Context Sensitive Health Informatics: AI for Social Good
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Mapping Challenges for Conducting Decentralized Clinical Trials in Denmark

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Abstract. This paper identifies challenges for conducting Decentralized Clinical Trials (DCTs) in Denmark from key stakeholders' perspectives. Challenges concern defining and disseminating DCT activities and implementing recruitment strategies. For remote access to source data and validating endpoints, challenges include quality assurance and data transfer. Challenges for IT systems include data capture, transfer, harmonization, and backup. Challenges are concerned with over/under-reporting when reporting side effects. Documentation and safety challenges occur for Investigational Medical Product (IMP) shipment and home administration. Concerning the surveillance of trial participants' (TP) safety, the principal investigator's (PI) oversight is the main challenge. National working groups are established for selected areas of DCTs.

Keywords. Decentralized clinical trials, telehealth, electronic data capture, patient-centered healthcare, accessibility.

1. Introduction

Denmark is the number one country in Europe for performing Clinical Trials (CTs) if measured per capita, and with a highly digitalized healthcare system, DCTs are not a new phenomenon [1,2]. Decentralized Trials & Research Alliance (DTRA) defines DCTs as *a clinical trial utilizing technology, processes, and/or services that create the opportunity to reduce or eliminate the need for participants to physically visit a traditional research site for some or all trial activities* [3]. DCTs are rarely fully decentralized, mainly hybridized with decentralized elements [2].

DCTs have been recognized in the national and international literature to have the potential to facilitate patient empowerment, and improve equity, diversity, and inclusion by enabling remote recruitment, e-consent, data collection, and monitoring. This can reduce logistical and geographical barriers to participation in CTs and facilitate collecting and integrating diverse data and knowledge from multiple information sources and technology [1,4–9]. There are regulatory and ethical guidelines in place for DCTs from The Danish Medicines Agency (DKMA) [10], The European Medicine Agency (EMA) [11], and The Danish National Center for Ethics [12], which support the

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implementation of DCTs in Denmark. DKMA has established a DCT dialogue forum with Trial Nation, where relevant stakeholders have discussed matters concerning DCT since 2021 [10]. Nevertheless, there is a need for operational guidelines and experiences within DCTs in Denmark. While the benefits of implementing DCTs are manifold, this paper seeks to map and address challenges for DCTs to optimize the current framework for DCTs in Denmark and internationally.

The work presented in this paper is conducted as part of a national project, *PACT: Patient-Centered Decentralized Clinical Trials*. This public-private partnership between Trial Nation, the five Danish regions, and seven life science companies is funded by the Innovation Fund Denmark, 2022-2026.

2. Methods

We identified and selected central stakeholders with experiences within DCTs through Trial Nations network. The stakeholders represented patient organizations, primary healthcare practitioners, legal and medical authorities, regional stakeholders from hospitals and clinical trial sites, and life science companies.

In the fall of 2022, we discussed operational experiences and challenges for DCTs with eight stakeholders through three individual interviews and two interviews with multiple participants. We held interviews online using a semi-structured interview guide. Interviews identified preliminary themes as part of an exploratory process. In March 2023, we conducted a physical workshop with 22 stakeholders at a DCT dialogue forum, none of whom participated in the interviews. The workshop aimed to explore additional challenges for DCTs and decide which DCT areas to prioritize moving forward. During the workshop, we divided participants into groups. We used a 'DCT roadmap' displaying DCT areas defined in DKMA's guidelines [10] to facilitate the exercise, cf. figure 1. Participants placed notes with challenges and possible solutions on the DCT roadmap and ranked the areas using color codes (green = action, yellow = next steps, red = not immediate). The PACT partners validated the prioritization in December 2022 and May 2023 and planned actions accordingly.

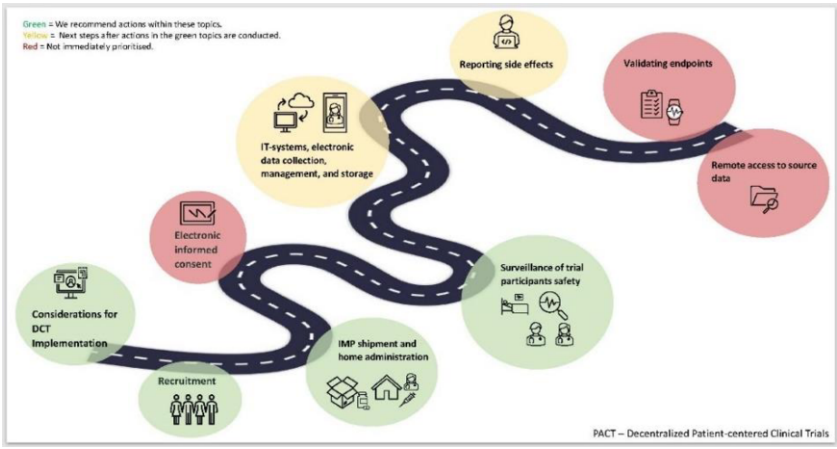

Figure 1: DCT road map

The interviews and workshop were audio and video recorded. The data was transcribed verbatim, an initial coding process was constructed, and the data was coded systematically using thematic analysis [13]. The analysis identified a thematic framework, which is presented in the following results section.

3. Results

Challenges were identified across all DCT areas, varying in character and complexity. Four areas were prioritized for action based on stakeholders' perspectives on what currently works in telehealth, CTs, or hybrid DCTs and urgent needs, cf. figure 1.

The primary consideration for **DCT implementation** is that not all CTs are eligible for decentralization. It is important to justify the use of decentral elements in CTs, the purpose of the study, the safety profile and development phase of the IMP, and the trial population. In addition, there is no unified agreed definition of DCT [1] and there is a lack of awareness about DCTs in the general population and the professional environment, and consequently, limited practical experiences. A working group was established under the PACT project to address the identified challenges. The working group has developed a short document to describe and disseminate knowledge about DCT simply and tangibly [14]. Other barriers related to DCT implementation were the inevitable flexibility in a hybrid study design, with variable preferences and possibilities for physical and virtual participation, which compromise data integrity and cross-country comparisons. Lastly, stakeholders identified a lack of resources in terms of workforce and budget to conduct DCTs as a challenge.

Decentralized recruitment initiatives, including online recruitment, recruitment through databases, remote recruitment at local pharmacies, and general practitioners (GPs) are already in place in some Danish regions. The PACT project established a working group to investigate how scaling up of existing tools and procedures can stimulate overall patient recruitment across CTs in all Danish regions. A persistent challenge in recruiting participants across countries is the variability in study design, differences in legislation and the infrastructure for conducting DCTs.

Telehealth initiatives, such as courier services, medicine boxes, drone transport, are in place for **IMP shipment and home administration** in Denmark. Stakeholders were mainly concerned that documentation and safety would be compromised if participants managed and stored their own medication and recorded their own data.

The primary concerns for **surveillance of TP's safety** at home are that the PI oversight is compromised, as trial activities are delegated to third parties (district nurses, local pharmacies, and labs), multiple sites, and IT systems. Although the PI is responsible for the CT, they must rely on the competence of third parties. In addition, it is complex for the PI to get a holistic view of the CT and TPs. The issue of contracting between different sites when trial activities are delegated to third parties makes contracting complex and timely, as there are various interpretations of the legislation in the healthcare sector in the five Danish regions.

PI's **remote access to decentral source data** and remote monitoring complicates the use of standards for quality assurance and assessing compliance with Good Clinical Practice (GCP). Decentral source data in TPs' homes or proximity is complicated because data transfer is done by proxy (TPs, district nurses, or primary practitioners). Data transfer is possible with devices that are processed directly into an electronic case report

form (eCRF). This means that the PIs cannot access source data remotely, compromising the **validity of endpoints** and the ability to follow GDPR.

Reporting of side effects is also challenging to monitor in DCTs since over – or underreporting may occur. Applications exist to validate endpoints, but the stakeholders deemed none of them adequate.

Proper training of health providers and TPs, explicitly focusing on documentation and administration of medication, may be the solution to proper surveillance of TPs and home administration, in line with ensuring proper training for pharmacies and GPs to handle their decentral trial activities. In addition, a suggestion was establishing a cross-regional legal task force to help formulate specific guidelines, protocols, standards, and contracts for PIs and the IT systems to ensure proper handover and PI oversight. Specifically, for GCP, there is a need for a detailed description of procedures for quality assurance in DCT protocols.

The possibilities of **IT systems, electronic data collection, management, and storage** are manifold: online video consultation, devices, wearables, apps, electronic Patient Reported Outcome (e-PRO), and Electronic Data Capture. The multiple applications and other technical or systematic solutions can facilitate the collection of a significant amount of data from multiple sources. This complicates regional collaboration, and especially PI oversight concerning backup data, data capture, IT system collaboration, harmonization and data sharing. Lastly, IT systems and technology need to be user-friendly to ensure that TPs and health providers can use them.

4. Discussion

This paper identifies challenges in all areas of DCTs by key stakeholders. It highlights challenges and possible solutions related to four prioritized DCT areas in Denmark: perception of DCT, decentralized recruitment, IMP shipment and home administration, and surveillance of TPs' safety, cf. figure 1.

The literature supports our results, addressing barriers to defining DCTs and whether a CT ought to be fully decentralized or hybrid [7]. Specific procedures or lab tests do not allow for remote measurement, and IMP shipment may be complex for certain experimental medicines [5,7,8]. Central distribution of IMP directly to TPs without local site dispensing is prohibited in some countries [4], but this is not the case in Denmark.

The literature also addresses how the transfer of activities from study personnel to TPs can be burdensome for TPs and compromise patients' safety [8]. The stakeholders also raised concerns regarding virtual communication, which can weaken trust and impose isolation [8]. Issues of PI oversight and delegation of activities to third parties were also addressed in the literature, as PIs may be held responsible for non-compliance by third parties [5], which likewise were a primary concern among the stakeholders. Lastly, the literature highlights barriers to harmonizing, capturing, and transmitting data across geographies, IT systems, and regulatory frameworks. These challenges also include ensuring data quality and integrity, particularly when validating endpoints, monitoring, and storing data remotely. When patients are responsible for taking measurements and entering source data electronically, it can compromise the data's validity, objectivity, and accuracy [4].

Our study possesses limitations. First, the results reflect the current perspectives of stakeholders, which can change with the rapid development of DCTs. Stakeholders' perspectives may also vary according to their own experience and interest; therefore, all

DCT areas may not have been addressed. Lastly, we cannot be sure to have included all important stakeholders in our mapping, as this was done as a networking activity. The perspectives of TPs, and not merely patient organizations, are important to include in future studies. A beneficial and unique element is that the public-private partnership between regions, authorities, and private companies is transparent and shares interests.

5. Conclusion

The paper has identified challenges to conduct DCTs in Denmark, through interviews and workshops with key stakeholders. Challenges occur in all areas of DCTs, for remote access to source data and validating endpoints (quality assurance and data transfer), IT systems, electronic data collection, management and storage (harmonizing, back up, capturing, and transfer of data), and reporting side effects (over – and underreporting). The PACT project has established national working groups for challenges related to the perception of DCT (definition and dissemination), decentralized recruitment (implementing initiatives), IMP shipment and home administration (documentation and safety issues), and surveillance of TP safety (PI oversight). These were considered urgent in optimizing the current framework for DCTs in Denmark, and further working groups will be established to remedy other challenges to conduct DCT in Denmark.

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