

VIEWS AND OPINIONS

INDUSTRY PERSPECTIVE



WHY IS THE UPTAKE OF DECENTRALISED ELEMENTS IN CLINICAL TRIALS SLOWER THAN EXPECTED?

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In the swiftly changing realm of clinical research, incorporating decentralised elements into clinical trials is becoming a transformative approach to drug development. Driving this approach is the need to not only improve the desirability of participating in clinical trials by reducing participant burden but also increase the utility of the data/evidence collected. The philosophy guiding this approach is both participant- and site-centred, thus ensuring decentralised elements truly add value to the clinical trial experience while still meeting a trial's scientific objectives. As the potential benefits of these innovative trial methodologies have become more clear, regulatory agencies worldwide have released numerous guidelines for incorporating decentralised elements into clinical trials. Despite these promising benefits and regulatory guidance, the adoption of these elements has not progressed as rapidly as anticipated. This commentary delves into some of the factors sponsors consider with regard to integrating decentralised elements into clinical trials and discusses several challenges they face in practice.

THE NEED FOR DECENTRALISED ELEMENTS IN CLINICAL TRIALS

The conventional clinical trial model often faces significant challenges with participant recruitment, geographical constraints, and high dropout rates. Decentralised clinical trials (DCTs), which incorporate decentralised elements, can make it easier to recruit and retain participants, for example when the participant pool is small (e.g. with rare diseases) or when participants face unique challenges (e.g. with some neurodevelopmental disorders). By incorporating decentralised elements, sponsors can significantly reduce the number of on-site visits, which lowers the access hurdle for par-

ticipants. This not only enhances the feasibility of trial participation but also underscores a participant-centred approach – and ultimately facilitates more inclusive and efficient clinical research processes.¹ In addition, incorporating decentralised elements can increase the catchment area for sites participating in trials, especially for geographically dispersed populations. Another benefit of using decentralised elements in clinical trials is the opportunity to enhance the scientific value of the trial design by utilising more meaningful endpoints that, in some cases, can only be measured remotely.²

SPONSOR CONSIDERATIONS FOR INCORPORATING DECENTRALISED ELEMENTS INTO CLINICAL TRIALS

When deciding whether and when to use decentralised elements in a trial (e.g. home health visits, telemedicine, community-based facilities, or shipping investigational medicinal products (IMPs) directly to participants), sponsors should consider a fit-for-purpose assessment that incorporates all factors for the different stakeholders (including sponsors, participants, investigators at sites, vendors, the regulatory landscape, and the local healthcare infrastructure). Sponsors also need to consider the safety profile of a drug as well as the trial phase, as decentralised elements are particularly feasible during the most established phases of a clinical trial. For example, in oncology trials decentralised elements might be most appropriate during the maintenance phase of the therapy, when participants have become used to the administered IMP and their disease is manageable with some level of stability.

Having options and flexibility are also key considerations. For example, home health visits can be alternated with on-site visits according to site and participant preferences, provided there is an adequate notice period to manage the logistics. The incorporation of decentralised elements should be evaluated on a case-by-case basis before they are offered, taking into account the assessment and safety considerations of the drug. These evaluations should be made before the protocol is finalised in order to ensure that data quality and integrity are not compromised. Furthermore, it is essential to ensure that optional decentralised elements do not introduce any bias in the analysis of critical data. This will help maintain the robustness and compatibility of data collected, for example through different visit types (home or local healthcare facility visits vs. on-site visits). This remains a crucial consideration for sponsors and requires careful implementation in a DCT.

WHY AREN'T DECENTRALISED ELEMENTS ROUTINELY INCLUDED IN CLINICAL TRIALS?

Additional oversight responsibilities

Regulatory guidelines such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH GCP) clearly assign the responsibility for a trial's tasks, activities, and assessments – even those carried out by third-party vendors and local healthcare providers (HCPs) – to the principal investigator (PI). This can be problematic when these vendors and HCPs are not selected by the PI (e.g. selected by the sponsor). Understandably, PIs may be unwilling to accept oversight responsibility for organisations and individuals they may not have met or even spoken to, because they have not

had the opportunity to develop the same level of trust and confidence as with their own staff or known vendors and HCPs (e.g. unknown mobile nurses compared to site nurses). This extra responsibility must be managed well in DCTs, for example by having a working agreement that clearly defines responsibilities and that can be created for new vendors and HCPs without significant administrative and legal efforts and by clearly assigning liability to third-party vendors when they do not follow the protocol and the PI's instructions. Additionally, PIs and their staff should be compensated for their additional oversight and responsibilities.

Impact on site revenues

When decentralised elements are used in a trial, it often means that tasks, procedures, and/or assessments traditionally performed at the trial site are instead performed by third-party vendors and local HCPs (e.g. local imaging facilities do computed tomography (CT) scans or home nurses perform physical exams). Along with this shift in tasks comes a shift in revenues, and sponsors need to make sure that the study site's revenue stream remains fair. Adequate compensation can be used to transform this potential risk of a decrease in revenue and an increase in responsibility into a potential opportunity to

generate additional revenue. For example, having a site's own nurses perform tasks remotely and delegating tasks to local HCPs as an alternative to third-party vendor solutions has the potential to not only sustain revenue streams but also increase adoption at both the site level and the participant level (e.g. by reducing travel time and costs and by maintaining existing patient-physician relationships). In fact, the responsibilities and activities related to third-party vendors and local HCPs in DCTs have the potential to generate additional work, and thus additional revenue, for sub-investigators and PIs.

Numerous stakeholders

It is imperative to involve key stakeholders across the entire healthcare ecosystem – including investigators, hospital administrations, regulators, and participants – in order to develop feasible and effective trials with decentralised elements. Indeed, maintaining participant

engagement and fostering the participant-investigator relationship can be challenging in a virtual environment. Only when key stakeholders are involved in planning a protocol for conducting a clinical experiment can the adoption of new and innovative elements be successful.³

Balance between customisation and feasibility

A successful DCT must tailor decentralised elements to the specific needs of both participants and study sites, which adds additional layers of complexity that need to be managed. Offering tailored options that accommodate participants' preferences and site capabilities can enhance both trial participation and retention. For

example, allowing participants to choose between on-site visits and remote assessments can improve engagement. However, the decision to offer decentralised options needs to be determined prior to protocol finalisation and planned carefully in order to ensure that data quality and data integrity are not compromised.

Operational complexity

To minimise operational complexity and the resulting burden on sites, it is crucial to implement decentralised elements judiciously. For example, when sites are confronted with various technologies from different vendors requiring them to have multiple login credentials and interact with disparate systems, there is a risk of diminishing site engagement. This disengagement

and frustration can affect recruitment rates. Mitigation strategies include utilising specialised DCT vendors that offer multiple decentralised elements under a single login, providing sites with robust help desk support, and ensuring thorough site training. Engaging with sites early on in the feasibility stage is essential for securing site acceptance of the proposed decentralised elements.

Regulatory and legal constraints

The extent of trial decentralisation varies across countries due to differing legal and healthcare frameworks. Globally, there is fundamental heterogeneity regarding the ability to implement decentralised elements, for example concerning who is authorised to perform specific assessments in a participant's home. These

country-specific differences bring additional operational complexity when conducting global trials. Navigating these constraints requires not only engagement with local regulatory authorities and ethics committees early on but also a tailored approach for each country.

Potential risks to data quality and integrity

A trial’s study design requires careful consideration when incorporating decentralised elements. Potential risks to a trial’s integrity must be identified early on in the process so they can be mitigated. Key parameters for a specific strategy depend on the therapeutic area being studied and specific measures. Some assessments – for example lab parameters with well-established concordance between local and central labs – can be collected remotely without compromising data quality or otherwise impacting data integrity. For other data assessments, establishing data quality and equivalence with site-generated data can be more challenging; for

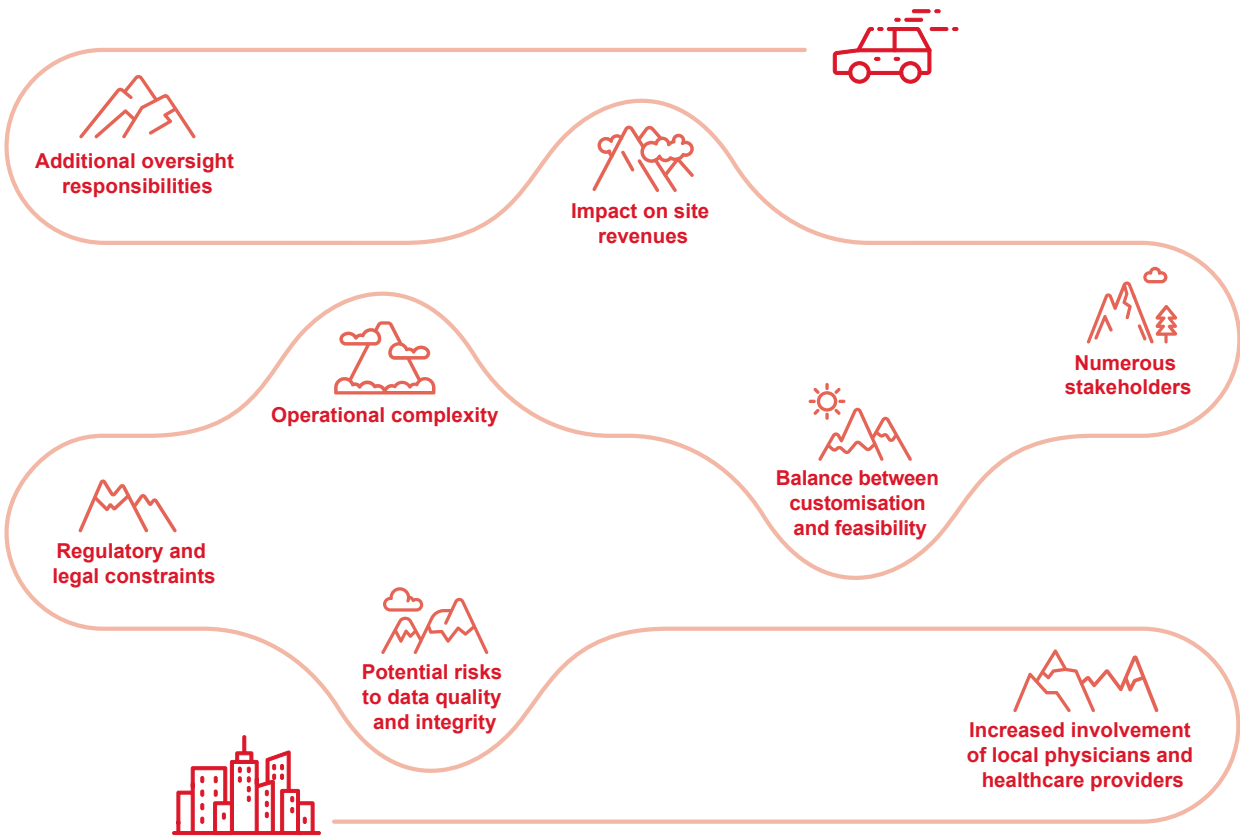
example, many participant scale ratings and investigator-rated clinical measures are conventionally validated to be conducted in person. In these cases, it is necessary to plan carefully and potentially conduct feasibility or equivalence studies. Industry is addressing the multifaceted challenges of decentralised data generation not only operationally (e.g. by establishing reliable frameworks that standardise DCT processes, training, and quality monitoring) but also scientifically (e.g. by developing data modelling approaches to account for biases and differences in data generation).⁴

Increased involvement of local physicians and healthcare providers

Delegating tasks to local physicians and healthcare providers in DCTs can reduce travel distances for participants, maintain existing patient-provider relationships, and sustain revenue streams. Yet facilitating local physician and HCP involvement beyond specialised research centres requires more administrative effort (e.g. making sure working agreements are in place and choosing suitable legal language related to responsibilities), involves

transferring more data, and uses more personnel and financial resources (e.g. for reimbursement). Sponsors also need to address access barriers and simplify participation for local physicians and HCPs involved in trials with decentralised elements in order to increase their awareness and willingness to promote these options with their patients.

Figure 1: Challenges to navigate in decentralised clinical trials



CONCLUSION

The healthcare ecosystem is moving towards more flexible, decentralised care in general. Therefore, it is becoming increasingly important for clinical trials to provide at least the same level of flexibility in order to remain attractive and viable for all the stakeholders within this ecosystem. Incorporating decentralised elements into clinical trials represents a promising paradigm shift in clinical research, offering more flexibility and solutions to longstanding challenges in participant recruitment and engagement. Despite the many benefits

of incorporating decentralised elements into clinical trials, many challenges exist for sponsors and PIs. These challenges can be overcome by planning carefully early on in the process, involving key stakeholders throughout the process, and promoting a mindset shift to embracing decentralised elements as an opportunity to increase site revenue streams and better accommodate patient preferences. Indeed, DCTs offer new opportunities for participants and sponsors alike and thus complement existing, more traditional trial work.

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