, a responsible and sustainable DCT practice.

## Scenarios for DCTs in the EU

The ethical and regulatory framework should continue to focus on the safety and integrity of the participant whilst helping to promote robust science and enabling researchers to pursue legitimate goals or improvements in trial conduct through DCTs.

Therefore, we describe four scenarios based on what DCTs should ideally aim to achieve, along with ethical and regulatory challenges, and potential solutions. For developing the scenarios in this deliverable we used an approach similar to "backcasting".[13] This approach involves creating a future vision of what should happen, and subsequently identifying the steps needed to reach this desirable scenario.[13] We developed four scenarios based on the aims of DCTs. These scenarios clarify what the introduction of DCTs should ideally achieve.

We identified the aims through an analysis of the literature on DCTs and the research that has been conducted as a part of the Trials@Home consortium. These include both empirical and conceptual work. The four aims that were identified are:

(i) Improving participant-centricity,
(ii) Generating data within a more real-world setting,
(iii) Improving the efficiency of clinical trial conduct, and
(iv) Improving the diversity of study populations.

Each scenario describes how DCTs can optimise clinical trial conduct in these specific aspects.

Subsequently, each scenario was analysed in light of the ethical and regulatory challenges and barriers for achieving this aim, and what is needed from an ethical and regulatory perspective to overcome these barriers and achieve and facilitate DCTs' aims optimally. We suggest ways in which researchers can contribute and propose adjustments to the ethical and regulatory framework that can facilitate the DCT aim. The term 'researchers' refers to sponsors and investigators or study site staff. Here, the sponsor is in principle responsible for the overall conduct of the clinical trial together with the investigators and study site staff.[14] With 'regulators', we refer to national competent authorities (NCAs) and research ethics committees (RECs).

We integrated results from all WP 4 sub-projects and other relevant scientific output of the Trials@Home consortium in this analysis of scenarios, including the following publications:

- De Jong, AJ, Y Santa-Ana-Tellez, GJMW van Thiel, MGP Zuidgeest, SJ Siiskonen, D Mistry, A de Boer, H Gardarsdottir. 2021. COVID-19 and the Emerging Regulatory Guidance for Ongoing Clinical Trials in the European Union. *Clinical Pharmacology and Therapeutics 109*(6): 1517-1527. https://doi.org/10.1002/cpt.2225.
- De Jong, AJ, RJ Grupstra, Y Santa-Ana-Tellez, MGP Zuidgeest, A de Boer, H Gardarsdottir, 2022. 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 12*(8): e063236. https://doi.org/10.1136/bmjopen-2022-063236.
- De Jong, AJ, TI van Rijssel, MGP Zuidgeest, GJMW van Thiel, S Askin, J Fons-Martinez, T De Smedt, A de Boer, Y Santa-Ana-Tellez, and H Gardarsdottir. 2022. Opportunities and Challenges for Decentralised Clinical Trials: European Regulators' Perspective. *Clinical Pharmacology and Therapeutics 112*(2): 344-352. https://doi.org/10.1002/cpt.2628.
- Van Rijssel, TI, AJ de Jong, Y Santa-Ana-Tellez, M Boeckhout, MGP Zuidgeest, and GJMW van Thiel. 2022. Ethics review of decentralized clinical trials (DCTs): Results of a mock ethics review. *Drug Discovery Today 27*(10): 1-6. https://doi.org/10.1016/j.drudis.2022.07.011.
- Coyle, J, A Rogers, R Copland, G De Paoli, TM MacDonald, and IS Mackenzie. 2022. Learning from remote decentralised clinical trial experiences: A qualitative analysis of interviews with trial personnel, patient representatives and other stakeholders. *British Journal of Clinical Pharmacology 88*(3): 1031-1042. https://doi.org/10.1111/bcp.15003.
- Coyle, J, A Rogers, R Copland, G De Paoli, TM MacDonald, and IS Mackenzie. 2022. A secondary qualitative analysis of stakeholder views about participant recruitment, retention, and adherence in decentralised clinical trials (DCTs). *Trials* 23 (1): 614. https://doi.org/10.1186/s13063-022-06521-4.
- De Jong, AJ, Santa-Ana-Tellez, Y, Zuidgeest, MGP, Grupstra, RJ, Jami, F, de Boer, A, and Gardarsdottir, H. 2023. Direct-to-participant investigational medicinal product

supply in clinical trials in Europe: Exploring the experiences of sponsors, site staff and couriers. *British Journal of Clinical Pharmacology*. https://doi.org/10.1111/bcp.15850

- Van Rijssel, TI, GJMW van Thiel, and JJM van Delden. 2023. The ethics of decentralized clinical trials and informed consent: Taking technologies' soft impacts into account. *Under review.*
- Van Rijssel, TI, GJMW van Thiel, H Gardarsdottir, and JJM van Delden. 2023. Which benefits can justify risks in research? *Under review.*

## Scenario 1: Improving participant-centricity

In this scenario, the decentralised approach should primarily improve participant-centricity in a clinical trial. DCTs have the potential of improving participant-centricity in several ways, compared to traditional clinical trials.

DCTs potentially reduce burdens on research participants. Patients often face burdens due to, amongst others, planning hospital visits and managing lifestyle changes.[15] Participating in research can significantly add to that burden by increasing the number of hospital or site visits.[16] DCTs can reduce this burden by providing alternative options to travelling to these research sites.[17,18] Moreover, the overall flexibility of clinical trial participation can be improved. Some or all trial activities that are normally carried out on-site under supervision of research staff are now moved to the participant's immediate surroundings. This increases the overall flexibility of clinical trial participation, and trial participation can therefore be more easily integrated into participants' daily lives.[17,19]

Second, the use of digital tools, such as (medical) devices or smartphone applications, can facilitate participant engagement and empowerment by enabling self-management and giving participants immediate feedback. More accessible contact between participants and researchers or healthcare providers (HCPs) through digital tools can lower barriers for participants and researchers to ask each other questions and/or give feedback on the trial process. Furthermore, participant empowerment can be promoted through transparency and timely accessible information. Digital information can be more flexible and adaptive than traditional information.[8,10,18]

We present the main ethical and regulatory challenges for achieving this scenario, along with potential solutions, in **Table 1.** The potential solutions include both advice for researchers, and proposals for adjustments of the existing ethical and regulatory framework.

**Table 1: SCENARIO 1 – DECENTRALISED CLINICAL TRIALS SHOULD IMPROVE PATIENT-CENTRICITY**

| **Potential ethical and regulatory challenges to this aim** | **Solutions and/or proposals from an ethical and regulatory perspective to achieve and facilitate this aim** | |
|---|---|---|
| | *What can researchers do?* | *Proposals for adjustments of the ethical and regulatory framework* |
| It is unclear how specific benefits of trial participation for participants of DCTs should be assessed in risk-benefit assessments. | • Describe different types of benefits for participants in research protocols, including collateral benefits (such as improved participant convenience, satisfaction, engagement, empowerment), so these can be taken into account in risk-benefit assessments. | • Collateral benefits should also be taken into account in risk-benefit assessments of DCTs. |
| Difficulties anticipated for informed consent with no in-person contact: assessing participants competency and understanding of information may be more difficult remotely. In-person visits may be important for assessing whether patients are suitable for a clinical trial and could help participants decide whether to participate. | • Possible mitigations include, offering information in multiple ways, add interactive features such as quizzes in informed consent process to test understanding, and include videocall (or home-visit, if possible) with a researcher to assess overall competency and understanding.<br>• Include an explanation of how digital tools can improve the informed consent procedure in research protocols. For example, digital platforms can enable adaptation to participants' personal needs (e.g., give control over amounts of information, and how, when, and where participants can receive information), and multiple ways of presenting information can have a positive impact on participant satisfaction and understanding of information. | |

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| Responsibility for data collection and execution of trial activities shifts to a greater extent to participants. | • Assess participants' competency, understanding, and especially digital literacy, during informed consent procedures.<br>• Offer additional assistance to participants during a trial if needed (if needed, through home visits).<br>• Plan data collection carefully to minimise active participant data entry and maintain data protection by design and default. | |
| Burden of conducting trial activities may shift excessively to participants when conducted at participants' homes. Participants may be overburdened by the complexity of using multiple apps, devices, and technologies. | • Researchers and potential research participants should co-create a participant-centred design and plan for executing the trial (e.g., flexibility of scheduling, and limiting the number of devices and mobile apps).<br>• Avoid excessive burden or disruption of participants' life by collecting disproportionate amounts of data, or by employing potentially intrusive data collection devices or technologies.<br>• Provide sufficient education and training on operating the apps, devices, and technologies.<br>• Provide specific information on the expected burden for participants in DCT protocols or protocol-related document (e.g., describe the amount of trial visits, what tools are being used, the amount and lengths of participant-reported data fields and time required to manually enter data if necessary, and frequency of reminders). This can be | • Facilitate remote eConsent by adapting regulatory framework (this is already possible in most EU member states).<br>• RECs need to develop appropriate assessment procedures for assessing the burden on participants resulting from the use of multiple apps, devices, and technologies. |

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| | described in a protocol-related document as described in the EMA recommendation paper on DCTs. | |
| Lack of in-person contact could impact participants' motivation, trust, participant-researcher relations, and engagement negatively. | • Use the possibilities of digital tools (e.g., more frequent telephone or video call interactions, and multiple ways of interacting) for keeping participants engaged. Contacting participants to actively ask about changes in their situation can be important for engagement.<br>• Use home visits, involve local healthcare centres, or general practitioners to introduce a "personal contact moment".<br>• DCTs offer the option to introduce decentralised or on-site activities according to a participant's preference (but this may impact data outcomes; it should be incorporated in both interventional and control arms with proper randomisation).<br>• More research needed on trust-building and keeping participants engaged and motivated in DCTs. | |

## Scenario 2: Generating data in a more real-world setting

In this scenario, a DCT generates evidence in a more real-world setting compared to traditional trials. Traditional clinical trials are often conducted in controlled circumstances and in relatively homogeneous populations, which historically has been considered necessary for studying the safety and efficacy of novel treatments.[20] However, the circumstances in which this evidence is generated may differ substantially from patients' usual circumstances and may not be sufficiently generalisable.[20] Moreover, this type of evidence may not be sufficient to guide clinical decision making in real practice.[21]

DCTs enable generating data reflective of a more real-world setting compared to traditional trials, by moving most or all data collection and site visits to the participants' usual surroundings. Moreover, the use of digital tools and technologies enables data measurements at more relevant and more frequent timepoints for participants instead of only during hospital visit – and potentially also on more clinically relevant endpoints, such as novel biomarkers or digital endpoints.[2,4,5,17]

Digital tools also offer the possibility to improve protocol compliance, treatment adherence, and retention, by providing more feedback and regular reminders to participants during the trial process.[17] Moreover, digital tools may collect more accurate, objective, and complete data. These tools offer the possibility of passively monitoring participants remotely in real-time – in some cases, 24/7 – on more objective endpoints.[5] Therefore, this data will be less influenced by recall- and observer bias, compared to traditional clinical trials.[17]

We present the main ethical and regulatory challenges for achieving this scenario, along with potential solutions in **Table 2.** The potential solutions include both advice for researchers, and proposals for adjustments of the existing ethical and regulatory framework.

**Table 2: SCENARIO 2 – DECENTRALISED CLINICAL TRIALS SHOULD GENERATE DATA IN A MORE REAL-WORLD SETTING**

| **Potential ethical and regulatory challenges to this aim** | **Solutions and/or proposals from an ethical and regulatory perspective to achieve and facilitate this aim** | |
|---|---|---|
| | *What can researchers do?* | *Proposals for adjustments of ethical and regulatory framework* |
| DCTs may cause an increased variability in measurements, due to participants' self-measurements, the inclusion of local healthcare professionals and laboratories. | • Use the possibility of apps and devices to collect more 'objective' data through continuous and passive unobtrusive data collection. Data may need to be collected or sampled at fixed timepoints (except for safety data)<br>• DCTs potentially need to enrol larger samples or use repeated measurements, due to the possible increased variability of measurements and/or missing data.<br>• It should be ensured that the participant-reported data are entered and generated by the trial participants themselves, for example, using adequate validated identification systems.<br>• Where there is potential for data obtained from multiple sources (e.g., patient reported, and electronic health records) to be inconsistent, researchers should plan how they will handle data inconsistencies. These plans may include favouring one data source or verification using additional data. | • Create guidelines for standardisation of measurements in DCTs that includes standard procedures for self-measurement. |
| Missing data and the reasons for these gaps could create challenges for data interpretation. | • Reduce missing data by improving protocol compliance, e.g., through passively and unobtrusively collecting data, training stakeholders, implementing monitoring and reminder systems, considering device practicalities, | |

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| | focusing on solely collecting 'core data' to prevent overburdening participants, and enabling visits through the use of home nurses. | |
| The generation of big data could be challenging to interpret. | • Primary (and secondary and exploratory) endpoints need to be clearly defined.<br>• Methods and approaches needed on how large amounts of data can be combined in a single endpoint. | • Regulators should offer guidance for developing endpoints that combine large amounts of data.<br>• Provide training for assessors. |
| Limited availability of validated novel digital outcomes in specific therapeutic areas. | • Researchers can adapt accepted outcome measures for at-home situations, dependent on the context of the trial (the population, measurements, etc.). Evidence and validation are needed for suitable outcomes for home environment. | • Regulators can facilitate the development of novel outcomes by offering guidance for developing digital biomarkers. Stimulate the use of validated digital, remote endpoints by describing accepted endpoints in guidelines and incentivising the qualification opinion or advice pathway. |
| The introduction of novel devices that generate results and give feedback immediately, and technologies such as artificial intelligence (AI), may introduce risks that are difficult to predict, due to a lack of knowledge on these technologies. This hinders adequate assessment of the risks associated with these technologies. Moreover, feedback from novel devices and AI systems potentially intervene in the outcome, creating a kind of looping effect for the phenomena trials may wish to capture. The introduction of these technologies may make a DCT less generalisable, as these might not be used in clinical practice. | • More research needed on the precise risks and benefits of novel decentralised approaches and related technologies, and the possibility of creating feedback loops. DCTs can be used as testing ground for such research.<br>• More research needed on how systems and tools that change due to AI technology should be regulated and approved. | |

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| DCTs make use of multiple remote technologies, such as smartphone applications and other digital health technologies, which may interact with each other. This may cause privacy related concerns. | • The consequences of the use of multiple remote technologies on compliance with the GDPR and other applicable laws and regulations need to be identified, mapped out, and described in protocols.<br>• The data flow — including the data transfer and (temporary) data storage — should be clearly described in informed consent documents and research protocols.<br>• Include technology and privacy as a training element for participants. Participants should receive information about processing of data. | • Regulators and others should provide more specific guidance on the impact of the use of remote technologies on compliance with the GDPR and other applicable laws and regulations. For example, clear and specific guidelines for data security, encryption, anonymisation, and consent procedures for data sharing.<br>• More guidance or tools needed on how to map out data flow. For example, establish guidance on what level of detail is required for informing participants on data flow. |
| Other privacy issues may arise due to participants' homes becoming research site (e.g., during videocalls, passive unobtrusive data collection, and home delivery of trial materials). | • DCTs can bring some specific additional privacy risks, apart from data collection-related risks. These need to be mapped out in order to inform and train participants adequately, and address and minimise these risks. | |

## Scenario 3: Improving the efficiency of clinical trial conduct

In this scenario, DCTs should improve the efficiency of trial conduct. While clinical trials are essential for determining the safety and efficacy of novel treatments, the conduct of clinical trials can be costly, time-consuming, and burdensome for participants, researchers, and sponsors. This causes challenges for recruitment and retention and hampers the conduct of trials.[1] DCTs can offer a solution for some of these issues and inefficiencies.[2]

First, DCTs can facilitate recruitment through employing online recruitment methods, and by improving the accessibility through removing (geographical) barriers to participation.[4] Moreover, retention can also be improved by lowering the burden on participants and making clinical trial participation more flexible.[2] Secondly, DCTs may facilitate and simplify other aspects of clinical trial conduct, through minimising in-person visits. For example, investigational medicinal products (IMPs) can under certain conditions be shipped directly to participants in several ways.[22] Moreover, safety oversight can be optimised in DCTs through the use digital tools, by for example enabling continuous monitoring, and reducing the time between an adverse event and reporting to the investigator.[17]

The improved efficiency of clinical trials through decentralised methods can potentially decrease the overall development time and costs of novel treatments, which should improve participants' timely access to these medicines and treatments. We present the main ethical and regulatory challenges for achieving this scenario, along with potential solutions in **Table 3.** The potential solutions include both advice for researchers, and proposals for adjustments of the existing ethical and regulatory framework.

| Table 3: SCENARIO 3 – DECENTRALISED CLINICAL TRIALS SHOULD IMPROVE THE EFFICIENCY OF TRIAL CONDUCT | | |
|---|---|---|
| **Potential ethical and regulatory challenges to this aim** | **Solutions and/or proposals from an ethical and regulatory perspective to achieve and facilitate this aim** | |
| | *What can researchers do?* | *Proposals for adjustments of ethical and regulatory framework* |
| There are regulatory/legal barriers for recruitment online, such as privacy regulations, and regulations surrounding advertising for pharmaceuticals. | • The impact of online recruitment on compliance with the GDPR and other applicable laws and regulations need to be identified, mapped out, and described in protocols. | |
| There are legislative barriers (and varied interpretations of these legislations) for the shipment of IMPs directly to participants. | • Ensure various options are considered when outlining the direct IMP shipment, for example, direct to participant from the study site, from a local pharmacy or from the sponsor. | • Individual EU member states are advised to follow the EMA recommendation paper on decentralised elements in clinical trials in order to ensure harmonised interpretation of applicable legislations. |
| There are safety concerns about including participants in research without in-person contact at start of a trial, for example with regards to a final check of eligibility. | • Provide adequate rationale in protocols for remote eligibility assessment (e.g., if not including a physical examination).<br>• Include optional in-person visits by local healthcare professional/general practitioner wherever necessary and possible.<br>• More research needed to show that the lack of in-person contacts or a physical examination at the start of a trial does not adversely impact the safety of participants. | • Assessors should allow the inclusion of participants without in-person contact in circumstances or interventions where this would also be allowed in the healthcare setting or justify why an in-person visit would be preferable in these cases. |
| NCAs and RECs indicated that safety monitoring requires in-person visits to perform physical examinations, for example related to (unplanned) safety observations. | • Involve participants' treating physician or relatives to mitigate safety risks.<br>• Include other opportunities to ensure timely review of safety data, e.g.: (i) monitoring the investigator staff's data review, (ii) provision of a stable data transfer connection, | |

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| | (iii) provision of mobile internet to trial participants if needed, and (iv) use of algorithms to assist manual safety review.<br>• Avoid putting too much responsibility for safety on the participant (e.g., using continuous safety monitoring through devices). | |
| DCTs may cause a (temporary) increased burden on researchers, as DCTs are a new way of working which may require other skills (e.g., digital skills, and skills specific for remote communicating with participants) and adaptation to new situation. | • Sponsors should provide sufficient (training) resources and use simple/lean design limiting the collection of noncore data. | |
| The use of multiple digital tools causes an increased risk of technology malfunctioning, which can hamper the trial process. | • Researchers need to have sufficient mechanisms in place to deal with technology malfunctioning. | |
| Distribution of responsibilities can become unclear in DCTs (e.g., between sponsors and sites, principal investigators, general practitioners, and research nurses). This includes challenges related to the use of third parties, such as the training of third parties, unclarity regarding qualifications and the overall responsibility of the investigator. This potentially causes hesitance in NCAs, RECs, and investigators to accept delegation of tasks to third parties. | • Oversight over and allocation of responsibilities of each involved partner in DCTs needs additional attention and needs to be specified in the protocol. In principle, the investigator remains responsible for the conduct and participant contact following ICH E6. Any delegations should be clearly specified. Collaboration needs to be specified in a contract with clear task allocation and description.<br>• Clear lines of communication among the investigator staff, local healthcare professionals, and vendors are needed. | |

- A possible solution is organising home visits via a site's existing infrastructure.
- Possible dependencies and conflicts of interest of the research team may need additional attention in a DCT protocol. Oversight over trial activities may become diffuse when a trial is conducted outside the clinical setting, which may be the case more often with DCTs.

## Scenario 4: Improving the diversity of study populations

In this scenario, DCTs should improve the diversity of study populations compared to traditional clinical trials. Clinical trials often fail to include a diverse population, and white, healthy, young or middle-aged men have generally been overrepresented in study populations.[23-26] People with lower socio-economic status, older individuals with comorbidities, children, and people living in rural areas tend to be underrepresented to a greater extent.[23-26] This can negatively impact the overall generalisability of study results, and cause an unfair sharing of the benefits or carrying the burden of participating research.

DCTs eliminate or reduce geographical barriers and may thereby increase accessibility to participation in clinical trials. Therefore, DCTs may improve diversity of populations by being more accessible for people living further away from research sites,[5,27] and people for whom it may be more difficult to travel or carry the burden of trial participation, such as elderly patients and patients with comorbidities.[5] DCTs may additionally enable trials in rare diseases with geographically dispersed patients.

Online recruitment, which DCTs may also employ, may also promote broader inclusion. Existing evidence, which is predominantly focused on the USA, suggests that (decentralised) trials with online recruitment methods can be successful for groups that are traditionally difficult to reach,[28] such as racial and ethnic minorities,[27] and could thus facilitate inclusion of a more diverse population.

We present the main ethical and regulatory challenges for achieving this scenario, along with potential solutions in **Table 4.** The potential solutions include both advice for researchers, and proposals for adjustments of the existing ethical and regulatory framework.

**Table 4: SCENARIO 4 – DECENTRALISED CLINICAL TRIALS SHOULD IMPROVE THE DIVERSITY OF STUDY POPULATIONS**

| **Potential ethical and regulatory challenges to this aim** | **Solutions and/or proposals from an ethical and regulatory perspective to achieve and facilitate this aim** | |
|---|---|---|
| | *What can researchers do?* | *Proposals for adjustments of ethical and regulatory framework* |
| Currently unclear what ethical requirements of fair participant selection specifically requires for individual studies. | • Aim of promoting diversity needs to be specified further. For example, are specific subpopulations relevant to include, based on previous research?<br>• Risk-benefit ratio needs to be taken into account as well. In research with sufficient direct benefits for participants – how can underrepresented groups be given appropriate access? In research that is expected to be burdensome – how are vulnerabilities of individual participants taken into account? | • Regulators should promote the aim of improving diversity in CTs more generally.<br>• Ethical guidelines for fair participant selection need to be specified further in terms of what is required for individual studies. |
| Generalisability of DCTs is unclear (precise impact of DCT on study population demographics is unclear; precise impact of study population demographics on generalisability is in some cases also unclear). | • More research needed on the impact of DCTs on population demographics, and the impact of population demographics on generalisability of study results.<br>• Sponsors should substantiate in protocols why they expect a DCT in their specific context to ensure generalisability. | |
| Inclusion of less digitally skilled participants may pose a challenge. | • The digital skills that are needed to participate in a DCT should be mapped, and skills digital skills required for participation should be minimised by creating appropriate and intuitive digital tools.<br>• Ensure sufficient training. | |

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| | • Provide adequate technological support for participants throughout the trial. | |
| Lack of infrastructure (internet, devices) can be a barrier for participation in DCTs – especially in the case of Bring Your Own Device (BYOD) approaches. | • Sponsors should present a plan on how to deal with these barriers for participation in research protocols. For example, providing participants with devices if necessary, or using smart phone technology (via cellular network) as an alternative to internet access where feasible. | • Ethical guidelines for the provision of the equipment and internet access for participants that could be excluded otherwise. |
| Not all populations or therapeutic areas (TAs) may be suitable for participating in DCT. | • Low risk diseases, chronic diseases and rare diseases may be more suitable for DCTs.<br>• TAs that require more intensive care or careful observation/specialist equipment (e.g., scanners) may be less suitable, or require a hybrid approach.<br>• Decentralised approaches and their potential to reduce burdens may also have important advantages for certain specific populations, such as paediatric populations, which can be considered as well. | |

## Discussion

In this deliverable, we presented four scenarios based on the most important aims of DCTs, alongside the related ethical and regulatory challenges, and potential solutions. The main aims of DCTs include improving participant-centricity, collecting data closer to real-world settings, improving the efficiency of clinical trials, and increasing the diversity of study populations.

### Main findings

Our findings reveal different challenges in the adoption of DCTs. These result from the fact that the effects of DCTs – for example, of the use of digital technologies and lack of in-person contact – are to a certain extent still unclear. Moreover, regulations and guidance need further development, for example on topics such as privacy, digital endpoints, provision of equipment and internet access, and diversity.

The use of several novel digital technologies and the interaction between those devices and apps raises several concerns. For example, it causes challenges related to privacy, ensuring accessibility for less digitally skilled participants, and collecting and analysing large amounts of data. Additionally, moving most or all trial activities to participants' usual surroundings may unintentionally shift burdens and responsibilities to participants, and may impact data quality negatively. Another aspect that introduces several challenges is the lack of in-person contact. A lack of in-person contact for example may have unfavourable consequences for training and informing participants sufficiently, building trusting relationships, and for ensuring participants' safety.

Researchers should aim to minimise these challenges by ensuring sufficient participant engagement and avoiding overburdening participants by employing too many different apps, devices, and other technologies in a study. Moreover, the (digital) skills that are needed in order to participate in a trial should be mapped out in protocols, and researchers should provide adequate training and support to participants on the technical aspects of participating in a DCT. It should be noted that the DCTs' benefits for participants need to be taken into account as well in weighing these potential disadvantages and burdens.

**Knowledge gaps**

We have provided several solutions and proposals to deal with the identified challenges. However, there remain many open questions that need to be studied further, while DCTs are becoming increasingly common.

Including participants without having a physical examination at the start of a trial, and applying novel devices and technologies in the context of a DCT may introduce unknown risks. Here, it may be relevant to distinguish *risks* and *uncertainties.* While in the case of risks, probabilities of certain outcomes are known, this is not the case for uncertainties.[29,30] In the case of DCTs, there is some experience with and evidence on several decentralised methods in clinical trials.[18,31] Therefore, for some of the risks that are associated with DCTs, there can be assessment made about their probability. On the other hand, however, knowledge on likelihoods of some risks may still be insecure. Additionally, there are always uncertainties involved in conducting research, such as the occurrence of (serious) adverse events ((S)AEs). These uncertainties may be exacerbated due to novel innovations such as DCTs, in which safety oversight is organised differently from traditional clinical trials. There is more evidence needed on DCTs' precise risks and benefits for participants in order to assess these appropriately. This especially concerns the risks related to having no in-person contact, such as safety oversight in DCTs and the relevance of a physical examination at the start of a trial.

Moreover, it is to a certain extent unclear what impact DCTs will have on aspects of researcher-participant relationships, such as trust, engagement, and motivation of participants. These aspects are important for participants to participate in any clinical trial. For DCTs specifically, the lack of in-person contact may (amongst others) impact these aspects. It is currently still unclear how and to which extent remote contact can replace in-person contact. Previous research in the context of digital healthcare has shown that frequent communication through, for example, phone calls can be important to build a trusting relationship with patients when in-person contact is lacking.[32] However, this has not yet been studied extensively in the context of clinical trials.

Finally, more ethical guidance is needed on the requirement of fair participant selection, which relates to the aim of improving diversity in DCTs. It is currently unclear to a certain extent what this requirement implies for individual studies, and there is less precise guidance compared to other ethical requirements.[33] This complicates the further specification of this ethical requirement, and subsequently, improving the diversity of study populations in a valuable way.

**Interaction between scenarios**

We have presented four separate scenarios which outline what is ideally achieved with the introduction of decentralised clinical trials. However, some of these aims may complement in practice, and be in conflict in some cases. For example:

- Lowering burden on participants – as a part of improving participant-centricity – may increase burden on researchers.
- Shift of trial-related activities to immediate participant surroundings may also increase burden for participation.
- Improving efficiency may decrease participant-centricity, and vice versa.
- Collecting large amounts of data and remote monitoring of adherence[34] and safety may impact participant-centricity by employing more intrusive technologies and data collection methods on participants, which may impact participants' privacy.
- Aiming to recruit a sufficiently diverse population can potentially impact efficiency, as it may take more effort to reach specific populations.
- The way that DCTs aim to improve patient-centricity – through the use of digital tools – may not be accessible for all populations as it requires access to technology and a certain level of digital skills. This may impact the aim of promoting diversity negatively.

This demonstrates that, while all four aims are important for DCTs, it is necessary to prioritise specific aim(s) and anticipate which challenges may arise in achieving these aims.

## Conclusion

This deliverable presented four main aims of DCTs, alongside the challenges for achieving these aims. These scenarios can guide the responsible implementation and sustainable conduct of DCTs.

Researchers should consider these various aims and prioritise, as different aims require a different emphasis or approach. For achieving (i) participant-centricity in DCTs, researchers should meaningfully strive for participant involvement and empowerment and lowering burdens of trial participation, through thoughtful use of devices and technologies. For achieving (ii) data collection in a more real-world setting with DCTs, an adequate vision on novel (digital) endpoints is needed, in order to avoid the collection of excessive amounts of data without sufficient plans for analysis. For achieving (iii) more efficient conduct of clinical trials, researchers should ensure adequate oversight, especially on participants' safety in light of the absence of in-person contact. For achieving meaningful attention for (iv) diversity in DCTs, further reflection is needed on what diversity specifically refers to in a specific context, what its underlying aims are, and what sufficient diversity would constitute in practice.

Regulators can facilitate the uptake of DCTs by requiring evidence and learnings to be fed back into the conduct, guidance, and assessment procedures for DCTs. At the same time, overregulation and unnecessary bureaucracy surrounding DCTs should be prevented. Finally, regulators should continue to develop more (specific) guidance on complex topics such as privacy, digital endpoints, provision of equipment and internet access, and diversity.

## 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*. Sep 2018;11:156-164. doi:10.1016/j.conctc.2018.08.001
2. Inan OT, Tenaerts P, Prindiville SA, et al. Digitizing clinical trials. *NPJ Digit Med*. 2020;3(101):1-7. doi:10.1038/s41746-020-0302-y
3. Santa-Ana-Tellez Y, Lagerwaard B, de Jong AJ, et al. Decentralised, patient-centric, site-less, virtual, and digital clinical trials? From confusion to consensus. *Drug Discov Today*. Apr 2023;28(4):103520. doi:10.1016/j.drudis.2023.103520
4. Dorsey ER, Kluger B, Lipset CH. The New Normal in Clinical Trials: Decentralized Studies. *Ann Neurol*. 2020;88(5):863-866. doi:10.1002/ana.25892
5. Khozin S, Coravos A. Decentralized Trials in the Age of Real-World Evidence and Inclusivity in Clinical Investigations. *Clin Pharmacol Ther*. Jul 2019;106(1):25-27. doi:10.1002/cpt.1441
6. Steinhubl SR, Wolff-Hughes DL, Nilsen W, Iturriaga E, Califf RM. Digital clinical trials: creating a vision for the future. *NPJ Digit Med*. 2019;2(126):1-3. doi:10.1038/s41746-019-0203-0
7. Izmailova ES, Wagner JA, Perakslis ED. Wearable Devices in Clinical Trials: Hype and Hypothesis. *Clin Pharmacol Ther*. Jul 2018;104(1):42-52. doi:10.1002/cpt.966
8. Carter A, Liddle J, Hall W, Chenery H. Mobile Phones in Research and Treatment: Ethical Guidelines and Future Directions. *JMIR Mhealth Uhealth*. Oct 16 2015;3(4):e95. doi:10.2196/mhealth.4538
9. Marquis-Gravel G, Roe MT, Turakhia MP, et al. Technology-Enabled Clinical Trials: Transforming Medical Evidence Generation. *Circulation*. Oct 22 2019;140(17):1426-1436. doi:10.1161/CIRCULATIONAHA.119.040798
10. Gelinas L, Morrell W, White SA, Bierer BE. Navigating the ethics of remote research data collection. *Clin Trials*. Oct 2021;18(5):606-614. doi:10.1177/17407745211027245
11. 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*. Aug 29 2022;12(8):e063236. doi:10.1136/bmjopen-2022-063236

12. Heads of Medicines Agencies, European Commission, European Medicines Agency. *Recommendation paper on decentralised elements in clinical trials*. 2022. https://health.ec.europa.eu/system/files/2022-12/mp_decentralised-elements_clinical-trials_rec_en.pdf

13. Vergragt PJ, Quist J. Backcasting for sustainability: Introduction to the special issue. *Technological Forecasting and Social Change*. 2011;78(5):747-755. doi:10.1016/j.techfore.2011.03.010

14. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Guideline Good Clinical Practice E6(R2)*. 2016.

15. Tran VT, Barnes C, Montori VM, Falissard B, Ravaud P. Taxonomy of the burden of treatment: a multi-country web-based qualitative study of patients with chronic conditions. *BMC Medicine*. May 14 2015;13(115):1-15. doi:10.1186/s12916-015-0356-x

16. Naidoo N, Nguyen VT, Ravaud P, et al. The research burden of randomized controlled trial participation: a systematic thematic synthesis of qualitative evidence. *BMC Medicine*. Jan 20 2020;18(6):1-11. doi:10.1186/s12916-019-1476-5

17. de Jong AJ, van Rijssel TI, Zuidgeest MGP, et al. Opportunities and Challenges for Decentralized Clinical Trials: European Regulators' Perspective. *Clin Pharmacol Ther*. Aug 2022;112(2):344-352. doi:10.1002/cpt.2628

18. Coyle J, Rogers A, Copland R, De Paoli G, MacDonald TM, Mackenzie IS. Learning from remote decentralised clinical trial experiences: A qualitative analysis of interviews with trial personnel, patient representatives and other stakeholders. *Br J Clin Pharmacol*. Mar 2022;88(3):1031-1042. doi:10.1111/bcp.15003

19. Apostolaros M, Babaian D, Corneli A, 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*. Jul 2020;54(4):779-787. doi:10.1007/s43441-019-00006-4

20. Rachel E. Sherman, Steven A. Anderson, Gerald J. Dal Pan, et al. Real-world evidence—what is it and what can it tell us. *N Engl J Med*. 2016;375(23):2293-2297.

21. Zuidgeest MGP, Goetz I, Groenwold RHH, et al. Series: Pragmatic trials and real world evidence: Paper 1. Introduction. *J Clin Epidemiol*. Aug 2017;88:7-13. doi:10.1016/j.jclinepi.2016.12.023

22. 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 2023;doi:10.1111/bcp.15850

23. Flores LE, Frontera WR, Andrasik MP, et al. Assessment of the Inclusion of Racial/Ethnic Minority, Female, and Older Individuals in Vaccine Clinical Trials. *JAMA Netw Open*. Feb 1 2021;4(2):e2037640. doi:10.1001/jamanetworkopen.2020.37640

24. Chen A, Wright H, Itana H, et al. Representation of Women and Minorities in Clinical Trials for New Molecular Entities and Original Therapeutic Biologics Approved by FDA CDER from 2013 to 2015. *J Womens Health (Larchmt)*. Apr 2018;27(4):418-429. doi:10.1089/jwh.2016.6272

25. 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*. Nov 3 2015;16:495. doi:10.1186/s13063-015-1023-4

26. Duma N, Vera Aguilera J, Paludo J, et al. Representation of Minorities and Women in Oncology Clinical Trials: Review of the Past 14 Years. *J Oncol Pract*. Jan 2018;14(1):e1-e10. doi:10.1200/JOP.2017.025288

27. Stewart J, Krows ML, Schaafsma TT, et al. Comparison of Racial, Ethnic, and Geographic Location Diversity of Participants Enrolled in Clinic-Based vs 2 Remote COVID-19 Clinical Trials. *JAMA Netw Open*. Feb 1 2022;5(2):e2148325. doi:10.1001/jamanetworkopen.2021.48325

28. Gelinas L, Pierce R, Winkler S, Cohen IG, Lynch HF, Bierer BE. Using Social Media as a Research Recruitment Tool: Ethical Issues and Recommendations. *Am J Bioeth*. Mar 2017;17(3):3-14. doi:10.1080/15265161.2016.1276644

29. Hansson SO. Ethical criteria of risk acceptance. *Erkenntnis*. 2003;59:291–30.

30. Hayenhjelm M, Wolff J. The Moral Problem of Risk Impositions: A Survey of the Literature. *European Journal of Philosophy*. 2012;20:E26-E51. doi:10.1111/j.1468-0378.2011.00482.x

31. Sommer C, Zuccolin D, Arnera V, et al. Building clinical trials around patients: Evaluation and comparison of decentralized and conventional site models in patients with low back pain. *Contemporary Clinical Trials Communications*. Sep 2018;11:120-126. doi:10.1016/j.conctc.2018.06.008

32. Oudshoorn N. Physical and digital proximity: emerging ways of health care in face-to-face and telemonitoring of heart-failure patients. *Sociol Health Illn*. Apr 2009;31(3):390-405. doi:10.1111/j.1467-9566.2008.01141.x

33. Meltzer LA, Childress JF. What is fair participant selection? . In: Emanuel EJ, Grady CC, Crouch RA, Lie RK, Miller FG, Wendler DD, eds. *The Oxford Textbook of Clinical Research Ethics*. Oxford University Press; 2008.

34. Van Biesen W, Decruyenaere J, Sideri K, Cockbain J, Sterckx S. Remote digital monitoring of medication intake: methodological, medical, ethical and legal reflections. *Acta Clin Belg*. Jun 2021;76(3):209-216. doi:10.1080/17843286.2019.1708152