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Decentralized Clinical Trials: Potentials for Equity in Digital Health

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Abstract. The COVID-19 pandemic has rapidly increased the possibilities for conducting Decentralized Clinical Trials (DCT). This paper addresses the potential for conducting DCT in Denmark and discusses how this potential can improve equity in digital healthcare. From stakeholder interviews, we learned that DCT has the potential to be implemented, as DCT guidelines are in place in Denmark. DCT can potentially improve equal access and inclusion of diverse populations, home administration of medication, retention and compliance, and monitoring of patients and side effects. While DCT has potential in a Danish context, the challenges regarding DCT need to be considered carefully, particularly concerning equity in digital health.

Keywords. decentralized clinical trials; equity; digital health

1. Introduction

During the COVID-19 pandemic, many processes within the healthcare system were forced to be held virtually and remotely. This catalyzed technological optimization and innovation. One such optimization was to extend the possibility of decentralizing Clinical Trials (CTs) and conducting some or all trial activities remotely [1].

In a highly digitalized healthcare system such as in Denmark [2], CTs have been conducted for years with decentralized elements. However, fully decentralized CTs are rare in Denmark where most CTs are hybrid [3].

In Decentralized Clinical Trials (DCT), the trial activities are transferred from clinical sites to trial participants' homes or their proximity. Thus, the trials become diversified and geographically spread out while various technological solutions are being increasingly adapted to facilitate remote or virtual participation [1,3–6].

DCT have been recognized in the literature as an efficient approach to reducing the burden of participating in CTs and for retention. Trial participants save time, resources, and dependence on health professionals because of remote recruitment, e-consent, and monitoring. This may improve accessibility for minoritized populations or populations with rare diseases, who are often underrepresented in CTs. Therefore, DCT have the potential to facilitate Diversity, Equity, and Inclusion [7] of marginalized populations via Personalized Health [8] and improve their health literacy, patient empowerment and autonomy [1,5,6,9–12].

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DCT can facilitate the collection of diverse data from multiple sources, such as digital biomarkers, electronic health records, clinical and demographic data sources and patient-reported outcomes (PRO). Wearables can, for example, provide continuous monitoring of trial participants to rapidly identify adverse events [1,11,13].

In Denmark, regulatory and ethical guidelines are in place on how to conduct DCT. These are formulated by the Danish Medicines Agency (DMA) [14] and the Danish National Center for Ethics (DNCE) [15]. In addition, The European Medicine Agency (EMA) has recently published recommendations for conducting DCT [16], which are valid and applicable in a Danish context. Researchers must consult these three guidelines when initiating and conducting DCT in Denmark.

This paper aims to map the potential for conducting DCT in Denmark as a showcase for other countries to implement and benefit from DCT.

2. Methods: Stakeholder Identification and Interviews

Identifying and selecting relevant stakeholders were complex due to limited practical experience with DCT among researchers in Denmark. In addition, the involvement of multiple organizations and stakeholders in the mapping was complex. These were primary healthcare providers, patient organizations, legal and medical authorities, regional stakeholders, Life Science Industry (LSI), and universities. Approximately fifty stakeholders were identified in the initial selection of stakeholders during a period of three month. Project managers from Trial Nation[2], the Danish regions, and LSI helped identify the stakeholders. Eight of these stakeholders where available and approached for the first round of interviews.

The stakeholder composition is visible in Table 1. All stakeholders have experience with elements of DCT.

Table 1. Stakeholder characteristics.

Stakeholders	Occupation
1	Clinical Operations Leads, Life Science Industry (LSI)
2	Clinical Operations Leads, Life Science Industry (LSI)
3	Clinical Operations Leads, Life Science Industry (LSI)
4	Clinical Operations Leads, Life Science Industry (LSI)
5	Associate Director, Contract Research Organization (CRO)
6	Regional Leader, Good Clinical Practice (GCP)
7	Regional Leader, Good Clinical Practice (GCP)
8	Regional Senior Consultant for Research and Strategy

The interviews were conducted online, individually or in groups of two-three stakeholders from the same organization. The interviews lasted approximately one hour. A semi-structured question guide was used to explore the potential for conducting DCT in Denmark with the stakeholders.

The data was analyzed thematically [17]. The first author and three interns transcribed the video recordings and familiarized themselves with the raw data by reading through it to identify preliminary and emerging themes. From the familiarization, a preliminary thematic framework was developed. Afterwards, the framework was used to recode the raw data material to establish a final thematic framework [17].

[2] Trial Nation is a public-private association established to attract CTs and improve CTs in Denmark.

3. Empirical Findings: Potential for Conducting DCT in Denmark

The empirical findings are preliminary and part of a more extensive mapping of potential and barriers to conducting DCT in Denmark.

3.1. Implementation of DCT in Denmark: DCT Guidelines

The LSI and the CRO stakeholders speak very positively of their experience with the Danish regulatory authorities. They see great potential in DCT implementation in Denmark, as they perceive the Danish authorities as progressive. The LSI stakeholders especially highlight the positive engagement of the DMA and mention that the DCT guidelines can contribute towards more effective implementation. For example, the CRO stakeholder elaborated on a case where the ethics committee rejected a hybrid CT. When she re-applied for the hybrid CT and referred to the DCT guidelines outlined by the DMA, the CT was accepted. From the CRO stakeholder's point of view, the committee had forgotten what was already approved by the DMA in the guidelines.

According to both the CRO, LSI and GCP stakeholders, there is a need for more practical experience and good scientific practice with DCT and hybrid trials in Denmark.

3.2. Recruitment and Consent: Demographic Inclusion, Diversity, and Equity

The CRO, LSI, GCP and regional stakeholders agreed that DCT could improve the inclusion of diverse populations in CT. LSI stakeholder 3, for example, mentions that finding a parking space at the hospital is troublesome for most patients, as well as travel time. The CRO stakeholder and LSI stakeholder 2 explain how DCT can enable broader inclusion of children, as their home environment feels safer and more familiar to them than a hospital. In addition, DCT can eliminate many of the time and practical constraints associated with combining family and work life. The CRO stakeholder further elaborates that age is not perceived as a barrier as many elderly patients can handle their own medicine and health at home and have a positive attitude towards DCT.

The LSI stakeholder 1 explains that while there is an increased possibility for diversity in inclusion, this does not necessarily mean more trial participants but a more diverse sample, and thereby increased equity.

Concerning E-consent, LSI stakeholder 1 explains that it is possible to read an informed consent form on a computer or smartphone from home, and a two-factor authenticator provides a safe way to verify the user identity. The process is simple and safe.

3.3. IMP Shipment, Home Monitoring, and Side Effect Reporting

The LSI stakeholders have experience with trial participants who can manage their medication from home. LSI stakeholder 1 describes his experience with dermatology trial participants, who could receive and manage their medication, as they could confirm that the medicine had been appropriately kept in transit by reading a thermometer. Additionally, an arrangement was made with the courier that they would only leave after the medicine had been quality assured.

The LSI and CRO stakeholders perceive DCT as inherently facilitating better retention and compliance. According to the LSI stakeholders, contact with trial participants is preserved through decentralization, merely redefined. The stakeholders give examples of trial participants who live far away or live with chronic diseases, and they have

experienced that these trial participants are more motivated to remain in the studies as the burden of travelling to hospitals gets lifted. LSI stakeholder 4 references a patient forum, in which patients in standard CT described that their barriers were not from technology but rather transport, parking, taking time off from work, and waiting at the hospital. The technology enabled them to participate in CT more easily.

3.4. Data Management

Lastly, all stakeholders mention using electronic PRO (e-PRO) in their studies, and they highlight the possibility of obtaining objective data via wearables or other devices. These can measure objective data rather than the trial participant's subjective evaluation, where re-call bias is likely to occur. In addition, all stakeholders highlight that the wearables make it possible for trial participants to report adverse effects frequently. Wearables also make it possible to monitor the trial participant closely and in real time.

4. Discussion

Denmark has recently been deemed eligible to conduct DCT by stakeholders from government agencies, CROs, LSI, and technological businesses in the US, which is a frontrunner in DCT [4]. A key argument is Denmark's highly digitalized healthcare system, and supportive authorities [2,4]. The stakeholder interviews point to the regulatory and ethical DCT guidelines developed by DMA, EMA and DNCE as essential for initiating and conducting DCT in Denmark. In other countries, the literature points to a need for more regulatory guidelines for conducting DCT [1,6,18], while attempts have been made to construct such a framework [9]. Furthermore, our findings indicate an increasing possibility for equal access and inclusion for diverse populations, home administration of medicine, retention and compliance, and monitoring of trial participants' safety. These findings comply with international literature [1,5,6,9–13]. However, the literature also raises concerns that DCT can be exclusive to demographic characteristics, such as age, race, socioeconomic status, and rural living with poor internet connection, thereby creating inequity [12]. In Denmark, the general population is advanced users of digital services [19], which supports the argument by stakeholders that DCT is feasible in all age groups. For example, 96 % of the population between 55-74 years, and 78 % of the 75–89-year-olds use the internet frequently [19]. This may serve as an argument for the feasibility of implementing DCT in Denmark.

Furthermore, the literature describes that handling their medication and collecting and reporting data may be burdensome for trial participants and affect retention and safety [6,9,11,12]. Furthermore, ensuring quality and integrity in data when monitoring the trial participant's health data remotely is complex [13,18]. In addition, e-consent and e-signature are not allowed in all countries [12,13,18].

While this paper argues for the potential to implement DCT in Denmark and improve inclusion, diversity and equity, future research should address the challenges associated with DCT and identity pitfalls that complicate equity in digital health in Denmark. Furthermore, the paper addresses the preliminary mapping of the potential for conducting DCT in Denmark. The stakeholders primarily represent the LSI; therefore, we must include a broader composition of stakeholders, such as legal stakeholders, practitioners, patients, and patient organizations.

5. Conclusion

This paper addresses the potential for conducting DCT in Denmark particularly regarding equity in digital health. From stakeholder interviews, we learned that DCT has the potential to be implemented as guidelines are in place. DCT has the potential to improve equal access and inclusion for diverse populations, home administration of medication, retention and compliance, and monitoring patients and side effects. While this is the case, the challenges concerning DCT must be considered, particularly concerning equity.

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