INNOVATION CENTRE DENMARK

DECENTRALIZED CLINICAL TRIALS

UPGRADING DENMARK'S CAPACITY TO CONDUCT NEXT GENERATION CLINICAL TRIALS THROUGH KNOWLEDGE EXCHANGE AND INSIGHTS INTO THE LATEST DEVELOPMENTS IN THE US

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UPGRADING DENMARK'S CAPACITY TO CONDUCT NEXT GENERATION CLINICAL TRIALS

When speaking to American stakeholders within the life science industry, the message is clear: Decentralized Clinical Trials (DCTs) are the future. The US has been working with DCTs for more than 10 years and there is already a burgeoning ecosystem supporting and facilitating this trend.

"The future of medicine is digital, personalized, data-driven and delivered directly to the patient"

Sunny Kumar, partner at GSR Ventures[1]

A thriving ecosystem requires investigators, patient demand, supportive public authorities, an industry, investors, and access to technology, resources and infrastructure. This begs the question: how do you best foster an ecosystem that supports this next generation of clinical trials?

In this report, we will shed light on the American ecosystem within DCTs and highlight important lessons for Danish stakeholders. The hope is that these insights and learnings can inspire Danish stakeholders working to upgrade Denmark's capacity to conduct DCTs and help accelerate this adaptation.

Innovation Centre Denmark in Silicon Valley & Boston

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INTRODUCTION

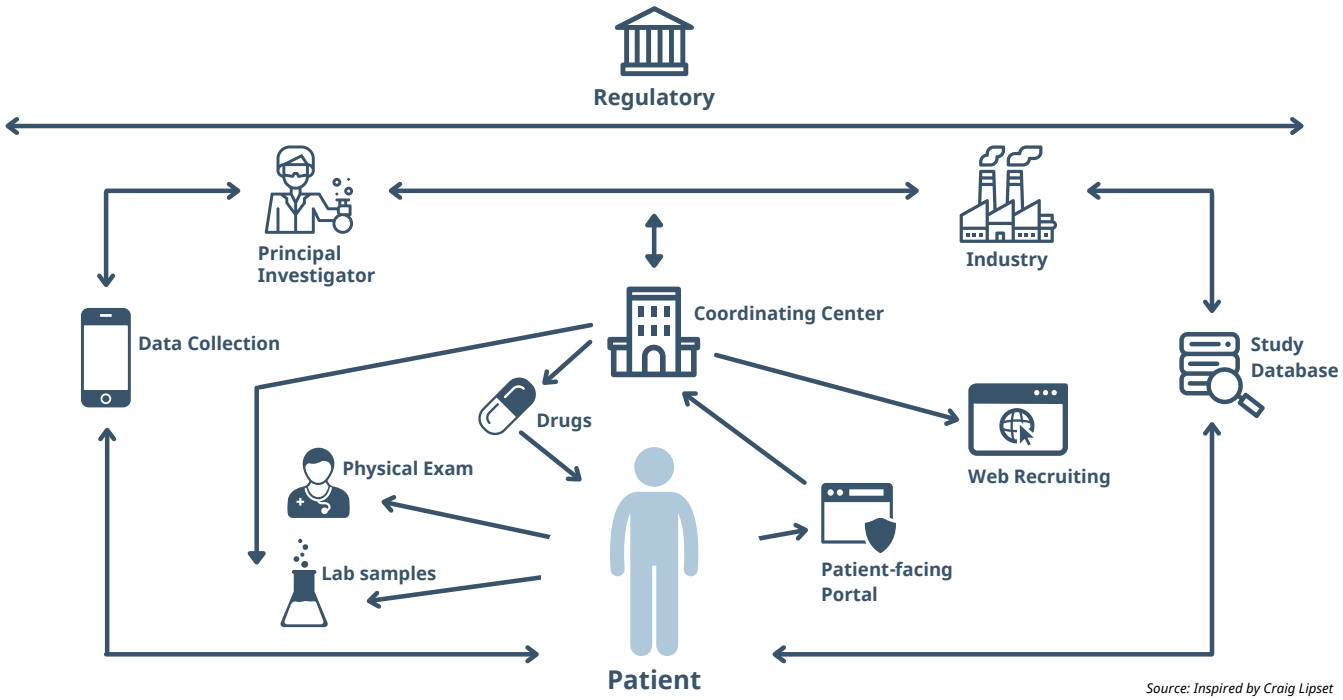
The modern digitalized world is changing the face of clinical trials. In traditional clinical trials, nurses and physicians perform physical tests at hospitals and investigation sites but now trials are increasingly moving into the patient's home. With new opportunities provided by telemedicine, electronic data collection systems, remote monitoring, direct-to-patient shipments, wearables, and other medical devices, clinical trials will continue to evolve in this digital age of research.

Clinical trials are accelerating when it comes to both digitization and decentralization. These trends have been long underway but they have gathered speed during the Covid-19 pandemic as remote capabilities are more important than ever. Moreover, many perceive decentralized clinical trials as a possibility to expand equity in healthcare, as patients - regardless of mobility and physical distance to the hospitals - can participate in trials. This potentially ensures a broader representation and facilitates the inclusion and retention of the patients.

Decentralized clinical trials have many advantages. However, there are also challenges and important considerations that need to be addressed in order to ensure the best conditions for clinicians and patients. It involves the entire ecosystem around a decentralized trial: investigators, patient demand, supportive public authorities, an industry, investors, and access to technology, resources, and infrastructure.

This report focuses on insights and experiences from the US that can help facilitate and upgrade the development of decentralized clinical trials in Denmark.

THE ECOSYSTEM AROUND A DECENTRALIZED CLINICAL TRIAL



Source: Inspired by Craig Lipset

WHAT IS A DECENTRALIZED CLINICAL TRIAL?

From virtual, to remote, to direct-to-patient, to decentralized, to software-enabled, to siteless, to mobile-enabled, to modern, to flexible, to digital, to 21st-century clinical trials, - there is no shortage of terms being used to describe a new kind of clinical trial that is no longer confined to the site of investigation. To make it simpler, this report refers to these trials under one of the most commonly used terms; decentralized clinical trials (DCT).

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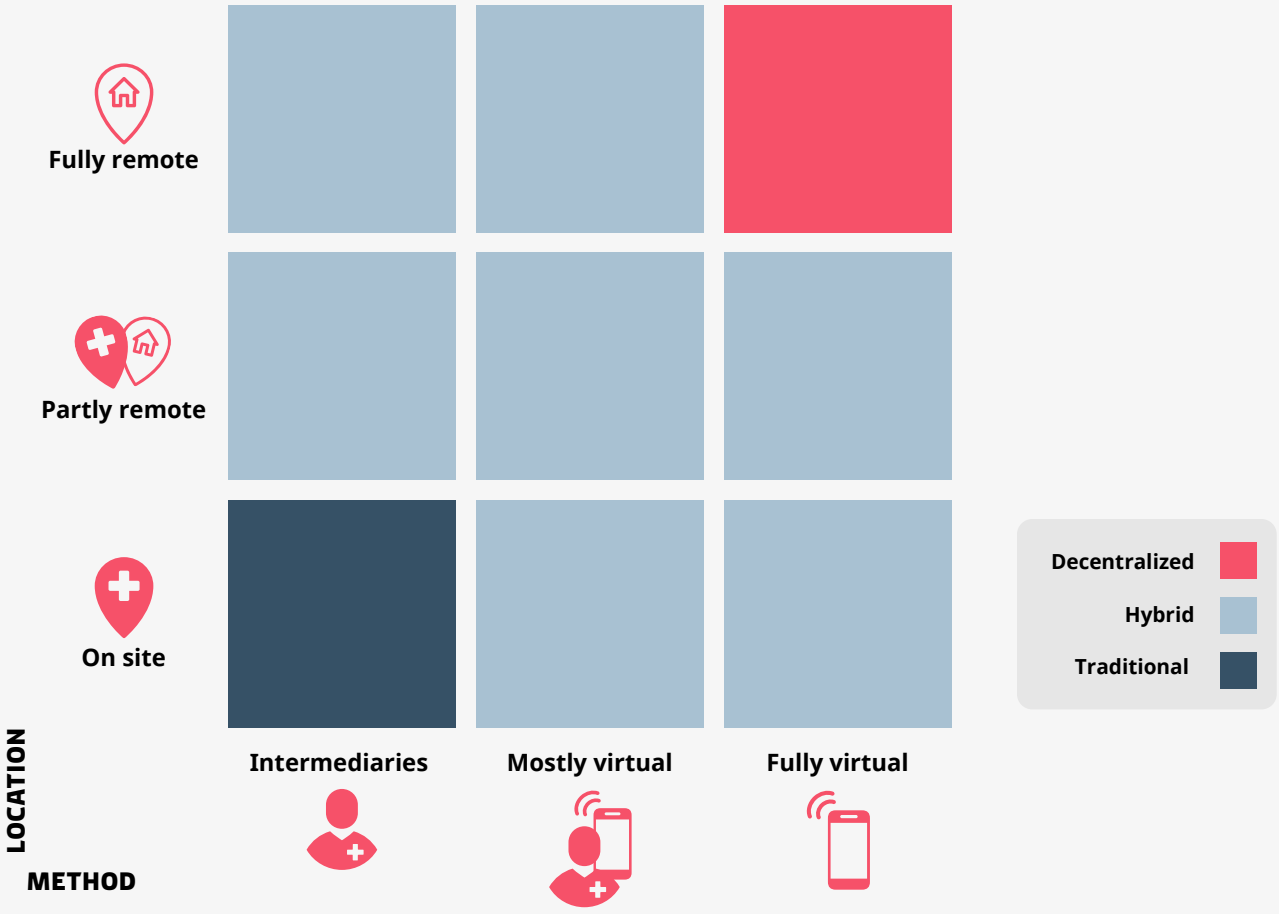
DCTs refer to a type of trial where physical visits to the investigation sites are no longer necessary. This development is enabled by new digital solutions and processes for both data collection and patient care. There are two dimensions to this change. First, it means that the location is changing from a conventional investigation site to the patient's home or other accessible locations. Second, tests and data collection are no longer only performed by doctors and nurses; instead, wearables and other data collectors send the information straight to the investigators. In some instances, patients also collect samples themselves using self-help kits.

In short, decentralized clinical trials refer to a model that has both remote and virtual elements to it (see Figure 1). While the purest and rarest form of DCT is a study that is both fully remote and fully virtual, the term is often used for many types of hybrid trials that are partly remote and/or »

"With decentralized clinical trials, the trials are coming to the patient instead of the patients coming to the trials"

Rajesh Dash, MD, Stanford Medicine speaking at ICDK webinar

FIGURE 1: WHAT IS A DECENTRALIZED CLINICAL TRIAL?



Source: Inspired by Leo Innovation Lab[3]

partly virtual. In some trials, a traditional investigation site is needed for some tests. Similarly it is not always possible or indeed desirable to conduct all communication and patient communication digitally. Sometimes, just having follow-up visits done via video will ease the burden on participants.

It is therefore important to note that there is no optimal place on the chart (see Figure 1). Instead a point that is reiterated by stakeholders working with DCTs is that every trial should be evaluated and designed with a fit-for-purpose approach.[2]

Generally, we can observe a movement away from traditional clinical trials conducted at conventional investigation sites towards more hybrid decentralized trials where parts of the trial take place in the patient's home. Indeed, some stakeholders foresee a new generation of hybrid trials where patients can choose how remote/virtual they want their trial participation, adapting the trial to patient preferences and patient journeys.


MEIJI
TECHNO
JAPAN

DESIGNING A DCT TRIAL

Stakeholders operating in the DCT arena emphasize the need to consider the design of the trial from the beginning. In short, they advise not to attempt to retrofit a traditional trial into a DCT if possible.

There are many factors to consider when determining whether a trial is suitable to be conducted as a DCT: trial population, trial phase, disease burden, product type etc. If the trial is deemed suitable, the next step is to consider which elements of the study could benefit from de-centralization: identifying and recruiting patients, consent, clinical assessment, remote monitoring and wearables DTP, labs nurses etc.[4]. Moreover, it is also useful to proactively map and consider data flow and communications.[5]

An all-or-nothing approach is not necessary for designing and implementing a DCT[6]. Instead, one can use a partially decentralized (hybrid) approach if applicable. In the US, stakeholders emphasize the benefit of implementing fit-for-purpose designs[7]. This involves choosing a device that is fit-for-purpose meaning that it supports the intended use case[8]. But fit-for-purpose design involves more than just choosing a device. The approach requires industry sponsors and investigators to consider every trial element and wheth-er decentralizing fits and supports the purpose of the study.

Engaging all stakeholders early on and often in the design phase might ensure a smoother process and roll-out and save time in the end. First, it is important to include patients early on (see chapter 5 on patient experiences) as well as regulatory agencies (see chapter 3 on regulatory frame-work). In general, it is helpful to engage with and think through the roles of all the different stakeholders involved. For instance; what should the role of nurses be and what tasks can they perform in the DCT in question?

CLINICAL CONSIDERATIONS

Decentralizing a clinical trial impacts greatly on the sponsor and investigators involved in the trial - from their interaction with patients to their choice of endpoints. This creates both opportunities and challenges. From personal and face-to-face contact with trial patients, DCTs require investigators to interact with patients remotely in a way that efficiently addresses patient engagement and keeps retention high.

Sponsors and investigators also need to design or adapt the trial so that it fits the DCT format. This transforms both tasks and delegation (e.g. study coordinators, visiting nurses etc.) as well as study operations (e.g. procedures, policies, endpoints)[9]. Depending on the type of trial, study phase etc. some trials might be more or less sponsor/investigator-driven. Therefore, the following clinical considerations might in some cases sit with sponsors, happen in a close dialogue between sponsor and investigators, or be purely investigator-directed. However, these clinical considerations will often be similar regardless of who is in charge of designing the trial.

DELEGATION & PROTOCOLS

Decentralizing a clinical trial entails moving certain activities away from a central site and into the patient's home. However, this does not infer a scattered organization with many isolated entities. Instead, one can often observe a centralized infrastructure supporting decentralized trials[10].

"The decentralized site model hinges on a single pivotal site managing patients within their usual environment by leveraging telemedicine, technology and local care providers"

Sommer et al. (2018), Contemporary Clinical Trials Communications[11]

Experts argue that it is necessary to consider the differences between a traditional trial and DCT when developing procedures for delegating responsibilities to investigators, sub-investigators, and local providers[12] and recommend talking to regulators early on[13]. This type of delineation of delegation is key to ensure adequate oversight of the trial. As DCTs differ in many ways from a traditional trial, the delegation and protocol design should reflect this.

Steve Cummings, Director of the San Francisco Coordinating Center, has emphasized the need to simplify protocols for DCT[14]. Even if some trials cannot completely be converted into siteless trials, there are many potential reductions in the number of assessments and visits to trial sites. Speaking at the Operationalize Decentralized Clinical Trials 2021 conference, Cummings and other experts also agreed that it is necessary to design a DCT protocol from the outset instead of trying to adapt an existing trial protocol to a DCT framework.

Because many of the functions are performed by the patients themselves, it is necessary to design the protocol from the patient's point of view[15] (see chapter on patient perspectives). In the same vein, some experts argue that the goal should be to develop protocols that allow participants to make choices, e.g. to decide whether they want to participate at a site or remotely[16]. This suggests that some choices as well as some tasks could be delegated to the patient, meaning less control for the investigator.

"Sponsors and investigators will have to become more comfortable with having less control over studies"

Dorsey, Kluger, Lipset (2020), Annals of Neurology

This is in line with early adopters who argue that "sponsors and investigators will have to become more comfortable with having less control over studies, in part by embracing data capture strategies that maintain high quality regardless of where the data are acquired. Many activities will happen outside research clinics and in environments where they have less control, and participants have more control"[17]. This might require additional training as many stakeholders – sponsors and investigators alike – only have limited experience with remote monitoring and assessment. Even so, a recent McKinsey survey indicates that investigators' comfort with remote technologies has increased as result of the COVID-19 pandemic[18].

FROM HUMAN CONTACT TO TECHNOLOGICAL TROUBLESHOOTING

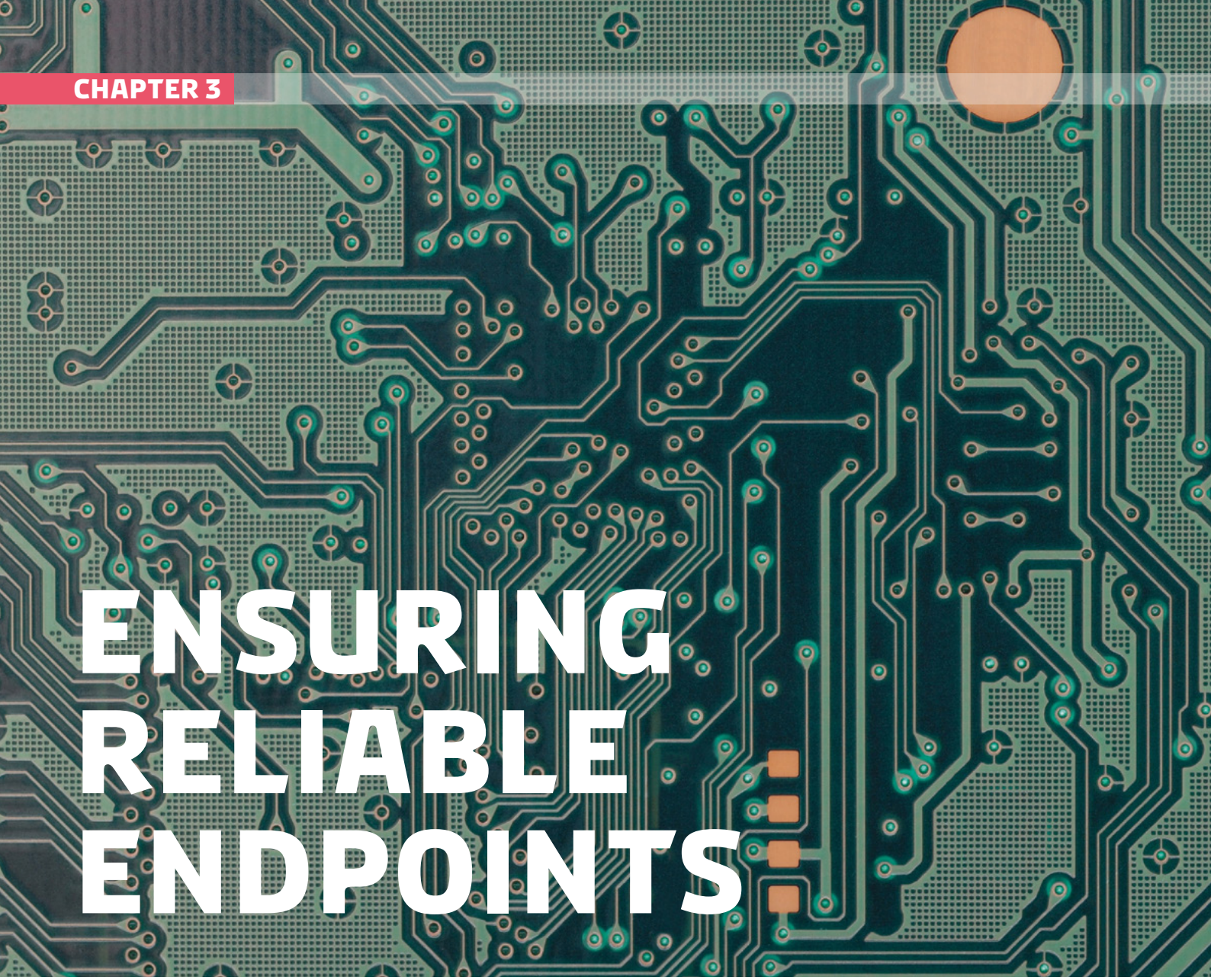
In DCTs, some of the traditional tasks like administering drugs and measuring endpoints are no longer done by investigators on-site. Instead, the drug is delivered by courier and self-administered or administered by a nurse. Consequently, DCTs require less in-person interaction with patients.

To some investigators, this can be a challenge as they might feel that they lose contact and feeling with their patients. Nonetheless, there are various solutions depending of the scope and scale of the study. Video conferences might be utilized more frequently and it ensures, in many ways, a more continuous follow-up rather than the episodic follow-up at traditional sites.

While investigators can be more engaged on screen, hiring good coordinators becomes key for larger studies. As Rajesh Dash, PhD MD from Stanford School of Medicine explains in an ICDK webinar: “Highly engaged and engaging coordinators are essential for quality in the consent and onboarding of patients in a medication intervention trial. Especially in a DCT design, where this is the patient’s only personal touchpoint. This has been reported as one of the most positive feedback points from patients”.

Nurses also play a large role in DCTs. In the US, a company like PCM Trials have specialized in Certified Mobile Research Nurses (CMRNs); that is, registered nurses who are specifically trained in supporting DCTs. They have thus completed training in Good Clinical Practice, home-visits and the specific technology utilized by the sponsoring company. One point to consider is that including more nurses in DCTs also means more operators having access to patient data, which is important when thinking about data integrity (see chapter 7 on technology).

In general, investigators have noted that they use increasing amounts of time setting up technologies and linking devices to specific users as well as troubleshooting problems with malfunctioning devices[19]. This underlines how DCTs are digitalizing the investigator’s role and tasks.



CHAPTER 3

ENSURING RELIABLE ENDPOINTS

Digital technology is also revolutionizing our ability to collect more specific data points and biomarkers, and these novel digital biomarkers and endpoints are integral in DCTs[20].

In traditional trials, endpoints are often investigator-delivered whereas DCTs involve more patient-reported and/or device-captured endpoints by taking advantage of these new technologies. This development alters both what can be measured and how it can be measured.

Involving patients in the trial design also leads to new considerations. As Craig Lipset, MD and Co-Chair of the Decentralized Trials Research Alliance argues, "giving participants the ability to decide on site-based or remote engagement during a clinical trial will require the development of endpoints that are resilient and agnostic to location"[21].

While some tests are difficult to perform at patients' home, private monitoring opens up for more continuous measurements during the course of the patient's daily life instead of discrete events[22]. This means richer data, the ability to detect rare events as well as information from patients who cannot self-report (e.g. infants or people with dementia). However, there are also some concerns. One challenge involves ensuring that aggregate measurements are coming from the person being observed; that is how to attribute data[23].

Digital measures can give new insights into patients' health. DHTs often have sensors that automatically collect location-based contextual factors related to patients, providing investigators with information and insights into possible underlying determinants of observed endpoints[24]. This leads to ethical concerns about the amount of data collected, with questions regarding the degree to which you need a prior theory/reason for collecting the data. While it is important to ensure patient safety and privacy, constraints might also limit discoveries that could potentially be beneficial to patients.

As stated above, decentralizing a trial affects the measurements being used. This naturally leads to the question of how we can justify, validate, and verify endpoints in a DCT. In short, the justification of an endpoint relates to the patient »

"Why are we compromising for snapshots when we can have the whole movie?"

Amir Lahav, speaking at the Operationalize Decentralized Clinical Trials 2021 conference

» and entails evaluating whether the endpoint is a clinically meaningful measure. Digital monitoring opens up space for novel endpoints, but the process of evaluation and justification will be similar in traditional and decentralized clinical trials.

Validation and verification of DHTs relate to the technology, and whether the technology is adequate and useful. Digital Medicine Society has developed the modular evaluation process "V3" for verifying and validating technologies[25]. Here, verification entails a systematic evaluation by manufacturers to make sure that the technology works. Validation means that the technology accurately measures what it claims to measure. In the V3 framework, this is further split into analytical validation and clinical validation, recognizing that measures from digital tools must not only be analytically sound but also clinically useful to the defined population in clinical trials. Recently, the European Medicines Agency endorsed the V3 framework[26].

In 2019, the FDA approved a primary endpoint from actigraphy sensors, which measured a symptom associated with interstitial lung disease. Similarly, the EMA approved a secondary endpoint from a wearable sensor that measured a symptom associated with Duchenne Muscular Dystrophy. By approving this, both devices were verified[27]. In studies of drug effects, this development is historical[28]. But it is also a development that benefits sick patients, who would otherwise have to travel great distances to sites for tests. This was the reality for patients with Duchenne's prior to the technological advances[29].

Standard endpoints might still be an important part of DCTs. However, it is clear that there is a trend towards more accompanying digital endpoints.

RESOURCES ON ENDPOINTS AND DCT

Novel endpoints:
The Clinical Trials Transformation Initiative (CCTI) has defined a pathway for developing novel endpoints. You can access the resources here

Existing digital endpoints:
Digital Medicine Society has developed an open-access crowdsourced library of digital endpoints. You can access the library here

Guide to remote monitoring:
Digital Medicine Society has developed a playbook on foundational processes for remote monitoring across clinical research, clinical care, and public health. You can access the playbook here

PATIENT EXPERIENCES

While the regulatory and clinical setup is essential for conducting successful DCTs, patient experience is arguably the most important factor to consider. DCTs offer a patient-centric approach with more flexibility for the patient compared to traditional trials.

Many patients face indirect costs of trial participation such as long transportation time to trial sites, having to take time off work, getting access to day care etc. DCTs can reduce this burden by offering a more efficient and flexible option. Early evidence from patient and caregivers confirms a positive attitude towards DCTs and the flexibility they offer, and these studies also show both high enrollment and high retention.

While most patients say that the remote option provides them with better access to their attending physician, there are also various concerns. Some patients miss the personal interaction offered by face-to-face meetings. To some, home visits might also feel invasive. Another challenge is the digital skills required as patients have to use digital devices and mobile platforms. This might exclude certain people who are not equipped to work with or comfortable with these types of technologies.

There are many questions to consider when designing a DCT that makes the patient feel secure and included. As several DCTs and hybrid trials have already been conducted in the US, we can begin to collect and analyze patient experiences from this region.

GIVING PATIENTS ACCESS TO CLINICAL TRIALS

In DCTs, trials are not confined to a specific geographical location, instead participants can take part in clinical trials remotely.

Therefore, outreach can be web-based and take place via social media, advertisements, and various online groups. Leveraging electronic or web-based enrollment strategies can ease outreach and enrollment, which improves access to clinical trials, thereby increasing diversity and inclusion. In theory, remote trials should thus make it possible to reach a wider patient pool. But challenges remain.

In practice, it has proven difficult to reach a diverse group of participants through web-based recruitment. The realization is that no one size fits all. In other words, advertisements and outreach efforts must be tailored to those persons that sponsors aim to reach. This starts with recognizing diversity and understanding the cultures and communities that exists within the targeted population groups.

"Understanding the target population's needs, values, and preferences, as well as their barriers to participation, is key to designing culturally and linguistically appropriate clinical trial recruitment material"

El-Toukhyn, at Virtual Clinical Trials: Challenges and Opportunities 2019 Workshop[30]

Any material used for recruitment has to be designed with culture and linguistics in mind to extend the reach to underserved groups. This may be less of a challenge in a Danish context, where the population is relatively homogenous compared to the United States.

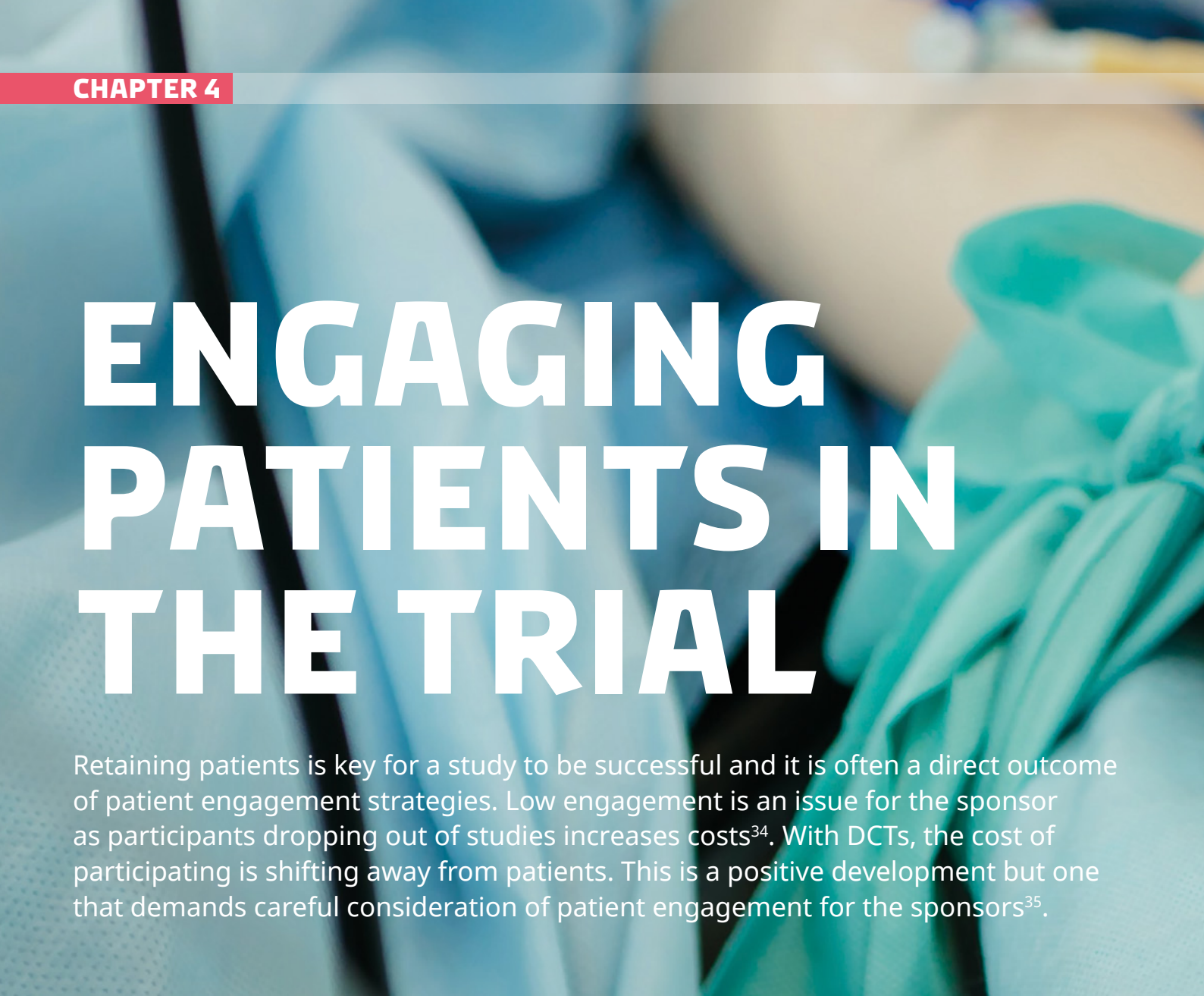
While a web-based recruitment strategy has clear advantages, it cannot always stand alone. It is challenging to reach certain underserved groups, which is necessary to ensure diversity and inclusion in the trials. To overcome this, it is key to recognize that some communities are skeptical of or even distrust the health care system. But it is also a question of overcoming the digital divide - an issue that is prevalent in communities of lower socioeconomic status as well as in the older population. While it is often about not having access to digital infrastructure, it can also be about lacking digital abilities.

Community-based recruitment is emphasized as one solution to these issues[31]. This often happens through local organizations where sponsors actively build trust from the ground up to overcome skepticism and understand the extent of the digital divide. In the US, faith-based organizations are highlighted as an entry point. While these challenges may be less prevalent in Denmark, the lessons learned may be key to sharpen enrollment procedures generally, e.g. by using senior organizations. They may also help ensure that the use of digital health technologies does not exacerbate existing health inequities or create new ones[32].

"Community- and provider-based recruitment may be more successful than strictly web-based recruitment"

Cummings, at Virtual Clinical Trials: Challenges and Opportunities 2019 Workshop[33]

To sum up, electronic recruitment has the potential to reach a broader and more diverse pool of participants. However, it has to be tailored to the target population. To not exclude certain groups and to enhance diversity and inclusion, employing both a web-based and community-based recruitment strategy can be beneficial. The above points are key learnings from the US and they may be used to refine enrollment strategies on a larger scale.



CHAPTER 4

ENGAGING PATIENTS IN THE TRIAL

Retaining patients is key for a study to be successful and it is often a direct outcome of patient engagement strategies. Low engagement is an issue for the sponsor as participants dropping out of studies increases costs[34]. With DCTs, the cost of participating is shifting away from patients. This is a positive development but one that demands careful consideration of patient engagement for the sponsors[35].

It is no longer the patients that must spend time and money to be on site and participate, but sponsors that foot the bill and send devices, drugs, and even health care personnel to the homes of participants.

"If it is too cumbersome for the patient, the trial will go off the rails"

Jen Horonjeff, speaking at the Operationalize Decentralized Clinical Trials 2021 conference[36]

First of all, the protocol and study design determine patient engagement. Studies have to be designed to ensure comfort, convenience, and confidentiality of patients. Otherwise, patients may become frustrated and demotivated, causing them to drop out of the trial. How to retain patients through engagement should be considered early on in the trial »

» planning phase. Including patients in the trial design process can be highly beneficial, because the set-up becomes patient-informed[37]. Fit for purpose is a guiding principle for designing and conducting DCTs that is often emphasized among sponsors and DCT operators[38]. The principle states that there is no standardized way of doing a DCT, which calls for consulting participants early on and throughout each trial to enhance patient retention. This is key, because patient engagement is highly dependent on the specific trial as the patient journey differs vastly, depending on the drug and the illness. In the US, there are various patient organizations that provide insights and share their experiences with the pharma industry. These include patient organizations related to specific disease areas and umbrella organizations like the patient-owned co-op Savvy cooperative.

One example of a patient informed study design revision comes from a study sponsored by the M.J. Fox Foundation. Based on patient feedback, researchers revised the language used for recruitment and engagement in order to make it more meaningful to the participants. Otherwise, participants felt like they were carelessly "inputting data onto their phones or computers"[39]. Importantly, patient engagement should also be assessed throughout and after the trial[40]. In practice, unforeseen issues may arise that require a protocol amendment. However, because the planning and preparation phase is long, protocol amendments can occur before the study officially starts, when you bring patient insights to the table – saving both time and resources, while strengthening participant engagement[41].

"Patient engagement is a verb not a noun – you do it continuously"

Jen Horonjeff, speaking at the Operationalize Decentralized Clinical Trials 2021 conference[42]

SHARING DATA WITH PATIENTS

In the US, studies have shown that giving patients access to their data enhances patient retention. A survey conducted by Clinical Trials Transformation Initiative (CTTI) shows that 98% of the 400 respondents preferred to view their data in real time[43]. This reflects "a broader cultural shift from paternalism to partnership in medicine and research"[44].

Patients want to be involved in the process to a higher degree. It makes them feel like partners as opposed to clinical trial subjects[45,46].

Moreover, patients often have many different providers and want to avoid repeat tests. Giving them access to e.g., recent blood sample results might rectify this. For very sick patients, it can be a major hassle to have both treatment and trial-related tests. Since they cannot stop their treatment, they will drop out of clinical trials if these are too cumbersome. For such patients, flexibility in terms of test-taking and use is preferred and increases patient retention[47].

However, data sharing is not always convenient from a scientific perspective. To avoid bias and to ensure constant drug effects, there will be blind periods where patients are unable to see their data. Here, it is key not to leave the participants in the dark, but carefully explain to them why data sharing is not an option[48]. In other words, maintaining a dialogue with the participants is important as it helps build trust, which in turn helps ensure that they do not drop out of the trial[49].

THE HOME AS A SITE

While many DCT patients in the US indicate that they prefer the flexibility and comfort offered by home visits, other patients do not feel comfortable opening their homes to mobile nurses or other health care personnel. This displays health struggles to other inhabitants, neighbors, and the wider community, which may violate their sense of confidentiality.

There might also be a feeling of shame in having to show your home to strangers. Particularly for participants in low-income households, it can be both inconvenient and uncomfortable to open their home. If such considerations are not accounted for, patient retention may be difficult. Again, patient insights are key to a successful DCT[50]. To accommodate some of these concerns, some consider the possibility of other no-site locations such as community health centers, local community physicians, pop-up clinics/mobile sites etc.

In general, dialogue and feedback are common factors, when it comes to ensuring patient engagement. They help ensure that a trusting partnership is built and maintained between sponsors and participants, leading to a higher chance of a successful trial. While engagement strategies and revisions to the protocol prior to and during the trial were highlighted, it is equally important to collect feedback once the trial is over. Although each trial is unique, patient insights may be generalizable across trials, e.g., when it comes to learnings regarding use of devices. While quantitative feedback has many advantages, various stakeholders argue that qualitative feedback should also be collected. Patient experiences cannot always be understood through surveys or statistics. In-depth interviews, focus groups, or advisory boards are examples, where each patient can be heard and deeper reflections are revealed.[51]

A PATIENT-CENTRIC APPROACH TO CLINICAL TRIALS

Hybrid trials might be a potential solution to some of the abovementioned challenges, because there is scope for personalizing the trial according to the individual participant's needs and constraints[52].

But this also raises a discussion about consistency and the ability to properly measure the effect of a drug, if the context of measuring varies. It is a question of patient choice against modalities/end points[53]. Some investigators therefore argue that patients should have a voice in study design, but that it is necessary to carefully consider the consequences of these choices.

Donna Cryer of Global Liver Institute defines a 'quality clinical trial' from a patient perspective as: "...one that generates the minimal amount of credible, replicable, and evaluable data needed to answer meaningful questions with the least time and cost burdens on participants"[54]. Moreover, it is key to recognize that cost and time have different meanings to different population groups. Otherwise, sponsors disregard challenges faced by underserved communities and unknowingly exclude them. Experiences show that success requires strong support for the participant at home; both in regards to clinical oversight, engagement, as well as technical support given the frequent use of unfamiliar technology.

HOW TO BEST ENGAGE UNDERSERVED COMMUNITIES?

ICDK participated in a workshop focused on best practices for patient engagement. The workshop was hosted by Ricky Fairley who shared patient experiences from the black community in the US, but her points are relevant across population groups.

No matter the degree of personalization and decentralization, underserved population groups - often of lower socio-economic status - find DCT participation insurmountable. They struggle with fundamental and pressing issues on an everyday basis which must be resolved first.

"Financial assistance, household support and mental health counselling are priority areas of logistical assistance"

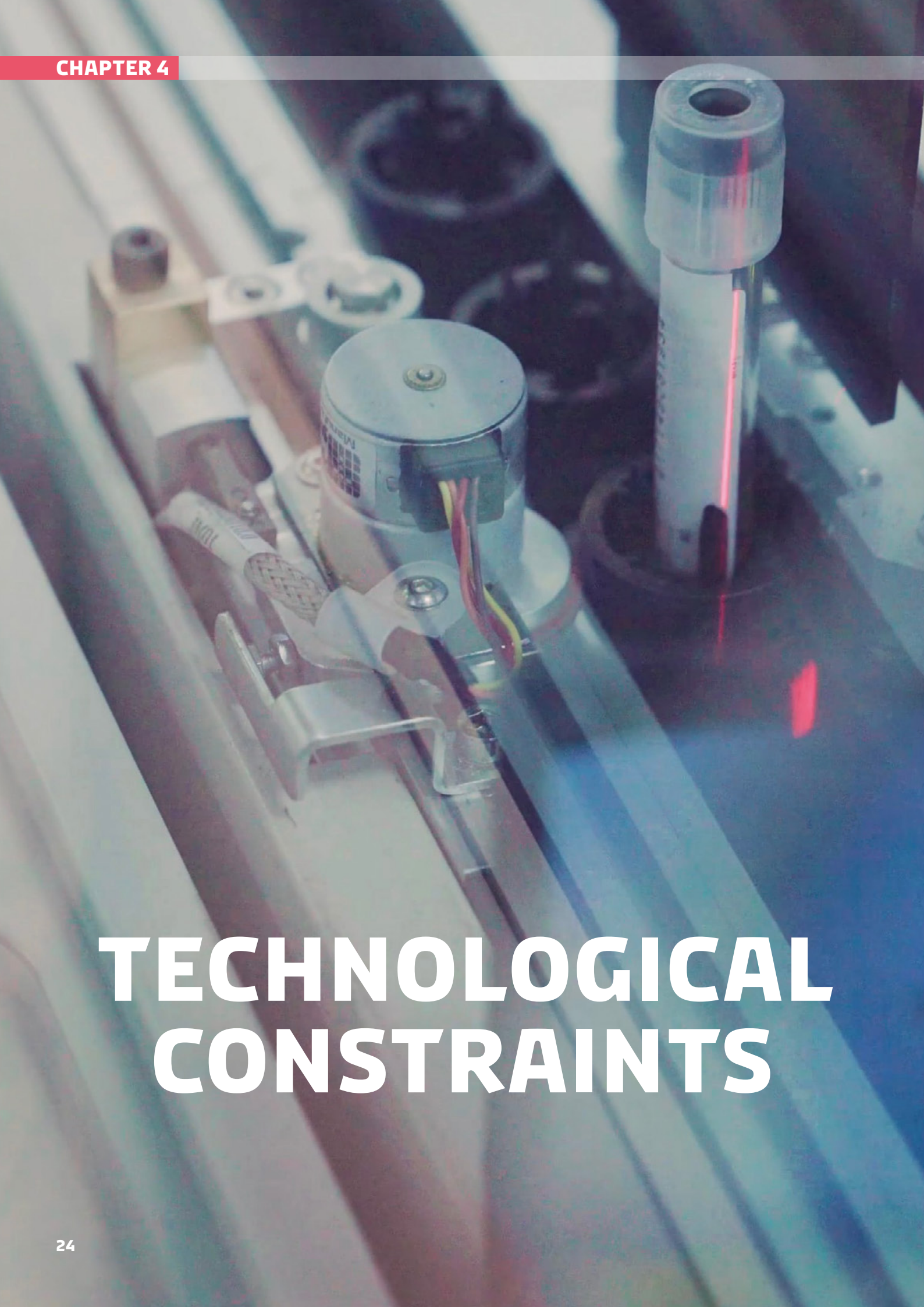
Ricky Fairley, 2021, speaking at Engaging Patients in Decentralized Clinical Trials: Best Practices Workshop

In other words, these groups have no surplus of time. And what other participants may view as minor hurdles, such as understanding and using a device, doing video-calls with a clinician, or having a mobile nurse visit are overwhelming and costly, because they take time away from family and work.

In the workshop, it was therefore emphasized that sponsors need to consider how to ensure equity in access to and participation in DCTs. Personalizing and giving patients choices as a solution is not always viable. It requires a commitment to understanding participants in their everyday home-setting, because that is also where they now physically take part in the trial. Fundamentally improving patient experience thus requires a keen awareness of the lives and challenges of underserved groups.

"Health equity is a daily habit"

Ricky Fairley, 2021, speaking at Engaging Patients in Decentralized Clinical Trials: Best Practices Workshop



TECHNOLOGICAL CONSTRAINTS

The use of technology is a condition of most DCTs, which places demands on the participants. A key consideration is how best to adapt to the patients' technological constraints and give technical support to patients, making sure that the use of technology is not too burdensome. Moreover, it is important to avoid bias in the participant pool because of technological constraints faced by specific population groups. This responsibility arguably falls on the shoulders of sponsors and DCT operators[55].

Each DCT is unique and therefore the requirements patients meet in terms of technological abilities might vary. Age can be a factor when it comes to technology, which can cause problems for trials seeking older participants. To convince less tech-savvy patients to participate, it is a possibility to conduct a hybrid trial rather than a fully remote trial. For instance, on-site elements or home visits may shift the burden of figuring out technology to trained health care personnel instead of the patient.[56] Some studies use a Bring-Your-Own-Device (BYOD) strategy where participants can use their own device, which they are already familiar with. While this can alleviate some patient concerns, it can potentially create problems with reliability between different devices as well as access to them.

While the digital gap is shrinking in the US, it is still significant. When it comes to smartphone ownership and access to broadband, groups of lower socio-economic status, older generations, and those with lower education attainment are still lacking behind[57]. In the US, the racial and ethnic make-up of underserved groups produces an additional bias. Because African Americans, Latinos, and other non-Caucasians are highly represented in groups of low income and low educational attainment, they are technologically constrained to a higher degree than other population groups.

This produces a technology-induced bias in the participant pool unless strategies are implemented to ensure inclusion of underserved groups. An example of such a strategy is the community-based recruitment method previously mentioned[58].

While the question of underserved groups may be different in a Danish context, US experiences show that attaining a diverse participant pool requires information about the technological constraints of underserved groups. Using a fit-for-purpose principle regarding technology might be a way of avoiding excluding certain groups.

INDUSTRY EXPERIENCES

The industry is an integral part of a DCT. A trial can be conducted by a sponsor; typically a pharmaceutical company, or a Contract Research Organization (CRO) that specializes in conducting trials on behalf of clients. Often it is the sponsor that intends to conduct a DCT, but CROs have also suggested it to the sponsor in some cases. Common for both CROs and sponsors is that they are seeing an increased demand for DCTs prompted by the COVID-19 pandemic.

"'Help me DCT my study' was the response after COVID started"

Amy Bohn, Director, DCT Operations DCT Operations at BayerSpeaking at Operationalize Clinical Trials Conference 2021

WHY DECENTRALIZE?

There are various reasons for why industry actors choose a decentralized format as well as a multitude of considerations about how to go about it.

For the industry, cost reduction is obviously a consideration[59]. However, many DCT elements may add direct costs to the study in the near term and enabling flexibility for participants may require certain redundancies. It is hoped that indirect impact on patient recruitment will help offset some of these costs in the long run. Generally, it is instead the impacts on experience, access, and diversity that are highlighted as main motivations. Many US stakeholders particularly emphasize convenience and accessibility to trials as advantages[60], although some stakeholders have experienced enrolment of participants to be harder than it seems[61]. Reaching participants digitally comes with its own set of challenges which need to be carefully thought through (see chapter 4 on Patient Experiences). Another advantage is access to more and better data that can provide sponsors with a more accurate picture of a drug's effectiveness, as opposed to discrete measures that are more sporadic in nature.

Overall, decentralization presents sponsors and CROs with many advantages; due to the optimized trial process, more, cheaper, and better medicine should be the outcome. However, as emphasized by several stakeholders, the benefits will take time to realize[62]. Because the trial format is changing, new challenges naturally arise and the industry has to adapt to a new way of operating. Moreover, while the overall costs might be lower in the long run, personalizing trials also means that there will be a longer list of services offered to participants. Speaking at the Operationalize Decentralized Clinical Trials Summit, Rebecca Jackson, Senior Manager Clinical R&D Innovation and Novel Modalities IT at Johnson & Johnson[63] advised CROs and sponsors to keep this in mind, because it may be more costly and logistically demanding than expected.

"Technology will make every study better, faster, and cheaper all at once... the benefits of technology will include reducing participant burden, speeding up medical product discovery and development, and significant cost savings. But these benefits will be realized over the course of decades".

Noah Craft, CEO of Science37Virtual Clinical Trials: Challenges and Opportunities 2019 Workshop

Another reason for decentralizing is that the industry has the opportunity to do trials within a broader spectrum of diseases. If conducting trials becomes cheaper and it gets easier to reach and engage hard-to-reach patients, this could be an incentive for the industry to broaden their trial scope to rare diseases and more specific patient groups concurrently with the development of more personalized medicine.

CHAPTER 5

WHICH STUDIES?

There are many factors to consider for determining whether a trial is suitable to be conducted as a DCT: trial population, trial phase, disease burden, product type etc., and some studies might be more of a natural fit with the DCT format.

According to Amy Bohn, Director of DCT Operations at Bayer, most DCT activity occurs in phase 3 trials. This is due to the fact that once phase 2 is completed, the safety profile is in place. Therefore, activities that are remote in nature are safer to perform. Moreover, phase 3 trials tend to be bigger in scale, which means they are more suited for DCTs[64]. However, Craig Lipset, Co-Chair of the Decentralized Trials Research Alliance emphasizes that sponsors should also be "investing in validation of new biomarkers in early research phases" for phase 3 DCTs to be possible[65].

Experience from the US shows that retrofitting is seldom a good solution. An enhanced focus on trial design fitting the needs of participants increases the trial complexity, which comes on top of regulatory, logistical and technological challenges[66]. As mentioned in chapter 4 on Patients Experiences, a trend is personalizing and tailoring the patient journey to each participant of a trial.

Often, it will not be the entire trial that is decentralized but particular elements: enrolment and recruitment, consent, clinical assessment, medication administration, lab test and imaging, remote monitoring etc. In the US, there are companies that specialize in helping sponsor companies »

"Interventional clinical trials have made good use of virtual or direct-to-participant methodologies when digital tools are incorporated into the trial design from the beginning rather than when a traditional clinical trial, with all of its complexity, is later modified to incorporate digital tools"

Simcox, Virtual Clinical Trials: Challenges and Opportunities 2019 Workshop

» and CROs evaluate what sort of trials and trial elements are the best fit for decentralization. An example is the company Health Pals which has developed a medical AI platform to optimize clinical trial design. Basically, the company uses AI to evaluate which elements can be decentralized in the clinical trial process from a clinical perspective[67]. At Health Pals, they also offer this service for trials that are not phase 3 which shows the evolving nature of DCTs.

A hands-on suggestion from US stakeholders is to do DCTs within therapeutic areas where telemedicine is already used extensively. This will ease the process for sponsors and CROs when learning how to operate DCTs[68]. For instance, cancer is a difficult area due to less independence in the process than other illnesses. Another key consideration is that decentralization requires some degree of centralization[69]. Some elements, like investigators or coordinator labs may be beneficial to keep centralized to fully realize the advantages of decentralization[70].

"It requires a fair amount of centralized infrastructure to support a decentralized clinical trial"

Vanessa Gertsen, VP of Study Operations at Care Access speaking at the Operationalize Decentralized Clinical Trials 2021 Conference

When it comes to the implementation of technology, it is important for sponsors and CROs to have a strategy for how to handle the data flow. Different data formats and operating systems might interfere with data flows. This is described in detail in chapter 7 on technology. Again, it is a matter of planning. For instance, Kimberly Hawkins, Global Head of Clinical Project Operations at Sanofi Genzyme, suggests mapping out data flows, technologies, and how they interaction[71].

INTERNAL STRATEGY: CHANGE MANAGEMENT

Decentralizing clinical trials is a major undertaking and the industry has to adapt to a new way of operating for the benefits to be fully realized.

Trials are complex, whether they be traditional or decentralized but importantly, they are complex in different ways. Therefore, many US stakeholders, both CROs and sponsors, underline change management as a vital internal strategy to employ in this process.

Change management refers to the process of continually renewing an organization's direction, structure, and capabilities to survive and succeed in a highly competitive and continuously evolving business environment[72]. Research shows that failure often happens when change is poorly managed: "poor planning, monitoring and control, lack of resources and know-how, and incompatible corporate policies and practices"[73].

The challenges and opportunities of a DCT are vastly different than those of traditional clinical trials and this development is a large change to manage. In practice, it requires more of sponsors and CROs to find the right stakeholders, navigate in regulatory frameworks on different levels, figuring out logistics, and implementing technology. In an ICDK webinar, Juliet Hulse and Noolie Gregory from the CRO Syneos emphasize that everyone has to work in a new way. While DCTs seem excellent in theory when discussing their potential with sponsors, their implementation is hard and often requires an organizational re-structuring across the system[74].

Similarly, Darcy Forman from the CRO Science 37 reiterates the importance of not going back to traditional protocols and retrofitting. Instead, she advocates creating a DCT strategy that fosters holistic change management. More specifically, she also mentions pre-planning, mapping out who you will work with[75].

EXTERNAL STRATEGY: STAKEHOLDER COLLABORATION

While internal strategies such as change management are crucial, it is equally important to engage in external strategies.

Stakeholder collaboration has been identified as one of the most important external strategies for ensuring a successful DCT. Both CROs and sponsors underline that the key factor for good stakeholder collaboration is to reach out early on[76].

The list of relevant stakeholders includes the FDA, IRBs, health care personnel, PIs, and sites. When it comes to regulatory agencies, the FDA recommends that DCT sponsors approach regulatory authorities early in the process. This ensures a smoother process and is the best premise for FDA approval of a drug or medical device.

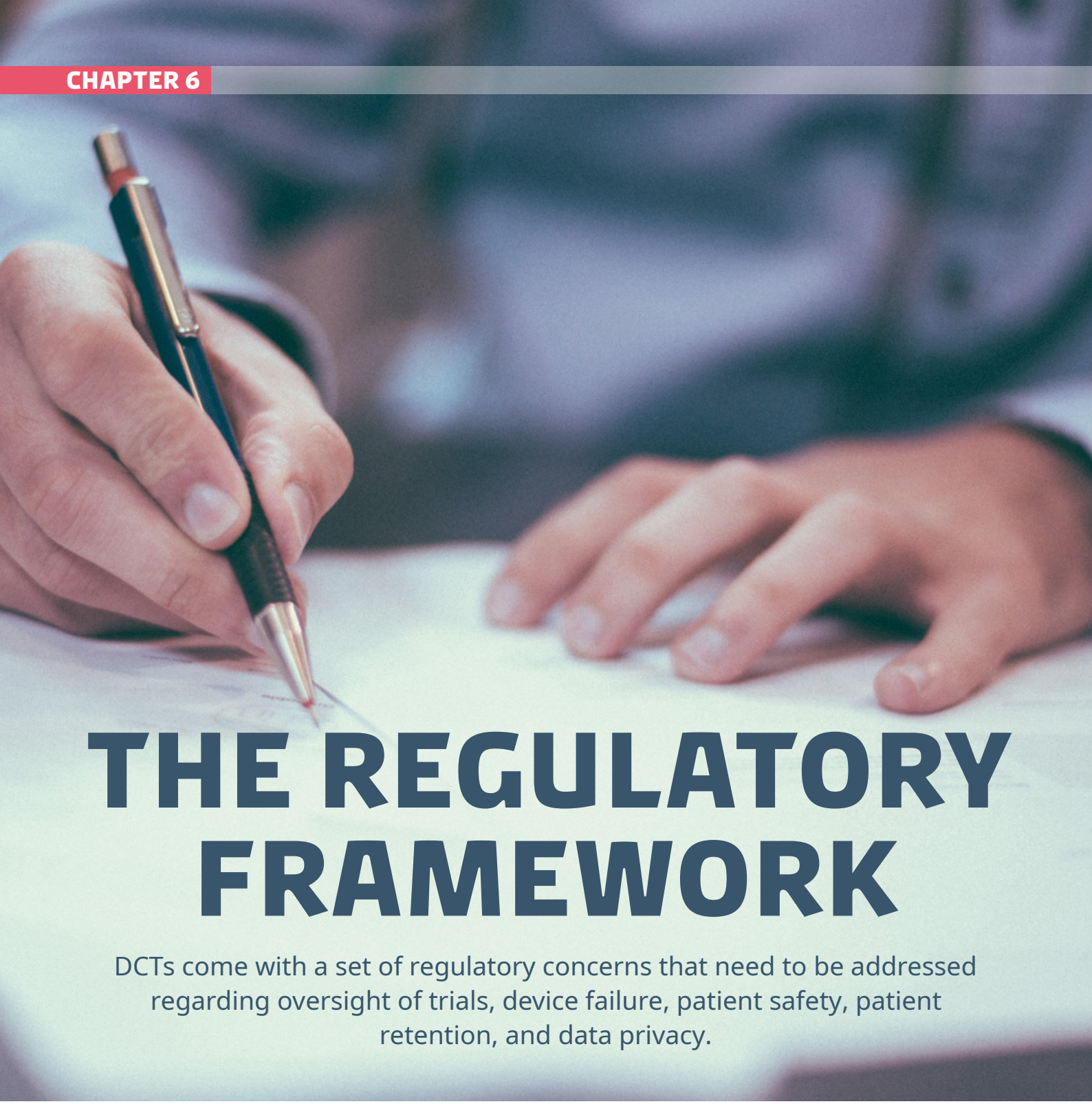
In collaboration with a CRO or sponsor, health care personnel, PIs, and sites often have to change how they operate. The rules of the game are different and therefore the roles and responsibilities of all these actors have changed. Darcy Foreman from Science 37 particularly recommends reaching out early on as it also allows time for educational training elements. This is needed in some DCTs depending on the skillset and abilities of health care personnel and other stakeholders.

Although sites are seen as belonging to traditional clinical trials, there are cases where it makes sense to have several remote sites in a DCT. For instance, it can be important not to overburden sites that are used to operating with traditional trial elements. However, it is also not necessarily a solution to find the capabilities elsewhere as that takes business away from the sites who in turn risk closure. Instead, it is a matter of thinking how else site capabilities may be used in DCTs[77].

ADVICE FROM CROs

- Focus on phase 3 trials, but invest in early phase research
- Collaborate with stakeholders early on and align expectations
- Ensure patients are involved in study design
- Start from scratch with protocols and processes (change management and fit-for-purpose)
- Be prepared to adapt operations
- Include educational training elements
- Map out data flows beforehand to ensure systems and data formats are aligned when integrating different types of data from DHTs
- In some cases, it is useful to do a proof of concept study internally in the CRO as a way to convince clients of the effectiveness of the trial design

CHAPTER 6



THE REGULATORY FRAMEWORK

DCTs come with a set of regulatory concerns that need to be addressed regarding oversight of trials, device failure, patient safety, patient retention, and data privacy.

While there are many advantages to DCTs, there are also regulatory challenges and concerns that need to be addressed regarding oversight of trials, device failure, patient safety, patient retention, and data privacy. This begs the question of how much central legislation is possible and necessary and if there is a need for greater flexibility to better support this fast-moving and evolving way of conducting clinical trials?

While the US system has some regulatory advantages when it comes to DCTs, it is still a complicated matter to conduct a DCT in the US. The sheer size of the system and the multitude of actors operating on multiple levels of governance complicate the process. Particularly, regulatory disconnects between technology and health care, state-specific legislation, and the logistics of DCT operations are pain points.

Nonetheless, the US has made many advances in the regulatory scene and this chapter explains the organizational structure and highlights the advances and challenges the US is facing in this area.

ORGANIZATION

There are three organizational levels when it comes to regulation of DCTs. On the federal level, the Food and Drug Administration (FDA) is the central regulatory authority when it comes to health care in the US. On top of federal regulations, it is also important to consider state legislature, which varies by state. Lastly, on an institutional level, the Institutional Review Boards (IRBs) implement FDA regulations and oversee clinical trials, ensuring that these are conducted ethically.

Federal level: FDA

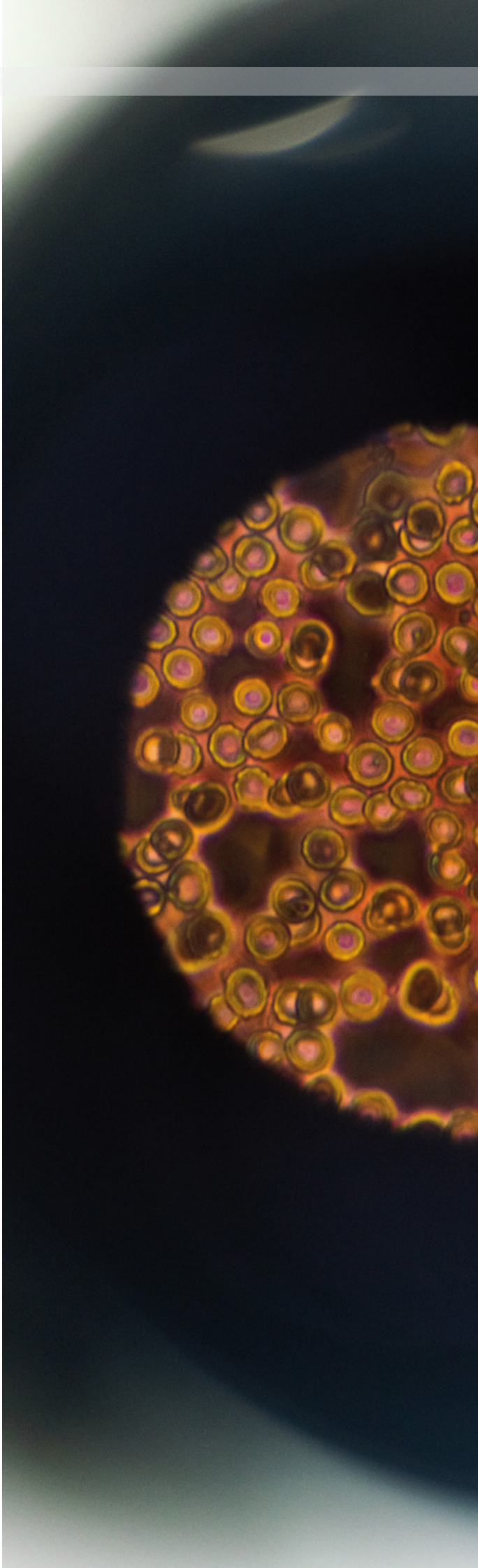
The FDA is the key authority in the US when it comes to the regulation of medicine, medical devices and software as well as data and privacy associated with this. They also regulate ethical conduct in clinical trials involving human participants[78]. When carrying out a DCT, it is crucial to know these regulatory areas if the results are to be validated by the FDA. The regulators are particularly mindful that DCTs must conform to existing norms and expectations with regard to both data integrity and participant safety.

The FDA is at the forefront of regulation regarding DCTs. In 2019, they made history by approving a primary endpoint in trial measured by wearable device.

The FDA recommends that DCT sponsors approach regulatory authorities early in the process. This ensures a smoother process and is the best premise for FDA approval of a drug or medical device. »

"The approval shows that the FDA is recognizing the power of remote monitoring"

Amir Lahav speaking at the Operationalize Decentralized Clinical Trials 2021 Conference



» But who to contact depends on the type of clinical trial. For drug evaluation trials, it is the Center for Drug Evaluation & Research (CDER) or the Center for Biologics Evaluation & Research (CBER), but for medical device evaluation it is the Center for Devices & Radiological Health (CDRH). When a clinical trial is decentralized to some extent, it will likely involve both drugs and medical devices. Consequently, sponsors have to seek advice with several parts of the FDA and it is therefore key to be aware of which health authorities to contact or seek guidance with.[79]

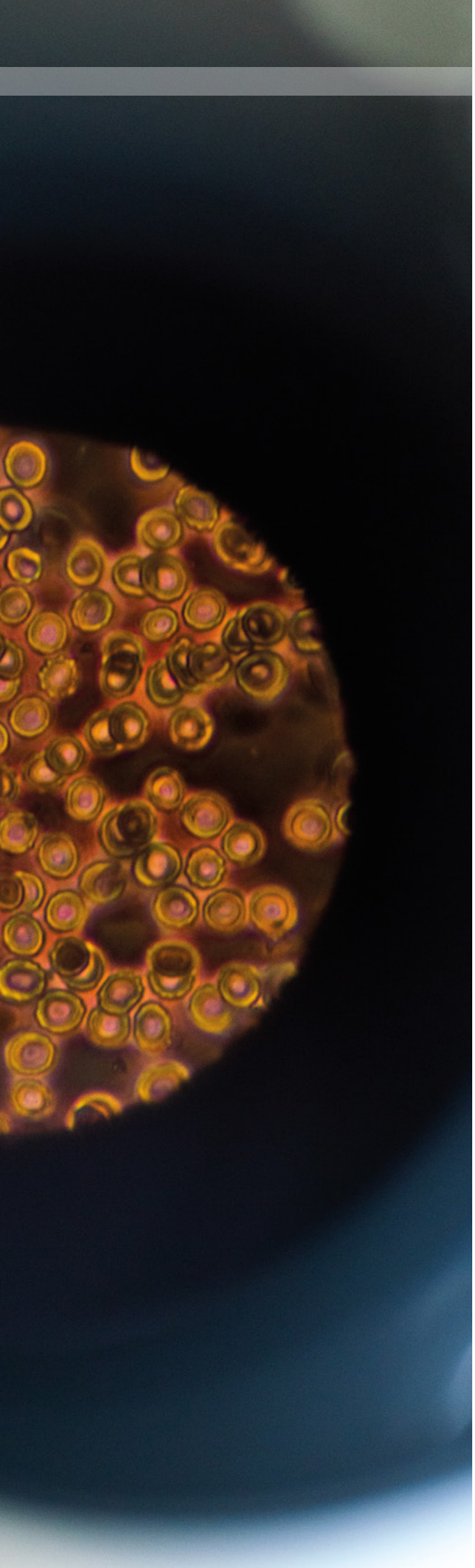
Because DCTs touch on several regulatory areas which fall under different FDA centers[80], there can be disconnects in the legislation. For instance, some stakeholders interviewed for this report mention a regulatory blind spot when it comes to the use of DHTs in clinical trials.

Historically, efforts to regulate digital health have been spread across FDA Centers. But in 2020, the unit regulating medical devices and software, CDRH, established a platform to align all digital health efforts. The role of this platform, named the Digital Health Center of Excellence (DHCoE) is to act as an advisor to CDRH in matters related to "regulatory reviews of digital health technology". [81]

While it is the CDRH that makes the final decision when it comes to approving or rejecting medical devices and software, the DHCoE should make it easier to navigate the regulatory cross field of technology and health[82,83]. Some of the key learnings for Danish stakeholders working with the regulatory aspects of DCTs are thus to ensure a clear overview of the different legislative offices and to facilitate communication between these.

State level

In the US, state-specific laws may impact DCTs. Although less relevant in a Danish context, this area might still provide important learnings when working across borders. For instance, sponsors in the US found that they need to be aware of the roles of trial personnel and telemedicine laws when working across state lines. Investigators and delegated health care personnel must be licensed to work in the home states of the trial participants. One of the advantages of DCTs is that you can span larger geographical areas, however, this can also be a challenge. In each state, involved licensed health care personnel must be at hand which means that employing a single team of trial personnel to work across the US is not always sensible. Rather, it can make sense to have a team in each state or to choose to work with investigators with medical licenses for all states where participants may be recruited. Secondly, differences in telemedicine laws are important to be aware of as they allow for medicine to be administered based on virtual consultations, which is necessary for the execution of some DCTs[84]. »



Institutional level: Institutional Review Boards

While the FDA is the supreme authority when it comes to medical regulation and ethical standards, it is often the Institutional Review Boards (IRBs) that implement ethical standards and oversee that both studies and investigators live up to GCP and other clinical standards set by the FDA[85].

IRBs are explicitly tasked with ensuring ethical conduct within research that involves human subjects. In some instances, these types of boards are also called Independent Ethics Committees (IECs). The FDA defines an IRB/IEC as " An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocols and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects"[86].

IRBs specifically focus on protecting clinical trial participants when it comes to safety, welfare, and their rights. In that sense, an IRB can be viewed as an ethical guard dog that implements FDA regulations and ensures that clinical trials live up to the principles of Good Clinical Practice. As these are very broad, the IRBs have a lot of power in how they interpret and implement rules.

The authority held by an IRB allows it to accept, reject, and demand changes to research projects and clinical trials[87]. They do this by monitoring and reviewing trials prior to their beginning as well as periodically during the project. In this way, the IRBs are on the ground communicating with sponsors and investigators on a running basis. In our interviews with investigators in the US, we got the impression that the IRBs often interpret the ethical guidelines quite strictly, ensuring high ethical standards in US clinical trials.

Most institutions or organizations that conduct research involving human subjects work with an IRB to ensure that the research meets ethical standards. For large clinical trials, there may be several IRBs involved. This is potentially cumbersome as what is acceptable to one IRB may not be acceptable to another. FDA legislation and guidelines serve to align IRBs across the US. However, IRB members have different prerequisites for evaluating research projects, which may cause irregular evaluation of research projects and differences in interpretation across IRBs.[88]

DCTs might offer an advantage in this regard; the potential for fewer physical research sites leads to fewer IRBs. Less uncertainty, simpler communication, and increased flexibility to make protocol changes are thus some of the positive effects of encountering a less crowded web of IRBs.[89]

Decentralizing elements can add complexity to the conduct of clinical trials. However, as regulators and sponsors learn and build the regulatory landscape that protects data, patients, and enables an easier and better trial process, they might also uncover opportunities within the existing system.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CENTRAL REGULATIONS

Good Clinical Practice (GCP)
The FDA operates under the Good Clinical Practice (ICH GCP)[90], which is an "international ethical and scientific quality standard" for clinical trials with human participants. These principles should be adhered to if data from a clinical trial are to be submitted to regulatory authorities for approval.

Some sponsors, investigators, and other health care actors have questioned whether the ethical and scientific guidelines for traditional clinical trials can be directly applied to DCTs. As a consequence, the Good Clinical Practice principles were updated in 2018 to reflect digital elements in the trial process. A recently published research article shows that investigators and sponsors are generally content with how the latest guidelines consider the increasingly digital landscape within clinical trials[91].

However, the report also flags some areas of concern that may need further revision. These include principles and topics addressing the implementation of systems that ensure "quality, providing medical care by qualified physicians/dentist, protecting confidentiality and privacy, obtaining informed consent, and documenting and storing information". The stakeholders also highlight a need to revise the principles on sponsor oversight with the trial process. However, the needs for revision highlighted above were never flagged by a majority of stakeholders in absolute terms, but only in relative terms compared to other sections, topics, or principles of the report.

Digital Health Technologies (DHT)
While legislation on DHTs exists, FDA regulation does not directly address the use of DHTs in clinical trials and the DHTs used in clinical trials do not need to be approved by the FDA for marketing. However, for drug approval, substantial evidence of effectiveness is required (1962 FD&C act). Often, it is easier for sponsors to get medical devices and software approved beforehand, because that lays the best foundation for a potential FDA approval subsequently. However, this may prolong the process of conducting a DCT, which is why some sponsors go ahead without a priori approval of medical devices. »

» As seen in the COVID-19 pandemic, there is now a clear demand for clinical trials where medical devices and software allow for participants to take part remotely. The FDA recognizes that there is a need for the legislation to evolve with the technology, which is why the newly founded DHCoE "serves to complement advances in digital health technology"[92]. One of the services offered by the DHCoE is "Innovating Regulatory Approaches", which can help ease the process for DCT sponsors. An example of this is Software as a Medical Device[93], which is a regulatory framework that views software as a tangible device. This is a way to regulate intangible technological systems, making it easier for DCT sponsors to to navigate the legislation. The Software as a Medical Device framework is currently being updated to include how machine learning and artificial intelligence can be used in health care.

Data Capture

In 2013, the FDA implemented The Electronic Source Data in Clinical Investigations which focuses on electronic communication platforms that address electronic data capture in clinical trials. The legislation specifically states that the electronic case report form (eCRF) can replace paper and that data elements may populate the eCRF from many sources, investigator, patient, PRO, EHR, and DHT. The legislation also affirms the need to identify the data originator as well as preserve source data and audit trails.

Once the data is captured, it has to be protected according to the Privacy Rule of the Health Insurance Portability and Accountability Act [HIPAA]. This legislation aims to strike a balance between using vital health care information and protecting the privacy of participants[94]. In a DCT context, any identifiable data collected has to be HIPAA compliant. The investigator is responsible for ensuring this, which means implementing security systems that protect data.

An issue pointed out by Deven McGraw, General Counsel and Chief Regulatory Officer, Ciitizen Corporation[95] is how to protect data that are collected on a participant's private device. Here, the legislation is less clear on who is responsible should a data breach occur. It is therefore key to be aware of the distinction between private devices and devices handed out by investigators when it comes to who can be held responsible for data protection.

The state of California has one of the most extensive data privacy laws in the US, which was implemented in 2018. The California Consumer Private Act (CCPA) is comparable to GDPR in its scope, and all health care actors have to comply with strict data protection measures that "de-identify" data to a higher degree and require the act of giving consent to be more explicit[96].

However, the California Consumer Private Act does not apply to all personal data. There are exceptions when it comes to primary data collection for "regulated clinical trials", which ease the initial demands on sponsors and investigators. But any secondary use of the data (replication and additional studies) is subject to regulation. The GDPR does not have such exceptions and it is thus more comprehensive and demanding to adhere to for sponsors and investigators[97].

Although there is currently legislation in place, it is key to recognize that data capture and electronic communication platforms develop at a high pace. Hence, there is a need for continuously updating the legislation to reflect new developments in order to safeguard data and information. For Danish stakeholders, it is crucial to be aware of legislation on data capture, electronic communication platforms, and how it interacts with regulations on data protection (e.g. GDPR).

GENERAL ETHICAL CONSIDERATIONS

On an international level, the ethics of conducting trials with human subjects are defined in the principles of Good Clinical Practice. The guidelines permeate national, regional, and local legislation, meaning the FDA, states, and IRBs adhere to them. However, the digital elements of DCTs give rise to new ethical concerns.

One ethical concern is patient safety. Ensuring that patients are safe in clinical trials depends on the design of the DCT, and also the type of drug or medical device being tested. In some cases, more action and involvement are demanded from the patient, and it will have to be evaluated whether these demands can be justified. Moreover, systems and medical devices can be overwhelming for the patients who are less tech-savvy. This can hurt patient retention and exclude certain groups from the trial. These discrepancies have to be thought through and extra support functions may need to be provided.

Another ethical concern is data protection. In the EU, the GDPR changes the playing field somewhat as participant data might be protected to a higher degree than in the US. Another related concern is medical devices and software, and whether the companies behind these technologies can in any way claim the data. Again, in the EU and in a Danish context, it would be worth looking into how GDPR rules address this issue.

Finally, DCTs often involve changing the location from a conventional investigation site to the patient's home. This shift requires some general ethical considerations regarding home visits and use of video (see also chapter 4 on Patient Experiences). For instance, additional information or individuals may become visible or even recorded during a remote visit. A way to address this issue is to plan for such situations by having specific risk mitigation plans in place.

CHAPTER 6

SPECIFIC CHALLENGES

Shipping

A specific challenge mentioned by various US stakeholders, is shipping and the distribution of drugs, devices, and protein therapeutics to trial participants. Direct-to-trial participant shipping is not allowed in some US states, which is hard to work around for DCT sponsors. In traditional clinical studies, drugs are administered on site by health care personnel, but when bringing drugs to the participants, challenges arise[98]. First of all, drugs and biologics/protein therapeutics have to arrive on time, demanding precision from delivery companies. Moreover, some drugs have to be stored under certain conditions, for instance extremely cold temperatures. Finally, the FDA differentiates between investigative and approved drugs. The status of a drug determines accountability and dispensing measures. This is key to keep in mind when transporting, distributing, and administering drugs, since processes around investigational drugs are much stricter. Questions that arise include: Who is licensed to transport and deliver the medication? What procedures ensure accountability during the shipment and upon delivery? What are the plans for home administering? Some of these considerations might also be relevant in a Danish context.

Electronic consent

A key element of clinical trials is ensuring that the participants have consented to all elements of the trial. Electronic consent (e-consent) is given by the trial participant through a digital channel, e.g., video, audio, text. In the US, e-consent has been used successfully in DCTs.

There are several upsides to e-consent. Studies indicate that knowledge retention is higher when the process of giving consent takes place electronically[99]. The reasoning behind this is that the use of interactive tools makes the process and reading of technical terms and conditions more intuitive. For instance, a way to ensure that patients read and understand what they are consenting to is simply to have the investigator quiz them. Or if possible, develop a more interactive digital solution that enhances knowledge intake. Additionally, it is more comfortable for participants to be in their own homes. They can take their time and thoroughly read what they are consenting to without feeling the pressure of an investigator sitting right across from them.

However, there are also challenges related to e-consent. Some potential participants might be less tech-savvy or functionally illiterate. In this case, giving consent and reading technical information about the trial may not be done properly. This may cause participants to quickly consent to something they in fact do not understand. However, investigators will be able to provide guidance and explain technical language over a video-call in the same way they would do in person. Nonetheless, limited technological abilities may keep interested participants from signing up.


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TECHNOLOGY

Technology is playing an ever-increasing role in the realization of DCTs. Technological development has been on a fast track and will continue to expand and open up for new opportunities; from cloud-based databases to wearables, audio-visual programs, biosensors, etc.

Digital trial technologies and new communication technologies have already slowly changed the way clinical trials are conducted, but the COVID-19 crisis amplified the application of technology in clinical trials in the US.

While COVID-19 has accelerated the role of technology in health care, stakeholders in the US also emphasize that remote DCTs are not just a temporary solution. DCTs challenge the status quo and arguably provide higher quality outcomes of clinical trials due to implementation of technology[101].

"Clear consensus emerges that COVID-19 is necessitating an acceleration of DCTs"

Rodriguez-Chavez[100], 2021 speaking at Operationalize Decentralized Clinical Trials conference

Technology removes the need for on-site visits and physical interaction between health care personnel and participants. Many different technologies exist to enable this remote set-up. Commonly, the regulatory distinction is between two key categories; medical devices and software. The current trend seen in the US is that new technologies within clinical trials tend to primarily be apps and wearables. Fewer new devices are developed. This is attributed to a Bring-Your-Own-Device (BYOD) mentality, where patients increasingly bring and use their own phones, tablets, and computers[102].

Applied technology allows for data to be collected continuously as patients live their daily lives[103]. This provides sponsors with many data points, which gives a more accurate picture of how a patient reacts to a drug[104]. Recently, technology-induced trials with digital endpoints have been approved by authorities in both the EU and the US.

Although applied technology evidently has the potential to transform clinical research, US stakeholders flag the expiration of digital health technologies (DHT) as problematic. As DCTs are evolving, so are digital measurements and devices and it is necessary to recertify DHTs. To ensure high quality outcomes, continuous regulatory efforts are therefore called for[105].

CHAPTER 7

DATA COLLECTION, MONITORING, AND ANALYSIS

Collecting data from participants presents both a number of possibilities as well as pain points to sponsors. Traditionally, data are gathered during on-site visits by means of various tests. In DCTs, sponsors often leverage sensor technology for remote monitoring of patients to collect data.

Examples of this include sensors that can measure movement, sleep, heart rhythm, coughing, and sneezing[106]. US stakeholders emphasize that the opportunities in terms of data collection and monitoring are vast and constantly evolving.

While various devices exist for monitoring patients, smartphones and wearables, like smartwatches, are increasingly used to capture data. In this regard, smartphones have proven particularly useful. There are a number of technologies within a smartphone, which can be used clinically to measure certain diseases. This goes hand in hand with the entry of big tech giants on the health care market where they are both responding to and driving the demand for these new technologies.

The different types of remote monitoring technology include wearables, passive monitoring, active monitoring, ePRO/eCOAS, and telehealth. Technology produces continuous data because a wearable, for instance, can be attached to the participant 24/7. Passive monitoring makes use of smartphone sensors and mobile apps, while active monitoring refers to home-based tests and functional assessments.

Remote monitoring allows for lab data to be captured outside of the traditional lab setting. Because measurements »

"Smartphones present new opportunities for remote patient monitoring"

Amir Lahav, Head of Digital R&D at Mitsubishi Tanabe Pharma Holding America speaking at Operationalize Decentralized Clinical Trials conference 2021

» are continuous and the opportunities to measure various body metrics and vital parameters have expanded, the amount of data collected is vastly increased. This is a powerful tool that can provide sponsors with a more accurate picture of a drug's effectiveness as opposed to discrete measures that are more sporadic in nature. This has made experts highlight that they can now determine efficacy with a much higher confidence because they have more data points[107].

One of the key debates among US stakeholders is how to deal with these large amount of data. Too much data presents sponsors with the overwhelming task of managing it. The study design should primarily be built around preferred outcomes and endpoints. Based on that, sponsors should consider what technology would be useful and thereby also what data is sensible to collect (fit-for-purpose). This has to be balanced against collecting a sufficient amount of data points to determine efficacy[108].
In short, not all data are meaningful and useful to understand the effectiveness of a drug.

There are many technologies out there and it can be tricky for sponsors to navigate in how best to do remote monitoring. Fit-for-purpose can similarly be an abstract concept to employ in the study design. Therefore, the Digital Medicine Society has developed V3 – an evaluation framework and clinical guide, which includes approved digital endpoints, remote monitoring guidelines, and sponsor experiences (see also chapter 3 on Clinical Considerations).

"The biggest challenge is to decide what data we want and how to use it"

John Reites, CEO of Thread Operationalize Decentralized Clinical Trials Conference 2021

DATA INTEGRITY & ETHICAL CONSIDERATIONS

The data collected from remote monitoring have to be accurate and consistent, otherwise the results will be useless since the data are compromised. Several things may violate data integrity. Often, it is a question of how many different people have access to the data[109] as this increases the probability of human error.

But it is also a question of patients performing their task correctly, typing in the correct information and taking the drug on time.

Some suggest monitoring participants via video as they perform a test or take the drug as a way of ensuring compliance and data integrity. However, there are some important ethical aspects to consider here. Patients may feel like they are under surveillance, which could cause them to drop out of the trial. Moreover, when patients go to trial sites, they are rarely under this kind of strict monitoring, instead you assume they take the medicine they are provided. Does enhanced uncertainty about compliance in a DCT justify this type of surveillance?

Many stakeholders choose only to send reminder texts to participants. Additionally, some stakeholders also send appreciation texts afterwards to enhance compliance as a more positive strategy[110]. They argue that compliance is a word that should be replaced by engagement because patients should be at the center of designing clinical trials. Instead of being perceived as patients, they should be considered partners (see chapter on Patient Experiences).

NEW TREND: GAMIFICATION

Patient retention is a major concern for sponsors and they employ various engagement strategies to limit trial drop out. A new trend in this area is Gamification. This term is often used in reference to social media and various apps with the purpose of keeping users hooked. Sponsors aim to leverage gamification as an approach to increase patient retention. An example is the user interface developed by Health Wizz[111], which "resembles a video game, with badges, prizes, leaderboards, and milestones related to a clinical trial".

Gamification is potentially an advantageous strategy. Experiences show that it has a positive effect on patient engagement, because the interest of participants is high throughout the trial. Some US stakeholders argue that it is a way to 'humanize technology' when the trial is siteless and thus devoid of physical human interaction. When patients do not meet with health care personnel in person, an interactive element is necessary to motivate and engage patients[112].

However, there are ethical concerns being raised. Although effective, some US stakeholders question whether the game approach is too extreme in the context of clinical trials[113]. There is a fine line between gamification and manipulation which has been flagged in the context of designing social media apps. In addition, it may have ramifications for data integrity if patients do not carefully follow instructions because the clinical trial now resembles a fun game.

US stakeholders emphasize the need to design clinical trials based on preferred outcomes and endpoints. With this as the study design foundation, relevant technology can be applied. Sponsors should be keenly aware of their responsibility and not use gamification without carefully considering its purpose and fit with the other elements of the trial[114].

THE ROLE OF "BIG TECH"

Big tech giants are seeing an opportunity in the life science industry and major tech companies are disrupting the health care market with their devices, software, and apps which are threatening traditional players[115]. Apple has even claimed that they will perceive themselves as a health company in the near future.

Big tech companies are entering a market in which they have limited knowledge, but their technologies are in high demand. With HealthKit, Apple is aiming to align different operating systems and aggregate different types of medical data (e.g. from Electronic Health Records) so that patients only need to have a single health platform on their devices[117]. In the US, where a centralized digital infrastructure within health care does not exist, this solution is attractive. However, as the digital health infrastructure in Denmark is centralized, it is already aligned to a high degree.

Health care actors and regulators may need to be aware of these powerful profit-oriented tech giants entering a domain in which they are not the experts. Danish stakeholders should also be aware of the devices and software they use in clinical trials, and whether using these devices gives big tech companies access to patient data.

"If you zoom out into the future, and you look back, and you ask the question: 'What was Apple's greatest contribution to mankind?' it will be about health. We're democratizing it. We're taking what has been with the institutions and empowering the individual to manage their health".

Tim Cook, CEO of Apple, 2019[116]

DATABASE MANAGEMENT

Once data are collected, they have to be managed in a database. Storing vast amounts of data places high demands on those tasked with database management. In principle, the remote data acquisition immediately uploaded to the cloud database allows for more data to be collected and to be at hand for sponsors in real time. However, managing the data meets several obstacles that are key to understand and handle according to US stakeholders[118].

First of all, data coming from many sources complicate database management[119]. Real-world data can stem from various sources, whether it be claims data, data from electronic health records (EHR) or data collected via digital health technologies. Technologies have to interact and operating systems have to be aligned for DCTs to run smoothly[120]. Because DCTs have a broader reach there is a need to align different operating systems to allow for data to flow in the most efficient way. In Denmark, the digital infrastructure within health care might make this process easier. However, the amount of data involved in DCTs must not be underestimated and it adds complexity to DCT operations.

In the US, it is possible to collect data via EHRs, if patients download it and make it available to sponsors. Legally, sponsors cannot gain access to the EHR themselves – the patient has to provide access[121]. However, some US stakeholders point out that it is key to consider the quality of the data from an EHR. The data may be sporadic and the information about the patient may be insufficient if the record is not updated. Hence, there is still work to be done in terms of EHR data and its usability in clinical trials[122].

Data integrity is a potential concern in database management. According to John Gardinier, retired statistician from the National Center for Health Statistics, there is reason to be concerned when it comes to data reliability. As already pointed out, EHRs can be faulty causing the data to be unreliable. Furthermore wearable sensors can also also be unreliable[123]. However, other US stakeholders point to the fact that the vast majority of the data used in DCTs have proven reliable. It is key to recognize that data per default are imperfect, but with large enough datasets it is possible to overcome this[124].

Secondly, the data have to be cleaned. The increased amount of data and the ease with which they can be collected, significantly increases data quantity. However, it is important to keep in mind that conducting meaningful analyses of this data is costly[125]. The data have to be cleaned and sorted. US stakeholders point out that even though the cloud database is a smart way to store massive amounts of data, it does not make sense to gather vast amounts without carefully considering its use in the trial[126].

Several solutions exist to help sponsors manage the increasing amount of data. Artificial Intelligence (AI) can be used in place of on-site monitors to review data. Since data are stored in the cloud and collected through apps, wearables, and devices, algorithms can be used to monitor the data and flag cases that need to be reviewed. Basically, the increased amount of data associated with DCTs can be sorted with the use of AI. Moreover, algorithms can be designed to warn about unusual data points. This reduces the work, although employing AI is not a cost-free solution[127].

"One challenge of new technologies, is that they can collect large amounts of data relatively cheaply, but that leaves the challenge and expense of analyzing those data and dealing with the consequences of unexpected findings"

Steve Cummings, Director of the San Francisco Coordinating Center, Virtual Clinical Trials: Challenges and Opportunities 2019 Workshop

FDA regulations require sponsors to monitor the conduct and progress of their clinical investigations. The process of source data verification (SDV), which involves verifying the data entered into a patient's medical record against the data recorded in the clinical trial database, is an important step in this regard.

During the COVID pandemic, some sponsors have used remote monitoring to oversee study conduct at clinical trial sites, including remote review of source data (rSDV). The FDA regulations are not specific about how sponsors must conduct such monitoring and open the space for sponsors using a variety of approaches to fulfil their responsibilities. In a new guideline issued to address the novel situation due to COVID, the FDA specifically states that modern, risk-based approaches, including remote monitoring, are considered part of these approaches and thus already included in existing guidelines. In short, remote monitoring as well as remote review of source data can be used when appropriate and should be based on the sponsor's ongoing risk assessment[128]. The Clinical Trials Transformation Initiative (CTTI) has also developed recommendations for advancing the use of mobile technologies for data capture and improved clinical trials, which are accessible here.

US PLAYERS

The US has been a frontrunner when it comes to DCTs. While there have been challenges, it has managed to build an ecosystem consisting of governmental agencies, contract research organizations, pharmaceutical companies, and technological businesses.

Such an ecosystem is important in order to support and facilitate DCTs and Danish stakeholders can learn from these experiences. Moreover, some actors operating in the American DCT space might be relevant for Danish stakeholders looking for international collaboration. While the US ecosystem is too large for every player to be mentioned, some of the main actors are highlighted below and in figure 2.

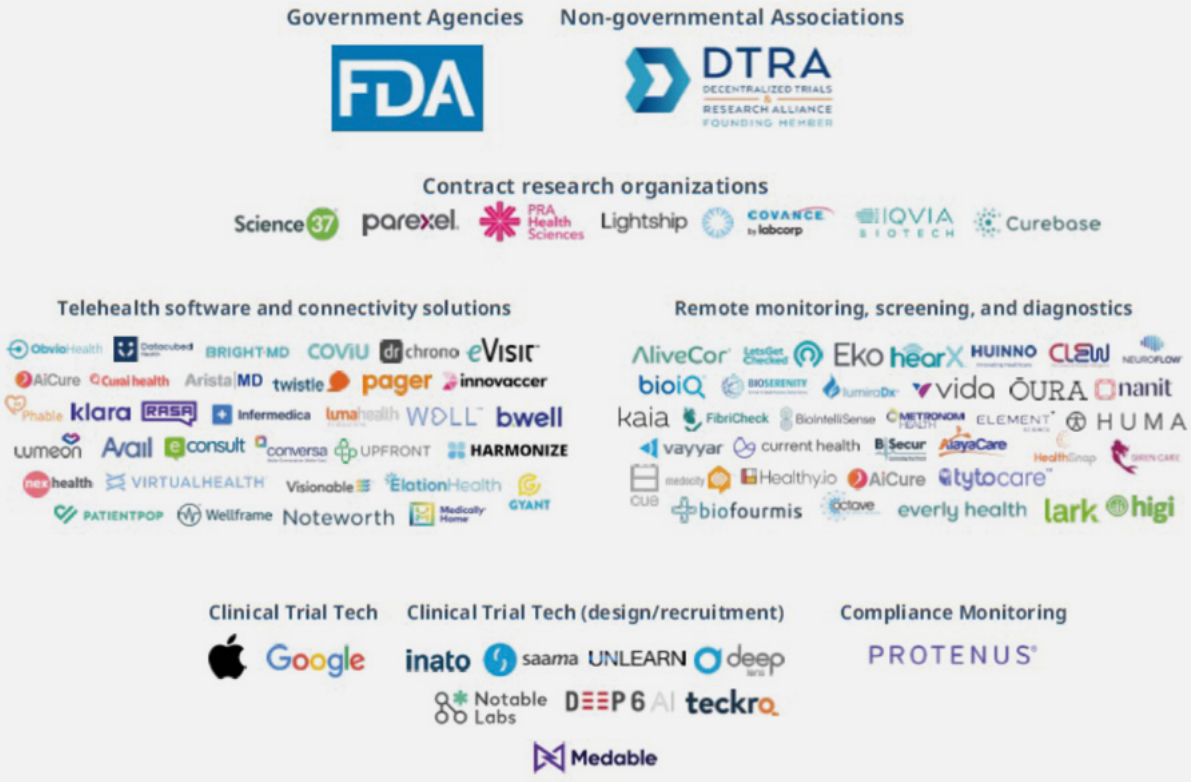
Governmental Agencies and non-Governmental Associations
The FDA is the most important governmental agency when it comes to clinical trials - for an overview of key regulatory actors, please see chapter 6 on the regulatory framework. The FDA is also part of the public-private partnership Clinical Trials Transformation Initiative (CTTI) with approximately 80 member organizations who discuss and offer recommendations on how to improve and modernize clinical trials. There are also significant non-Governmental Associations who shape the DCT agenda. In this regard, the Decentralized Trials and Research Alliance (DTRA) is a key stakeholder working with the explicit aim of accelerating the adoption of patient-focused, decentralized clinical trials.

Sponsor companies
Many of the sponsor companies operating in the US are multinational companies. When it comes to DCTs, companies such as Janssen Pharmaceuticals/Johnson & Johnson, Sanofi, Bayer, GlaxoSmithKline and Pfizer are all invested in the agenda and conducting smaller or larger DCT trials.

Contract Research Organizations
Science37 and Lightship are two important American CROs who both specialize in DCTs with platforms designed specifically for this kind of trial. Irish-headquartered ICON is another actor who is very visible in the American DCT system.

DCT technology platforms
Recent years have seen new companies specializing in technological platforms tailor-made for DCTs. The company Medable provides sponsors and CROs with an end-to-end global cloud platform for DCTs. In a similar vein, the company THREAD enables pharma and CRO customers to conduct decentralized studies from a singular, dedicated technology platform.

FIGURE 2: US PLAYERS WORKING IN THE DCT SPACE



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