ELSEVIER

Check for updates

Feature

Ethics review of decentralized clinical trials (DCTs): Results of a mock ethics review

Tessa I. van Rijssel [a,*], Amos J. de Jong [b], Yared Santa-Ana-Tellez [b], Martin Boeckhout [c], Mira G.P. Zuidgeest [a], Ghislaine J.M.W. van Thiel [a], on behalf of the Trials@Home Consortium[1]

Decentralized clinical trials (DCTs) can be a valuable addition to the clinical trial landscape. However, the practice of DCTs is dependent on a regulatory system designed for conventional (site-based) trials. This study provides insight into the ethics review of DCTs. A 'mock ethics review' was performed in which members of European ethics committees (ECs) and national competent authorities (NCAs) discussed and reviewed a DCT protocol. Respondents expressed hesitancy toward DCTs and focused on potential risks and burdens. We advise to address these aspects explicitly when submitting a DCT protocol. We propose that both the benefits and risks of DCTs should be carefully monitored to advance the review and practice of this innovative approach to ethically optimize drug development.

Keywords: Decentralized clinical trials; DCT; Research ethics; Ethics review; Ethics committee

Introduction

DCTs are an operational approach to move clinical trial activities from research sites to a participant's immediate surroundings. Digital technologies, such as apps, devices, and wearables, are used for data collection and communications between researchers and trial participants. Moreover, DCTs can include the shipping of investigational medicinal products (IMPs) directly to participants, and home visits by healthcare professionals (HCPs). DCT approaches can be combined with regular site-based elements, which is referred to as a 'hybrid trial'.[1]

DCTs could be a potential solution for some of the existing issues and inefficiencies in the conduct of clinical trials,[2,3] by decreasing burdens for participants and researchers, enabling larger and more diverse populations to participate, and generating more representative data.[3–5] Moreover, it has been suggested that DCTs help empower participants by giving them more control over the trial process.[6–8] However, one of the main challenges is that the current ethical and regulatory frameworks are conceptualized with site-based trials in mind. Ethical and regulatory guidance on the use DCTs and decentralized methods is still scarce.[9,10]

Spurred by the coronavirus disease 2019 (COVID-19) pandemic and associated restrictions, regulators offered guidance for clinical trials and the advantages and potential of decentralized methods became increasingly visible.[11,12] Furthermore, there is an increased interest in DCTs in general, given that some Euro-

[1] Website: trialsathome.com.

https://doi.org/10.1016/j.drudis.2022.07.011

pean national competent authorities (NCAs) and ethics committees (ECs) recently published guidance on the conduct of DCTs.[13–15] The Clinical Trials Transformation Initiative and the US Food and Drug Administration (FDA) are exploring opportunities and challenges for DCTs in the USA.[1,16] Recent studies also reflect on the ethical aspects associated with the use of specific remote technologies in clinical research, which include, among others, privacy, safety, accessibility, and informed consent.[6,8–10,17–21] However, regarding the ethics review of DCTs, there is currently little insight into the relevant issues, and specific standards are lacking.[9,19]

This study identifies issues that might be raised in ethics reviews of DCTs and explores possible solutions. This could advise researchers and sponsors and facilitate the future development of guidance on ethics reviews of DCTs.

TABLE 1

Description of the mock DCT protocol.

Trial activity	Description
Recruitment and enrollment	Social media and patient organizations Online prescreening questionnaire Phone contact with investigational site staff
Informed Consent	Study information through study app eConsent obtained in videocall
Screening	Provision of electronical medical records
Identification of participant	Electronic identities and trust services (eIDAS) certified identification method
Drug dispensation	IMP direct-to-patient (DTP) shipping from central pharmacy
Training [study procedures, device(s), study drug]	Videocall with investigational site staff Web-based study platform
Data collection	Electronic patient-reported outcomes (ePROs) in the study app CE-marked CGM device CE-marked electronic insulin pen adaptor cap measuring insulin dosing and injection data
(S)AE identification	Videocall (with investigational site staff) based upon participant self-reporting events ePROs and study app reviews
Hypoglycemic events	Videocall (with investigational site staff) based upon participant self-reporting ePROs and study app reviews
Engagement/encouragement	Digital/app engagement strategies

The case study

We performed a 'mock ethics review' of a fully DCT as a case study in three focus groups. Members of European ECs and NCAs discussed and reviewed a mock study protocol of a DCT.

Case study protocol

The case study protocol described a Phase IV randomized, open-label, multinational DCT to determine the real-world effectiveness of insulin glargine 300 U/ml compared with standard basal insulin with continuous glucose monitoring (CGM) in adult patients with type 2 diabetes mellitus (T2DM) (Table 1). A synopsis of the mock protocol is included in Appendix 1 in the supplemental information online.

Sample

A purposive sample of members of ECs and NCAs from European countries were invited for a focus group interview. Potential respondents were contacted through email via their committees or organizations between July and September 2021. Respondents were eligible if they were experienced in the ethics review of clinical trials in Europe.

Data collection

Respondents received the case study protocol ~2 weeks before the focus group meeting to prepare for the discussion. Some respondents discussed the protocol within their own organizations or committees before the focus group meeting.

G.T. (experienced qualitative researcher, PhD, associate professor) moderated the focus groups, guided by a script and a topic list (Appendix 2 in the supplemental information online). Respondents were first asked to respond to the protocol and discuss their comments and concerns, in an unstructured manner. After exploring the issues that respondents raised, the moderator asked open questions on topics that did not come up during the discussion. These topics, relevant for the ethics review of DCTs, were selected based on literature and expert knowledge.

Three researchers made field notes during and after each focus group session (T.R., A.J., and G.T.). In addition, some respondents provided their preparation materials for the ethics review, including their comments and feedback on the protocol, after the meeting.

Data analysis

The focus groups were videorecorded, transcribed verbatim, and pseudonymized. The qualitative data were analyzed using interpretative thematic analysis.[22] First, the pseudonymized transcripts were read and re-read to get familiar with the data. Second, the relevant fragments to answer the research question were analyzed and coded. Two researchers (T.R. and A.J.) independently coded one transcript in duplicate, to enhance validity. These initial codes were reviewed, discussed, and adjusted when necessary. One researcher (T.R.) coded all transcripts with the adjusted code tree, using NVivo 12. The observations made during the focus groups in field notes and feedback that some respondents provided after the focus groups were used to interpret the results. These steps were repeated several times to enhance validity. The research group subsequently established the (sub) themes.

The seven requirements for ethical acceptability of research described by Emanuel et al. were used to structure the results and develop themes.[23] These requirements are derived from existing codes, declarations, and regulations for research, and include: (i) social or scientific value; (ii) scientific validity; (iii) fair subject selection; (iv) favorable risk–benefit ratio; (v) independent review; (vi) informed consent; and (vii) respect for potential and enrolled subjects. Comprehensive consolidated criteria for Reporting Qualitative research (COREQ) were used to report the results.[24]

Ethical considerations

All respondents provided verbal informed consent. On 29 July 2021, the Medical Research Ethics Committee METC Utrecht decided that, in accordance with applicable Dutch law, the study was exempt from ethics review (dossier number 21-496/C).

Mock ethics review results

A total of 34 respondents were interested in participating in the focus groups. Mainly because of difficulties with planning and availability, eight respondents cancelled their participation. Three focus groups were conducted involving 26 members of ECs ($N = 21$) and NCAs ($N = 5$), who were all experienced in reviewing clinical trials. Representatives from eight European countries were included, and all European regions were represented in the focus groups.[25] Each focus group comprised between seven and ten participants, with at least three different countries and professional backgrounds represented in each group. Respondent characteristics are described in Table 2.

Three meetings of ~1.5–2 h each took place in October 2021 through videoconference. No new themes emerged during the final focus group, suggesting thematic saturation. Results are grouped into four themes, which cover six of the seven requirements identified by Emanuel et al.[23]: (i) social value and scientific validity; (ii) fair subject selection; (iii) favorable risk–benefit ratio and respect for subjects; and (iv) informed consent.

TABLE 2

Respondent characteristics ($N = 26$).

Characteristic	*N* (%)
Gender	
Female	17 (65)
Male	9 (35)
Country	
Spain	8 (31)
Germany	5 (19)
Italy	4 (15)
Belgium	3 (12)
The Netherlands	2 (8)
Poland	2 (8)
Denmark	1 (4)
Switzerland	1 (4)
Background	
Medical	8 (31)
Pharmacy	6 (23)
Medical/clinical pharmacology	5 (19)
Clinical pharmacology	3 (12)
Bioethics	2 (8)
Biology	1 (4)
Biochemistry	1 (4)

Social value and scientific validity

While respondents did recognize the potential added value of DCTs in general, we observed little discussion around the possible beneficial aspects of DCTs during the mock review. DCTs were thought to bring uncertainties and challenges with regards to data quality, participant safety, and organizational aspects. Respondents deemed more evidence on the equivalence of DCTs on these aspects to site-based trials necessary. Therefore, an additional and specific justification for using a DCT was considered necessary.

Respondents raised concerns on the validity and accuracy of data, because participants were responsible for measurements and entering data. By contrast, the possibility of apps and devices to gather more objective data was also mentioned. Moreover, some respondents expected that the compliance and motivation of participants will be lower in DCTs, because there might be less of a relationship between researchers and participants:

> 'Because whether we like it or not, this sort of context that we have doesn't raise the same kind of attachment or warmth of feeling or relationship like it does when you meet each other in a consulting room, I think. (...) it will help probably that you know who's the other person who you are doing it for. (...) there is this sort of interaction that might help you think: oh well, she's a nice person, she's working on her PhD, let me go on recording on my data. And if you do it from a distance, I'm afraid that that sort of thing might get lost.'.

Fair subject selection

Respondents expected certain groups to be excluded from DCTs based on the level of digital literacy and because of recruitment through online methods. Therefore, the results of DCTs might be less, or only very limitedly, generalizable. For example, the case study included patients with T2DM in a DCT. Respondents deemed these patients to be less suitable and difficult to include in a DCT, as opposed to patients with T1DM because the latter are generally younger and more used to self-administration of medication. Involving the physicians treating the participants or providing in-person training for devices was thought to be a possible solution for the fair inclusion of participants.

Favorable risk–benefit ratio and respect for subjects

Respondents generally perceived multiple risks and burdens for participants related to the decentralized trial approach, mainly because of the lack of in-person contact. Few benefits for participants were mentioned by respondents. Overall, respondents noted a shift of burden and responsibility toward participants in DCTs. Participants become more responsible for the data collection and overall execution of trial activities when these are moved from the trial site to the participants' surroundings.

> 'It shouldn't interfere too much with their daily lives (...). The question is how many minutes a day they can spend for that'.

DCTs were thought to be both burdensome and complex for participants. This burden and complexity were also associated with the use of multiple apps and devices and manual data entries, because the case study included three apps and two medical devices for participants:

> 'What I wanted to mention also is (...) the complexity of what the patients have to do. So, they are equipped with a lot of stuff. They get a welcome package. And just think about what happened when you last time installed your TV, with just one TV. Now you get a pen, you can you get three or four apps at the same time, which interact, you have to be able to connect the devices with Bluetooth (...). So you have a lot of technical requirements.'.

Respondents deemed specific information on the burden for participants in DCT protocols necessary. For example, the amount and lengths of participant-reported data fields and time required to manually enter data, and frequency of reminders should be described.

Apart from the participant burden, respondents perceived multiple risks regarding safety. For example, the absence of an in-person physical examination in the case study, and the reporting of potential (serious) adverse events [(S)AEs] by participants themselves, was thought to be unsafe.

> 'But for me this chapter, Benefit-Risk Assessment, is just wishful thinking, because you move the responsibility for the judgement to the participant. (...)

> On this description it means you will be safe if you keep your safety on a good level by your own, which is... (...) I mean, it's not enough.'.

The reporting of potential (S)AEs and risks of hypoglycemia were mentioned as important safety concerns in the context of DCTs, whereas these aspects would be similar in a site-based trial. The DCT approach was thought to only be suitable for trials or IMPs that are low risk. Insulin, the market-authorized IMP in the case study, was considered to be too risky to study in a DCT. However, the potential advantages of the ability to monitor safety continuously (e.g., using CGM) in a DCT was also mentioned. Furthermore, involving participants' general practitioners (GPs) or relatives were thought of as possible solutions to mitigate the safety risks.

A separate issue that the respondents brought up was the distribution of responsibilities and relation between principal investigators (PIs) and participants' GPs. It was thought to be unclear how the responsibilities of all parties involved (e.g., PIs, GPs, and research nurses) are distributed in a DCT. Moreover, it was noted that the possible dependencies and conflicts of interest of the research team need additional attention in a DCT protocol compared with a regular clinical trial. The industry was thought to have a larger, and possibly interest-driven, impact when a trial is conducted completely outside the clinical setting. This was thought to impact the data quality and integrity of the research. Therefore, it was advised to include information on the research team and possible conflicts of interest in a DCT protocol.

Additionally, data and privacy aspects also required extra attention in study protocols, according to respondents. For example, the data flow should be clear to (potential) participants, especially when countries outside the European Union are involved.

Informed consent

Several issues related to remote informed consent procedures were identified by respondents. The conditions for giving consent, which include the competency of participants and the voluntariness of their decision, did not come up during the discussion in detail. Respondents deemed an informed consent discussion with an investigator necessary. With regards to doing this remotely, by means of, for example, a videoconference system, we observed several doubts and hesitancy in respondents. In principle, it was considered to be possible, because eConsent systems and systems for remote ID verification exist. However, there was no broad acceptance by everyone. Moreover, it was noted by multiple respondents that older people, with a lower digital literacy, would not be able to use these systems.

> 'As the trial is right now in terms of the informed consent process (...) it's not necessarily a showstopper, but it is something that they are very cautious about, you need to justify really well that this is a study design that is well suited for using decentralized elements. It's not a showstopper as such, but you need to argue and justify the particular choices of studies.'.

With regards to giving consent, issues such as the verification of identity and validity of electronic signatures came up. Regarding the latter, this was considered acceptable in some countries but not (yet) in others.

In-person contact was deemed important during informed consent procedures for several reasons. Assessing participants' understanding and digital literacy in-person was deemed especially important in a DCT, because participants have more responsibilities. Participants in DCTs need to be extra informed on data-processing aspects and safety procedures, and need sufficient, preferably in-person, training, according to several respondents.

The informed consent procedure, and the perceived need for in-person contact, was regularly associated with screening activities, such as the verification of diagnosis and checking the inclusion and exclusion criteria. Given that these are only based on information coming from the participant themselves in the pre-screening phase of a DCT, respondents deemed this to be less reliable. Moreover, an in-person informed consent discussion was associated with doing a physical examination of a participant, which was often seen as indispensable.

> 'You definitely need a really well-done physical examination and including looking at the hands and feet of the patients – to have a look into the eyes.'.

Lastly, face-to-face contact was also thought to be important for building trust. It was noted that research participation is, to a large extent, based on trust, which stems from the relationship between researchers and participants. Respondents mostly anticipated that the physical distance and communication through digital means will have a negative impact on participant–researcher relationships and trust.

To conclude, most respondents generally agreed that, for several reasons, a hybrid trial, with at least one in-person visit at the start of the trial, was preferable above a fully DCT. Before DCTs could be acceptable, many respondents deemed more evidence on its safety and quality necessary.

Discussion

In this study, EC members expressed predominantly hesitant attitudes toward the mock case study and had requirements for ethical approval that would prohibit a full DCT. In general, DCTs were anticipated to be more burdensome and less safe, because responsibilities are shifted toward participants and in-person contact is lacking. Furthermore, DCTs were thought to be less accessible because of a certain required level of digital literacy. The potential benefits of DCTs for participants did not carry much weight, whereas the risks for the integrity of research and the safety of participants were prioritized. Additionally, we observed that, across the topics that usually are assessed in ethics reviews, more fundamental themes came forward that develop within researcher–participant relationships, such as trust and participants' motivation.

According to respondents, additional information or measures were required compared with site-based trials, especially with regards to safety and responsibilities. The quality, safety, and organization of DCTs were perceived as more problematic than in conventional, site-based clinical trials. These hesitant attitudes toward novel approaches can be understood in the context of regulatory protectionism, which was initially the paradigm within research oversight. It considers research to be inherently risky for participants, instead of potentially beneficial and, therefore, prioritizes the protection of participants.[26] Additionally, risk-aversiveness

and avoiding uncertainties by regulators and ECs is often related to the immediate and obvious bad consequences of allowing drugs or trials that turn out to be unsafe for patients. Especially with novel treatments or concepts, such as DCTs, regulators are often hesitant, because there is limited experience and evidence, which entails more uncertainties. On the other hand, overprotectiveness, for example in the case of DCTs, could hinder more efficient trials, which could in turn delay the access to new treatments for patients, which can also be harmful.[27,28]

DCTs aim to include a larger and more diverse population through the inclusion of groups that have been commonly excluded from research, such as people living further away from research sites.[3,4,29] However, the concern of excluding certain populations when using apps and devices in trials, which was frequently raised in this study, has been described previously as well.[6,21] The existing evidence, which is predominantly focused on the USA, suggests that (decentralized) trials with online recruitment methods can be successful for groups that are traditionally difficult to reach and could enable a more diverse population to be included.[18,30–31] This might indicate that DCTs could contribute to diversity and fair inclusion in specific aspects, which should also be taken into account in the ethics review.

The shift of responsibility and control toward participants in DCTs, which was identified in this study, has also been recognized in previous studies, including the possible overburdening of participants with devices and technologies.[4,32] However, previous studies do also emphasize the possible benefits of DCTs in this area, such as the absence of a travel burden, continuous safety monitoring, and the possibility for patient engagement through digital platforms.[4,8,29,32] Nonetheless, these impacts of introducing technologies in existing practices, which include, aside from the shift of control and responsibilities, also impacts on trust, motivation, and relationships, have not yet been elaborated extensively in existing literature in the context of DCTs. However, these 'soft' impacts of technology do turn out to be important. For example, trust is an important factor for individuals to participate in medical research.[33,34] Thus, an important ethical question for the conduct of DCTs is how the relationship between participants and researchers can be fostered over greater physical distances.

Strengths and weaknesses

This study performed a mock ethics review of a case study DCT that comprised a variety of decentralized methods. Experts from all European regions were included in the study. Therefore, this study provides a comprehensive perspective of the issues that arise in the ethics review of DCTs. However, the artificial nature of the case study protocol and ethics review session might have affected the results, because there was no actual study that would be stopped by a negative assessment of the respondents. Moreover, the results are, to a certain extent, directed by the specific decentralized elements that were included in the case study. This also implies that it is not always possible to determine whether the identified issues and solutions would be applicable only to the case study or to DCTs in general. Lastly, no patient representatives participated in this study, causing their perspective to be lacking while typically represented in the ethics review of a clinical trial.

Concluding remarks

In this study on the ethics review of DCTs, additional risks, burden, and complexities in the conduct of DCTs were anticipated, which resulted in a hesitant attitude toward DCTs. We recommend an approach of advancing DCTs, in which these issues are monitored and addressed, while avoiding the unfavorable consequences of overprotectiveness and overregulation. First, sponsors and researchers should reflect the existing evidence on both the risks and benefits of DCTs within research protocols to promote an evidence-based review practice. In the meantime, the impact of these changing practices in clinical trials should be carefully observed and reflected upon while allowing DCTs and hybrid trials to proceed. These learnings should be fed back into conduct and guidance for the ethics review of DCTs. In addition, the impacts of these technologies on aspects of researcher–participant relationships, such as the shift of control and responsibilities, need to be studied and reflected upon further.

Authors' contributions

All authors contributed to the concept and design of the study; T.R., A.J., M.B., and G. T. collected the data; T.R., A.J., and G.T. analyzed and interpreted the data; all authors contributed to writing and critically reviewing the manuscript.

Declaration of interests

None declared by authors.

Acknowledgments

We thank the focus group respondents for their contribution to this study. We thank Helga Gardarsdottir, Scott Askin, Solange Corriol-Rohou, and Johannes J. M. van Delden for their contributions in critically reviewing the manuscript. The Trials@Home project has received funding from the Innovative Medicines Initiative (www.imi.europa.eu) 2 Joint Undertaking under grant agreement No 831458. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. 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 here.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.drudis.2022.07.011.

References

1 M. Apostolaros, D. Babaian, A. Corneli, A. Forrest, G. Hamre, J. Hewett, 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 (2020) 779–787.
2 D.B. Fogel, Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: a review, Contemp Clin Trials Commun 11 (2018) 156–164.
3 O.T. Inan, P. Tenaerts, S.A. Prindiville, H.R. Reynolds, D. S. Dizon, K. Cooper-Arnold, et al., Digitizing clinical trials, NPJ Digit Med 3 (2020) 1–7.
4 E.R. Dorsey, B. Kluger, C.H. Lipset, The new normal in clinical trials: decentralized studies, Ann Neurol 88 (2020) 863–866.
5 E.S. Izmailova, J.A. Wagner, E.D. Perakslis, Wearable devices in clinical trials: hype and hypothesis, Clin Pharmacol Ther 104 (2018) 42–52.
6 A. Carter, J. Liddle, W. Hall, H. Chenery, Mobile phones in research and treatment: ethical guidelines and future directions, JMIR mHealth uHealth 3 (2015) 1–8.
7 G. Marquis-Gravel, M.T. Roe, M.P. Turakhia, W. Boden, R. Temple, A. Sharma, et al., Technology-enabled

clinical trials: transforming medical evidence generation, Circulation 140 (2019) 1426–1436.
8 L. Gelinas, W. Morrell, S.A. White, B.E. Bierer, Navigating the ethics of remote research data collection, Clin Trials 18 (2021) 606–614.
9 C. Nebeker, J. Harlow, R. Giacinto-espinoza, R. Orozco-, C.S. Bloss, N. Weibel, Ethical and regulatory challenges of research using pervasive sensing and other emerging technologies: IRB perspectives, AJOB Empir Bioeth 4515 (2017) 266–276.
10 C. Nebeker, R.J. Bartlett Ellis, J. Torous, Development of a decision-making checklist tool to support technology selection in digital health research, Transl Behav Med 10 (2021) 1004–1015.
11 A.J. de Jong, Y. Santa-Ana-Tellez, G.J.M.W. van Thiel, M.G.P. Zuidgeest, S.J. Siiskonen, D. Mistry, et al., COVID-19 and the emerging regulatory guidance for ongoing clinical trials in the European Union, Clin Pharmacol Ther 109 (2021) 1517–1527.
12 M. Anderson, How the COVID-19 pandemic is changing clinical trial conduct and driving innovation in bioanalysis, Bioanalysis 13 (2021) 1195–1203.
13 SwissMedic, SwissEthics. Decentralised Clinical Trials (DCTs) with Medicinal Products in Switzerland. www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/clinical-trials/clinical-trials-on-medicinal-products/publikationen.html. [Accessed July 19, 2022].
14 Danish National Center for Ethics, Section for the Medical Research Ethics Committees. Guidance on Decentralised Clinical Trials (DCT). www.dvmk.dk/~/media/vmk/ansoger/dct/Guidance-on-decentralised-clinical-trials-Version-1-Danish-National-Center-for-Ethics.pdf?la=da. [Accessed July 19, 2022].
15 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. [Accessed July 19, 2022].
16 US Food and Drug Administration. Advancing oncology decentralized trials: learning from COVID-19 trial datasets. www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials. [Accessed July 19, 2022].
17 A.J. Bharucha, A.J. London, D. Barnard, H. Wactlar, M. A. Dew, C.F. Reynolds, Ethical considerations in the conduct of electronic surveillance research, J Law Med Ethics 34 (2006) 611–619.
18 L. Gelinas, R. Pierce, S. Winkler, I.G. Cohen, H.F. Lynch, B.E. Bierer, Using social media as a research recruitment tool: ethical issues and recommendations, Am J Bioeth 17 (2017) 3–14.
19 J. Torous, C. Nebeker, Navigating ethics in the digital age: introducing connected and open research ethics (CORE), a tool for researchers and institutional review boards, J Med Internet Res 19 (2017) e6793.
20 J. Tu, W. Gao, Ethical considerations of wearable technologies in human research, Adv Healthc Mater 10 (2021) 1–8.
21 C.M. Ulrich, G. Demiris, R. Kennedy, E. Rothwell, The ethics of sensor technology use in clinical research, Nurs Outlook 68 (2020) 720–726.
22 V. Braun, V. Clarke, Using thematic analysis in psychology, Qual Res Psychol 3 (2006) 77–101.
23 E.J. Emanuel, D. Wendler, C. Grady, What makes clinical research ethical?, J Am Med Assoc 283 (2000) 2701–2711.
24 A. Tong, P. Sainsbury, J. Craig, Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups, Int J Qual Heal Care 19 (2007) 349–357.
25 United Nations (Statistics Devision). Geographic regions. https://unstats.un.org/unsd/methodology/m49/. [Accessed July 19, 2022].
26 E.J. Emanuel, C. Grady, Four paradigms of clinical research and research oversight, Cambridge Q Healthc Ethics 16 (2007) 82–96.
27 H.G. Eichler, B. Bloechl-Daum, D. Brasseur, A. Breckenridge, H. Leufkens, J. Raine, et al., The risks of risk aversion in drug regulation, Nat Rev Drug Discov 12 (2013) 907–916.
28 C. Wirthumer-Hoche, B. Bloechl-Daum, Current issues in drug regulation, in: M. Müller (Ed.), Clinical Pharmacology: Current Topics and Case Studies, Springer International, Cham, 2016, pp. 19–31.
29 S. Khozin, A. Coravos, Decentralized trials in the age of real-world evidence and inclusivity in clinical investigations, Clin Pharmacol Ther 106 (2019) 25–27.
30 J. Stewart, M.L. Krows, T.T. Schaafsma, K.B. Heller, E.R. Brown, J. Boonyaratanakornit, 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 5 (2022) e2148325.
31 A. Caplan, P. Friesen, Health disparities and clinical trial recruitment: Is there a duty to tweet?, PLoS Biol 15 (2017) 4–7.
32 J. Coyle, A. Rogers, R. Copland, G. De Paoli, T.M. MacDonald, I.S. Mackenzie, Learning from remote decentralised clinical trial experiences: A qualitative analysis of interviews with trial personnel, patient representatives and other stakeholders, Br J Clin Pharmacol 88 (2021) 1031–1042.
33 D.B. Resnik, Informed consent, understanding, and trust, Am J Bioeth 21 (2021) 61–63.
34 T. Swierstra, Identifying the normative challenges posed by technology's 'soft' impacts, Etikk i Praksis 9 (2015) 5–20.

Tessa I. van Rijssel [a,*], Amos J. de Jong [b], Yared Santa-Ana-Tellez [b], Martin Boeckhout [c], Mira G. P. Zuidgeest [a], Ghislaine J.M.W. van Thiel [a], on behalf of the Trials@Home Consortium[1]

[a] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[b] Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
[c] Med Law Consultancy Foundation, The Hague, The Netherlands

* *Corresponding author.*

[1] Website: trialsathome.com.